



International Lewy Body Dementia Conference
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ORAL PRESENTATIONS

Session 4: Clinical I

Category: Clinical - Oral Presentation

O.1 Improving the Diagnosis and Management of Lewy Body dementia (the DIAMOND-Lewy Study)

Author: John O'Brien

Additional Authors: John O'Brien, Department of Psychiatry University of Cambridge and Institute of Neurosciences Newcastle University

John-Paul Taylor, Institute of Neurosciences Newcastle University

Alan Thomas, Institute of Neurosciences Newcastle University

Claire Bamford, Institute of Health and Society Newcastle University

Tracy Finch, Northumbria University

Louise Allan, University of Exeter

Ajenthnan Surendranathan, Department of Psychiatry University of Cambridge

Joseph Kane, Institute of Neurosciences Newcastle University

Allison Bentley, Department of Psychiatry, University of Cambridge

Sally Barker, Institute of Neurosciences Newcastle University

Richard McNally, Institute of Health and Society Newcastle University

Louise Hayes, Institute of Health and Society Newcastle University

Sarah Dunn, Clinical Trials Unit Newcastle University

David Burn, Institute of Neurosciences Newcastle University

Ian McKeith, Institute of Neurosciences Newcastle University

Background

Lewy body dementia, comprising both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), has an even worse outcome than other dementias in terms of functional decline, reduced quality of life and increased mortality. There are some effective treatments for Lewy body dementia and its symptoms, but there is considerable heterogeneity in approaches to management. Within the DIAMOND-Lewy study, we aimed to test whether the introduction of evidence-based, standardised, diagnostic and management toolkits could improve patient and carer outcomes.

Methods

We developed evidence-based toolkits aimed at improving both the diagnosis and management of Lewy body dementia. We introduced the diagnostic toolkits into 22 Movement disorder and Memory services in the UK, and cluster randomised these services to the introduction of the management toolkit (12 services) or usual care (10 services). Within both intervention and control (usual care) services we recruited patients and carers and undertook assessments at baseline, 3 and 6 months by raters blinded to which arm subjects were in. Patient assessments included global outcome, cognition, neuropsychiatric symptoms, motor features and quality of life; Carer assessments included measures of depression, anxiety, carer stress and quality of life. Median regression analysis or Chi square tests were used to determine differences between groups.

Results

127 subjects with DLB (n=77) or PDD (n=50) were recruited into the study and underwent baseline assessments (75 in the intervention arm and 52 in the control arm), of whom 108 (85%) completed the study. After adjustment for baseline values and effect of clustering, there were benefits in the management toolkit arm for patients at 6 months for global outcome (fewer subjects experienced mod/severe worsening) and significant improvements in carer outcomes of reduced burden (Zarit scale) and depressive symptoms (Hospital Anxiety and Depression Scale). There was no evidence that one

subgroup (DLB or PDD) responded better than the other. Parallel qualitative studies suggested implementation of the management toolkit was variable.

Conclusions

This cluster-randomised trial of a new, evidence based, management toolkit for Lewy body dementia demonstrated improvements in some important patient and carer-related outcomes. Whilst a larger trial, with more systematic implementation of the toolkit, is warranted, our results show that a standardised approach using currently available treatments produces significant benefits for patients and carers.

Acknowledgments

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Reference

Thomas AJ, Taylor J-P, McKeith I, Bamford C, Burn D, Allan L, O'Brien J (2018). Revision of assessment toolkits for improving the diagnosis of Lewy body dementia: The DIAMOND Lewy study. *International Journal of Geriatric Psychiatry*; 33(10): 1293-1304. doi: 10.1002/gps.4948.

Category: Clinical - Oral Presentation

O.2 Symptoms, Biomarkers and Cognitive Profile in Mild Cognitive Impairment with Lewy Bodies

Author: Alan Thomas

Additional Authors: Paul Donaghy, Newcastle University

Background

Mild cognitive impairment (MCI) is the predominant clinical presentation of prodromal DLB but has been little studied. We have conducted two prospective observational studies (LewyPro and SUPERB, the latter ongoing) to evaluate MCI with Lewy Bodies (MCI-LB).

Methods

We have recruited 192 subjects to date (99 MCI-LB (NIA-AA MCI criteria with core symptoms and/or biomarkers); 59 MCI-AD (NIA-AA); 34 controls). Both studies include comprehensive clinical evaluations, cognitive assessments and biomarkers (FPCIT, CSF, blood). The current SUPERB study additionally includes: MIBG, MRI, EEG, PET amyloid, repeat FPCIT. We will report our up-to-date findings on: prevalence and diagnostic accuracy of core and supportive clinical symptoms of DLB; diagnostic performance of the imaging biomarkers (MIBG and FPCIT); and the cognitive profile of MCI-LB compared with MCI-AD.

Results

Clinical Symptoms: In LewyPro we found that in MCI-LB cognitive fluctuations occurred in 56%, visual hallucinations in 29%, Parkinsonism in 46% and RBD in 49%. In SUPERB the frequencies to date are: cognitive fluctuations 52%, visual hallucinations in 20%, Parkinsonism in 36% and RBD in 65%. Using the combined data to date, for distinguishing MCI-LB from MCI-AD specificities for core symptoms are all >80% (specific up-to-date figures will be presented at the meeting). Looking more widely at other symptoms, in LewyPro we did not find hyposmia or autonomic symptoms to be useful, due to a high frequency in MCI-AD. However, supportive neuropsychiatric symptoms (depression, apathy, non-visual hallucinations, delusions, anxiety), rated using the Neuropsychiatric Inventory, occurred more often in MCI-LB and the presence of two of these five features occurred much more frequently (67% vs 16%) giving a likelihood ratio of 4.2.

Imaging Biomarkers: In LewyPro we have reported that FPCIT imaging has good diagnostic accuracy for MCI-LB versus MCI-AD (sensitivity 54%, specificity 89%) and in SUPERB sensitivities and specificities are similar to this and similar for MIBG (up to date data will be presented at the meeting).

Cognitive Profile: In LewyPro we reported that MCI-LB had significantly worse performance on visuospatial function (Line Angle discrimination and Visuospatial domain on ACER), executive function (ACER verbal fluency) and attention (digit vigilance). In SUPERB we have found a similar profile with worse performance in visuospatial function (visual patterns and pareidolia tests), executive function (ACER verbal fluency) and information processing speed (digit symbol substitution and Stroop C). But MCI-AD performed more poorly on verbal learning and memory (RAVLT).

Conclusion

In summary, the cognitive profile of MCI-LB appears similar to that in DLB and the core clinical symptoms and biomarkers for DLB have sufficient specificities and occur with high enough frequencies to be important for diagnosis. Other features, e.g. amnesic vs non-amnesic profile, visuospatial impairment and neuropsychiatric symptoms, have potential but need further investigation.

Category: Clinical - Oral Presentation

O.3 *Prodromal Dementia with Lewy Bodies: Clinical characteristics and risk factors for progression*

Author: Marleen van de Beek

Additional Authors: Marleen van de Beek¹, Inger van Steenoven¹, Jessica J. van der Zande¹, Wiesje M. van der Flier¹ and Afina W. Lemstra¹

Department of Neurology and Alzheimer Center, Amsterdam Neuroscience, VU University Medical Center, Amsterdam, The Netherlands.

Background: Little is known about the clinical presentation and rate of decline in patients with prodromal Dementia with Lewy Bodies (DLB). We aimed to describe the clinical characteristics and cognitive decline of prodromal DLB patients and compare these to prodromal Alzheimer's disease (AD). Furthermore, we aimed to identify risk factors associated with progression to dementia in prodromal DLB. **Methods:** We included 196 patients with mild cognitive impairment (MCI) from the Amsterdam Dementia Cohort, of which 71 patients with prodromal DLB and 125 with prodromal AD. Prodromal DLB (MCI-DLB) was defined as MCI + (1)two or more DLB core clinical features (hallucinations, parkinsonism, fluctuations or RBD), or (2)one core clinical feature and abnormal DAT-SPECT or (3)probable DLB at follow-up. Prodromal AD (MCI-AD) was defined as MCI + AD biomarker profile in CSF, matched on age with MCI-DLB. Outcome measures were clinical characteristics, neuropsychiatric symptoms (NPI, GDS), caregiver burden (ZARIT), MRI markers, APOE- ϵ 4 and CSF status. Patients were invited annually for follow-up, including neuropsychological testing. Mean follow-up time was 2.7 ± 2.1 years. Mixed models were used to assess longitudinal cognitive functioning in five cognitive domains (attention, memory, language, executive and visuospatial functioning). MCI-DLB patients with at least one follow-up visit ($n=53$) were included in survival analysis, to identify risk factors for progression to dementia. **Results:** Of MCI-DLB patients, 11% had all four core clinical features at baseline, while 7% had no core features, but did develop to DLB at follow up (figure 1). Parkinsonism was the most frequently reported feature (69%). 33% of MCI-DLB had a biomarker profile compatible with AD-pathology and 47% were APOE- ϵ 4 carrier. MCI-DLB patients scored higher on NPI, GDS and ZARIT than MCI-AD patients (table 1). There were no differences in cortical atrophy and other MRI characteristics between MCI-DLB and MCI-AD (table 1). Mixed models showed lower baseline scores on attention, executive functioning and visuospatial functioning in MCI-DLB, while MCI-AD had lower memory scores. MCI-DLB had faster decline over time on attention scores, whereas MCI-AD had faster decline on MMSE and language scores. Of 53 MCI-DLB patients with follow-up available, 29 patients (55%) progressed to dementia after an average of 2.8 ± 1.8 years. Progression rate and time to dementia were similar in MCI-AD. Age- and sex-adjusted Cox regressions showed that attention impairment ($HR=3.6$ [95%CI:1.2-11.4], $p=0.03$) and global and posterior cortical atrophy on MRI ($HR=4.5$ [95%CI:1.3-15.3], $p=0.02$ and $HR=7.3$ [95%CI:1.4-38.9], $p=0.02$) were associated with faster progression to dementia in MCI-DLB. **Discussion:** In MCI-DLB, the presence of core clinical DLB features is common, but patients without core features at first presentation also exist. MCI-DLB patients present with more non-cognitive symptoms and have a distinct cognitive profile with prominent attentional impairment, compared to MCI-AD. Higher caregiver burden in MCI-DLB might be associated to the higher degree of non-cognitive symptoms. Attention impairment and global/posterior atrophy are potential risk factors for progression towards dementia in MCI-DLB. Our results highlight the need for early diagnosis, since clinical symptoms already have impact in the prodromal stage of the disease and could be treated. Further studies should elucidate whether early treatment has impact on disease progression.

Category: Clinical - Oral Presentation

O.4 Subtypes of dementia with Lewy bodies associated with α -synuclein and tau distribution

Author: Tanis Ferman

Additional Authors: Tanis J Ferman PhD1, Naoya Aoki, MD2, Bradley F. Boeve MD3, Jeremiah Aakre MPH3, Jonathan Graff-Radford MD3, Kejal Kantarci MD3, Ryan Uitti MD1, Joseph Parisi MD3, Melissa E. Murray PhD1, Otto Pedraza PhD1, Neill R. Graff-Radford MD1, Zbigniew Wszolek MD1, Owen A. Ross PhD1, David S. Knopman MD3, Ronald C. Petersen MD, PhD3, Dennis W. Dickson MD.1

Mayo Clinic, Jacksonville, FL, Yokohama University Medical Center, Yokohama, Japan, Mayo Clinic, Rochester, MN

Introduction: In dementia with Lewy bodies (DLB), the deposition of α -synuclein occurs in brainstem-limbic regions and often extends to the neocortex. It is estimated that about half of those with DLB also have comorbid neocortical neurofibrillary tangles (NFT). Given this pathologic heterogeneity, we sought to determine whether the distribution of α -synuclein with or without neocortical tau is associated with differences in the clinical expression of DLB.

Methods: Participants included autopsied patients with antemortem dementia and either Lewy body disease (n=254) or pure Alzheimer's disease (n=210). Patients with Lewy body disease were grouped based on transitional-limbic vs. diffuse-neocortical Lewy body disease (TLBD vs. DLBD) and by the absence vs. presence of neocortical tangles based on Low (L) Braak NFT stage of 0 to 3 or a High (H) Braak NFT stage of 4 to 6. The four Lewy body disease subgroups of TLBD-L, DLBD-L, DLBD-H, and TLBD-H were compared to each other and to AD-dementia on clinical and cognitive variables and on MMSE and DRS rate of decline.

Results: Patients were followed an average of 6.2 ± 3.8 years. The diagnostic sensitivity for TLBD-L and DLBD-L was 87% and 96% for probable DLB which increased to 98% when possible DLB comprised of dementia and either parkinsonism or probable RBD were also included. The DLBD-H group had 70% diagnostic sensitivity for probable DLB which increased to 77% when possible DLB comprised of dementia and either parkinsonism or probable RBD were also included. Patients with DLBD-H were similar to TLBD-L and DLBD-L with an early onset of each of the four core features, greater parkinsonism severity, and worse baseline attention and visual processing than the AD-dementia group. Nonetheless, DLBD-H differed from TLBD-L and DLBD-L with greater female representation associated with lower reports of RBD, milder parkinsonism severity and worse baseline memory and naming performance. For the TLBD-H group, the diagnostic sensitivity of probable DLB was 43% and increased to 57% when possible DLB comprised of dementia and either visual hallucinations, parkinsonism or probable RBD were also included. TLBD-H was most similar to AD-dementia with better baseline attention and visual processing and worse baseline memory and naming compared to TLBD-L and DLBD-L but were still more likely to eventually develop visual hallucinations and parkinsonism than the AD-dementia group. Fluctuations developed earlier in the Lewy body disease groups compared to the AD-dementia group. Rate of decline was slowest for TLBD-L (least pathology) and fastest for DLBD-H (most pathology).

Conclusions: Patients with greater α -synuclein relative to tau (TLBD-L, DLBD-L) were more likely to exhibit an early DLB phenotype than those with less α -synuclein relative to tau (TLBD-H, AD-dementia). Patients with neocortical α -synuclein and tau were also likely to exhibit the DLB phenotype and had the fastest trajectory, though lower reported RBD associated with greater female representation, milder parkinsonism and greater memory and naming impairment distinguished this group from those with pure Lewy body disease.

Category: Clinical - Oral Presentation

0.5 Clinical Characterization of Mild Cognitive Impairment Associated With Eventual Lewy Body Disease Pathology

Author: Brad Boeve

Additional Authors: Bradley F. Boeve MD, Tanis J. Ferman PhD, Neill Graff-Radford MD, David S. Knopman MD, Jonathan Graff-Radford MD, Rodolfo Savica MD, David T Jones MD, Daniel A. Drubach MD, Julie A. Fields PhD, Mary Machulda PhD, John Lucas PhD, Leah Forsberg PhD, Toji Miyagawa MD PhD, Laura Allen APRN CNP, Kejal Kantarci MD, MS, Melissa E. Murray PhD, Joseph E. Parisi MD, Dennis W. Dickson MD, Ronald C. Petersen MD, PhD.
Mayo Clinic, Rochester, Minnesota, and Jacksonville, Florida

Background: The clinical characteristics of prodromal Lewy body disease (LBD) preceding the phenotype of dementia with Lewy bodies (DLB) are still being defined.

Methods: Antemortem data were analyzed from autopsied patients with either limbic-transitional or diffuse-neocortical LBD diagnosed with mild cognitive impairment (MCI) and followed prospectively through the Mayo Alzheimer's Disease Research Center. Patients were compared based on absence vs. presence of neocortical neurofibrillary tangles (NFT) (Braak stages 0 to 3 vs. stages 4 to 6).

Results: The sample included 74 patients (34 transitional, 40 diffuse), of whom 54 (73%) were male, all were Caucasian, mean education was 15 ± 3 years, mean MMSE was 27 ± 2 , and all had a CDR score of 0.5. The pathologic findings were neocortical-predominant LBD in 40 and limbic-predominant LBD in 34, with 32 (43%) having coexisting AD pathology. There were no clinical or demographic differences based on distribution of Lewy-related pathology. The mean age or duration \pm SD in years for key features were as follows: onset of cognitive decline 71 ± 9 , onset of REM sleep behavior disorder (RBD, $n=44$) 63 ± 14 , age of MCI diagnosis 73 ± 8 , age of dementia diagnosis ($n=69$) 75 ± 8 , duration from MCI to dementia diagnosis 2 ± 1 , age at death 81 ± 8 , and duration from dementia diagnosis to death 6 ± 4 . During the MCI stage, 69% had at least one core DLB feature and 45% had two features. Probable REM sleep behavior disorder (RBD) was evident in 55%, parkinsonism in 35%, visual hallucinations in 24%, and fluctuations in 26%. When distinguished by the absence ($n=36$) vs. presence ($n=38$) of neocortical NFT, the latter group had greater amyloid- β neuritic plaque density ($p < 0.01$) and fewer males (58% vs. 86%, $p < 0.01$). One or more core DLB features during the MCI stage was more likely in LBD without neocortical NFT (83% vs. 55%, $p < 0.01$). Specifically, before dementia was diagnosed, those without neocortical NFT were more likely to have RBD (72% vs. 40%, $p = 0.005$), parkinsonism (47% vs. 24%, $p = 0.03$), and visual hallucinations (36% vs. 13%, $p = 0.02$) but fluctuations were equally likely (31% vs. 21%, $p = 0.35$). By the end of life, 92% had at least one core DLB feature, and 80% had two or more core features, with greater frequency in LBD without comorbid neocortical NFT (97% vs. 63%, $p < 0.01$).

Conclusion: In the MCI stage of evolving DLB, 69% had at least one core DLB feature. Although RBD was present in the majority at MCI diagnosis, each of the other core DLB clinical features was present in less than a third. Patients with neocortical NFT were less likely to have core features in the pre-dementia stage. While most developed features warranting the clinically probable DLB diagnosis prior to death, a significant minority (20% in this cohort) did not. The absence of many core features in the MCI phase and variable development of these features in the dementia-predominant phenotype of LBD underscore the need for biomarkers which are sensitive and specific to LBD pathology, particularly in the prodementia phase.

Session 5: Clinical II

Category: Clinical - Oral Presentation

O.6 The contribution of multiple co-existing neurodegenerative and cerebrovascular pathologies to clinical diagnosis of Alzheimer's disease dementia and Dementia with Lewy bodies

Author: Melissa Murray

Additional Authors: Jolien M. Schaefferbeke¹, Julia Crook², Elizabeth R. Lesser², Fadi S. Hanna Al-Shaikh¹, Jessica F. Tranovich¹, Kayla J. Vinson¹, Amanda M. Liesinger¹, Nilufer Ertekin-Taner^{1,3}, Owen A. Ross¹, Tanis J. Ferman⁴, Ranjan Duara⁵, Neill R. Graff-Radford³, Dennis W. Dickson¹, Melissa E. Murray¹

Department of Neuroscience,¹ Health Sciences Research,² Neurology,³ Psychiatry & Psychology⁴ Mayo Clinic, Jacksonville, FL. Mount Sinai Medical Center⁵, Miami Beach, FL, USA.

Introduction Significant Alzheimer's disease (AD) neuropathologic changes are associated with a low likelihood of clinically diagnosed dementia with Lewy bodies (DLB) (McKeith 2017). However, a subset of neuropathologically-diagnosed AD cases present clinically as DLB. To further complicate clinicopathologic studies, co-existing neurodegenerative pathologies and/or cerebrovascular disease are often observed in the context of significant AD neuropathologic changes (Schneider 2009). Thus, we sought to investigate how each of these co-existing neuropathologic changes may affect the predicted probability of a clinical diagnosis of AD dementia or DLB in the context of neuropathologically-diagnosed AD cases.

Materials and Methods We investigated the FLorida Autopsied Multi-Ethnic (FLAME) cohort, which comprises a series of patients derived from memory disorder clinic referral services across the State of Florida who elected to donate their brains for research. We identified 1485 neuropathologically-diagnosed AD cases who were Braak tangle stage >IV. The presence of co-existing hippocampal sclerosis of a TDP-43 etiology (HpScl-TDP), Lewy body disease, and amygdala predominant Lewy bodies was recorded for each AD case. A modified Kalaria scoring method (Deramecourt 2012) was applied to assess global cerebrovascular disease score based upon retrospective assessment of vessel wall modifications, white matter injury, and presence of microinfarcts and large infarcts in the cortex and basal ganglia. Two nomograms were constructed for the clinical diagnosis of AD dementia and DLB using logistic regression. We abstracted clinical diagnosis made by the neurologist on record of AD dementia or DLB as the predicted variable. Patients who received both an AD dementia and DLB in their clinical differential were examined in both nomograms. The presence of co-existing neurodegenerative pathologies and the cerebrovascular disease score were added as the independent variables.

Results Clinical diagnosis of AD dementia was associated with the absence of Lewy body disease (OR 0.61, $p=0.011$), the presence of HpScl-TDP (OR 4.5, $p=0.004$), and higher cerebrovascular disease score (OR 1.4, $p=0.015$). The presence of amygdala predominant Lewy bodies did not predict a clinical diagnosis of AD dementia (OR 1.21, $p=0.40$). Clinical diagnosis of DLB was associated with the presence of Lewy body disease (OR 3.0, $p<0.001$) and lower cerebrovascular disease score (OR 0.72 $p=0.027$). Neither the presence of amygdala predominant Lewy bodies (OR 0.82, $p=0.46$), or HpScl-TDP (OR 0.76, $p=0.38$) significantly contributed to the clinical diagnosis of DLB. These predictors were applied to develop two nomograms. The AD dementia and DLB nomograms showed good prediction with area under the curve of 0.63 and 0.67, respectively.

Discussion As expected the presence of Lewy body disease, even in the context of neuropathologically-diagnosed AD, significantly predicts a clinical diagnosis of DLB. Given the contribution of HpScl-TDP to an amnesic syndrome, it was not surprising to see its striking contribution to the prediction of AD

dementia. The nomograms illustrate effectively the interesting inverse relationship of cerebrovascular disease with higher scores predicting AD dementia, but lower scores protective against DLB.

Category: Clinical - Oral Presentation

O.7 Differential impact of amyloid, tau-related pathology, and hippocampal atrophy on the clinical phenotype of DLB: a collaboration between Mayo Clinic DLB Consortium and the European DLB Consortium

Author: Daniel Ferreira

Additional Authors: Daniel Ferreira, Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden.

Zuzana Nedelska, Department of Radiology, Mayo Clinic, Rochester, MN, USA; and Memory Clinic, Department of Neurology, Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic.

Carla Abdelnour, Fundació ACE Institut Català de Neurociències Aplicades, Barcelona, Spain.

Ketil Oppedal, Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway; Department of Radiology, Stavanger University Hospital, Stavanger, Norway.

Christopher G. Schwarz, Department of Health Sciences, Mayo Clinic, Rochester, MN, USA.

Jonathan Graff-Radford, Department of Neurology, Mayo Clinic, Rochester, MN, USA.

Matthew L. Senjem, Department of Radiology, Mayo Clinic, Rochester, MN, USA.

Julie A. Fields, Department of Psychiatry and Psychology, Mayo Clinic Rochester, MN, USA.

David S. Knopman, Department of Neurology, Mayo Clinic, Rochester, MN, USA.

Rodolfo Savica, Department of Neurology, Mayo Clinic, Rochester, MN, USA.

David T. Jones, Department of Neurology, Mayo Clinic, Rochester, MN, USA..

Jakub Hort, Memory Clinic, Department of Neurology, Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic; International Clinical Research Center, St. Anne's University Hospital Brno, Brno, Czech Republic.

Frederic Blanc, Day Hospital of Geriatrics, Memory Resource and Research Centre (CM2R) of Strasbourg, Department of Geriatrics, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; University of Strasbourg and French National Centre for Scientific Research (CNRS), ICube Laboratory and Fédération de Médecine Translationnelle de Strasbourg (FMTS), Team Imagerie Multimodale Intégrative en Santé (IMIS)/ICONE, Strasbourg, France.

Tanis F. Ferman, Department of Psychiatry and Psychology, Mayo Clinic, Jacksonville, FL, USA.

Neill Graff-Radford, Department of Neurology, Mayo Clinic, Jacksonville, FL, USA.

Val J. Lowe, Department of Radiology, Mayo Clinic, Rochester, MN, USA.

Clifford R. Jack Jr., Department of Radiology, Mayo Clinic, Rochester, MN, USA.

Ronald C. Petersen, Department of Neurology, Mayo Clinic, Rochester, MN, USA.

Eric Westman, Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden.

Bradley F. Boeve, Department of Neurology, Mayo Clinic, Rochester, MN, USA.

Dag Aarsland, Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway;

Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; and Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway; Department of Radiology, Stavanger University Hospital, Stavanger, Norway.

Kejal Kantarci, Department of Radiology, Mayo Clinic, Rochester, MN, USA.

Introduction: Despite the clinical differentiation between probable dementia with Lewy bodies (DLB) and Alzheimer's disease dementia (ADem), the comorbidity between the two diseases is high. Amyloid and tau-related pathology, the hallmarks of AD, are commonly found in DLB patients. Furthermore, hippocampal atrophy is frequently observed in typical ADem and in probable DLB patients with overlapping Lewy body and AD pathologies. We investigated the relationships among biomarkers of AD and their contribution to the cognitive impairment and clinical features of DLB in this collaborative study between the Mayo Clinic DLB Consortium and the European DLB Consortium.

Materials and Methods: We included probable DLB patients diagnosed according to the 3rd report of the DLB consortium criteria (n=122) from the Mayo Clinic DLB Consortium (n=69) and European DLB Consortium (n=53) who had structural MRI, amyloid, and tau biomarkers measured. Positivity on amyloid (A+) and tau-related (T+) biomarkers were determined using center-specific cut-offs for CSF amyloid-beta 1-42 and phosphorylated tau in the European DLB consortium cohort, and PiB-PET SUVR >1.23 and a

AV-1451 SUVR ≈ 1.25 in the Mayo Clinic DLB Consortium cohort. Hippocampal volume was estimated with SPM12 using tissue priors and atlases from the Mayo Clinic Adult Lifespan Template (MCALT). The effects of total intracranial volume and site on the hippocampal volume were regressed out.

Results: Mean age was 69.2 (SD = 8.8) years and mean education was 14.3 (3.8) years. 70% of the patients were males and 42% were APOE $\epsilon 4$ carriers. Parkinsonism was the most common clinical feature (93%), followed by cognitive fluctuations (88%) and visual hallucinations (60%). The frequency of probable REM sleep behavior disorder (RBD) was 75%. Among the probable DLB patients, 48% were A-T-, 22% were A-T+, 15% were A+T-, and 15% were A+T+. The A-T- group had the lowest proportion of males (47%) and APOE $\epsilon 4$ carriers (15%), and had the highest MMSE scores. The A+T+ group was oldest in age, with a low proportion of males (55%), and lower MMSE scores. A+ in probable DLB patients was significantly associated with older age, lower MMSE, and the presence of visual hallucinations. T+ was associated with older age and lower MMSE. Lower hippocampal volume was associated with older age, lower MMSE, and the absence of cognitive fluctuations. Correcting for age did not change these results. Furthermore, the age correction revealed that patients with probable RBD had a lower frequency of T+ and more preserved hippocampal volume. APOE $\epsilon 4$ had no significant effect on MMSE or the clinical features.

Discussion: Our data from multiple sites across Europe and US suggest that amyloid pathology is associated with the Lewy body pathology-related pathway, contributing to both global cognitive impairment and clinical features of probable DLB such as visual hallucinations. In contrast, tau-related pathology and hippocampal atrophy also contribute to the cognitive impairment, but both are related to a lower frequency of DLB features such as fluctuations and probable RBD, which suggest a relative independence from Lewy body-related pathology.

Category: Clinical - Oral Presentation

O.8 *Gait impairment distinguishes Lewy body disease from Alzheimer's disease and normal ageing*

Author: Riona Mc Ardle

Additional Authors: Brook Galna, Alan Thomas, Lynn Rochester - Institute of Neuroscience, Newcastle University

Background: Distinguishing Alzheimer's disease (AD) and Lewy body disease (LBD) can be difficult due to similarities in clinical presentation and underlying pathology. Diagnostic accuracy is important for effective treatment and disease management. As discrete gait impairments are closely associated with cognitive impairments, gait analysis may be a potential clinical tool to aid differential diagnosis early in the diagnostic process. Gait impairment may reflect underlying neurodegeneration; therefore, AD and LBD may have unique signatures of gait impairment. This study aims to assess the potential for gait analysis to distinguish AD and LBD from each other and from normal ageing.

Methods: 110 participants were recruited across three groups; 36 AD ((mean±sd) Age: 77±6; sMMSE: 23±4), 45 LBD (Age: 77±6; sMMSE: 24±4) and 29 controls (Age:74±9; MMSE: 29±1). Dementia disease subtypes ranged in severity from mild cognitive impairment to moderate dementia and were diagnosed using appropriate criteria and consensus diagnosis from two clinicians. Gait was assessed using an instrumented walkway (GAITRite). A battery of cognitive tests were employed. One-way ANCOVA controlling for age, sex and height were used to identify group differences ($p \leq .01$) and backwards multivariate regression explored which cognitive variables explained discrete gait impairments across disease subtypes. Overall accuracy for each gait characteristics, which distinguished LBD from AD was assessed using area under the curve (AUC).

Results: Both disease groups walked slower, with shorter steps and greater variability (swing, step and stance time, step length; $p \leq .01$ for all) compared to controls. Participants with LBD also had greater step velocity variability, wider steps, longer step time with greater asymmetry for step and swing time compared to controls ($p \leq .01$ for all). In LBD, executive function (measured by FAS test) explained 11% of the variance for characteristics of variability, while in AD, global cognitive impairment (measured by sMMSE) explained 14% of the variance of characteristics of gait variability. The LBD group could be distinguished from AD with greater step time and length variability, and greater step and stance time asymmetry ($p \leq .01$ for all) with strong effect sizes ($\eta^2 > .12$) and modest accuracy (AUC > .62). Backward binary regression revealed the combination of step length variability and step time asymmetry could more accurately distinguish the groups ($p \leq .001$; $\eta^2 = .198$, AUC = .739).

Discussion: Results provide evidence that gait analysis can distinguish AD and LBD from each other and from normal ageing. Distinguishable gait characteristics demonstrated large effect sizes and modest accuracy. Gait variability is partially explained by global cognition and executive function, both mediated by the prefrontal cortex. This area of the brain is affected early in LBD and later in AD; therefore gait impairment in LBD may support prefrontal involvement in gait. Greater gait asymmetry in LBD may be due to the unilateral onset of the disease, reflecting an asymmetrical neurodegeneration. No imaging or biomarkers were taken as part of this study – therefore certainty in clinical diagnosis is limited. Future research should investigate a large disease cohort and investigate if a combination of gait characteristics and other biomarkers improves accuracy.

Category: Clinical - Oral Presentation

0.9 Clinical and imaging characteristics associated with color vision impairment in Dementia with Lewy Bodies and prodromal Lewy body disease

Author: Robert Unger

Additional Authors: Robert H. Unger, BS1,2, Patrick M. Flanigan, MD3, Mitra Khosravi, MD4, James B. Leverenz, MD2, Babak Tousi, MD2

1 Cleveland Clinic Lerner College of Medicine
9500 Euclid Ave, Cleveland, OH 44195, USA

2 Lou Ruvo Center for Brain Health, Cleveland Clinic
9500 Euclid Ave, Cleveland, OH 44195, USA

3 Department of Neurosurgery, UCLA David Geffen School of Medicine
10833 Le Conte Ave, Los Angeles, CA 90095, USA

4 Department of Cardiovascular Surgery, Mayo Clinic
200 1st St SW, Rochester, MN 55905, USA

Introduction: Color vision impairment (CVI) is prevalent among patients with dementia with Lewy bodies (DLB) and may differentiate DLB from Alzheimer's dementia (AD). In order to better characterize the diagnostic value of CVI testing, we examined clinical and imaging characteristics associated with CVI in patients with AD, DLB, and suspected prodromal Lewy body disease (pro-LBD).

Methods: We retrospectively reviewed medical records and volumetric MRI results from patients with AD, DLB, and suspected pro-LBD who underwent an online Farnsworth D-15 color arrangement test. Chi-square or Fisher's exact test were used for categorical variable comparison, and Wilcoxon rank-sum test or Student's t-test were used for continuous variable comparison.

Results: 111 patients (62 DLB, 25 pro-LBD, and 24 AD) were included with a median age of 75 years. Four patients (2 DLB, 2 AD, all male) were identified as having a remote history of CVI from a young age and were excluded from the final analysis. Among 107 remaining patients, patients with DLB were significantly more likely to demonstrate CVI compared to patients with AD (67% vs 18%, RR: 5.21 [95% CI: 1.93-14.1], $p < 0.001$). CVI was present in 44% of patients with pro-LBD compared to 67% of patients with DLB ($p = 0.05$). Among patients with DLB, those with CVI had lower total MoCA scores (median 15.0 vs 18.5, $p = 0.04$) and lower MoCA sub-scores in visuospatial and executive function (median 1.5 vs 2.0, $p = 0.05$), naming (median 2.0 vs 3.0, $p = 0.01$), and language (median 1.0 vs 2.0, $p = 0.003$). Seventeen patients with DLB had volumetric MRI scans available, 9 of whom had CVI. Compared to patients without CVI, patients with DLB and CVI demonstrated significantly lower volumetric percentiles in the right transverse superior temporal lobe (median percentile: 6 vs 39, $p = 0.02$).

Conclusions: We provide further evidence that CVI can help differentiate DLB from AD, and we suggest that CVI may be an indicator of disease progression in Lewy body disease as indicated by lower MoCA scores in patients with CVI and a higher prevalence of CVI in DLB compared to pro-LBD. We also entertain the hypothesis neuroanatomical changes may in part underlie CVI in DLB.

Category: Clinical - Oral Presentation

O.10 Impaired colour discrimination is associated with hallucinations in Dementia with Lewy Bodies

Author: Elie Matar

Additional Authors: Elie Matar 1 , Joseph R Phillips 2 , Kaylena A Ehgoetz Martens 1 , Glenda M Halliday 1 , Simon JG Lewis 1

Brain and Mind Centre, University of Sydney, Camperdown, NSW, Australia

MARCS Institute for Brain, Behaviour and Development, Western Sydney University, Sydney, New South Wales, Australia

Introduction: There is emerging evidence indicating that color discrimination impairments can predict the development of Lewy body dementia across a range of prodromal conditions. Despite its assumed role as a marker of dementia, color vision deficits are not seen uniformly in patients with Dementia with Lewy Bodies (DLB), suggesting a more nuanced association. Visual hallucinations (VH) represent a discriminating feature of DLB, and recent evidence implicates visual pathway dysfunction as a significant contributor to this phenomenon. We therefore hypothesized that color impairment will correlate more specifically with VH in DLB rather than overall measures of cognition.

Methods: In this study, we examined the relationship between color vision impairment and VH, along with other clinical and neuropsychological features in 24 patients with early probable DLB alongside 25 age-matched controls. Color discrimination was assessed using the Farnsworth-Munsell-100 Hue (FM-100) test.

Results: Color discrimination impairment was seen in 16/24 DLB participants (67%) with a higher error score relative to controls ($p=0.001$). We demonstrate a strong specific association between color discrimination errors and both the presence and severity of VH in DLB based on clinician-derived ($p=0.008$) and questionnaire-derived ($p=0.03$) measures. Correlation with clinical and neuropsychological variables revealed that color discrimination is significantly related to visuospatial impairment ($p=0.02$) but not to global measures of cognition, motor severity, age or disease duration. Factor analysis confirmed a unique relationship between color discrimination, visual hallucinations and visuospatial function.

Conclusion: Our results suggest that color discrimination does not simply relate to dementia but rather is a biomarker of visual hallucinations and associated visuoperceptual deficits in Lewy body disorders thus indicating a common pathophysiological substrate.

Category: Clinical - Oral Presentation

O.11 Neuropsychiatric and motor symptoms in prodromal dementia with Lewy bodies

Author: Matthew Barrett

Additional Authors: Kathryn A. Wyman-Chick, Psy.D1, 2

Daniel Weintraub, MD 3, 4

Lauren O. Erickson, M.S. 1, 2

Michael H. Rosenbloom, M.D. 1, 2

Phillip K. Martin, Ph.D.5

Terry R. Barclay, Ph.D. 1, 2

Matthew J. Barrett, M.D., MSc6

HealthPartners Center for Memory and Aging, St Paul, MN

HealthPartners Institute, Bloomington, MN

Departments of Psychiatry and Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC), Department of Veterans Affairs, Philadelphia VA Medical Center, Philadelphia, PA.

University of Kansas School of Medicine-Wichita, Wichita, KS

University of Virginia School of Medicine, Charlottesville, VA

BACKGROUND: Characterization of prodromal dementia with Lewy bodies (DLB) patients would inform new clinical guidelines for early disease detection and support recruitment for disease-modifying treatment studies.

METHODS: We analyzed data for 121 healthy participants included in the National Alzheimer's Coordinating Center Uniform Data Set (NACC-UDS) database who entered the study without a diagnosis of dementia and converted to a diagnosis of DLB at a subsequent visit. The NACC database is funded by NIA/NIH Grant U01 AG016976. We examined informant responses on the Neuropsychiatric Inventory Questionnaire (NPI-Q) and data from a structured clinical interview regarding the presence of REM sleep behavior disorder (RBD), visual hallucinations, and cognitive fluctuations across annual visits leading up to DLB diagnosis. Parkinsonian symptoms were assessed through structured clinical interview and clinical exam and were defined as the presence of either rigidity, resting tremor, motor slowing, parkinsonian gait disorder, or postural instability. Cognition was measured using the Mini-Mental State Examination (MMSE; NACC-UDS Versions 1-2) or the Montreal Cognitive Assessment (MoCA; NACC-UDS Version 3).

RESULTS: At the time of DLB diagnosis, participants were, on average, 76.2 (SD± 8.2) years old with 15.9 (SD±3.6) years of education. At the first visit with a DLB diagnosis, median MMSE was 24 (interquartile range: 21, 27; n=97) and median MoCA was 19 (interquartile range: 16, 22; n=13). The most common symptoms endorsed on the NPI-Q included depression/dysphoria (50.4%), "nighttime behaviors" (57.0%), and apathy/indifference (52.1%). Based upon structured clinical interview and motor exam, gait disorder (75.2%), motor slowing (83.5%), and RBD (52.1%) were also common symptoms at the time of DLB diagnosis.

Parkinsonian symptoms were the most common symptoms prior to DLB diagnosis. Motor slowing was present in greater than 50% of participants in each of the 5 years prior to DLB diagnosis. A parkinsonian gait disorder was present in 50% or more of participants in each off the 4 years prior to DLB diagnosis. The most prevalent symptoms in the year prior to diagnosis were nighttime behaviors (53.8%), apathy (44.3%), anxiety (40.6%), depression (39.6%), and irritability (34.9%). Depression, anxiety, and irritability were present in greater than a third of participants in most of the 5 years prior to DLB diagnosis. RBD was present in 41.5% of participants in the year prior to diagnosis (Table 1).

Approximately 30% of the sample met ≥2 core diagnostic criteria for DLB three years prior to diagnosis, 40% met ≥2 criteria two years prior, and 50% of the sample met ≥2 core criteria one year prior to a DLB dementia diagnosis. As expected, >99% of the sample demonstrated at least one core diagnostic criteria at the time of DLB dementia diagnosis.

DISCUSSION: A range of neuropsychiatric and motor symptoms are common prior to a diagnosis of DLB. A significant proportion of individuals with DLB experience parkinsonism several years prior to diagnosis,

which may have implications for diagnosis of prodromal DLB given the “one-year rule.” Future studies will compare this sample to other prodromal neurodegenerative disease states to help inform prodromal diagnostic criteria.

Session 6: Therapeutics

Category: Therapeutics - Oral Presentation

O.12 Clinical drug development for Dementia with Lewy Bodies: Progress and Setbacks

Author: Marwan Sabbagh
Additional Authors: Garam Lee Pharm D,
Jeffrey Cummings MD, ScD
Boris DeCourt PhD,
James Leverenz MD

Clinical drug development for Dementia with Lewy Bodies: Progress and Setbacks

Garam Lee Pharm D1, Jeffrey Cummings MD, ScD1, Boris DeCourt PhD, James Leverenz MD, Marwan N Sabbagh MD1,

Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas NV

Cleveland Clinic Lou Ruvo Center for Brain Health, Cleveland OH

Keep Memory Alive Foundation and NIH COBRE 5P20GM109025

Send reprint requests and correspondences to:
Correspondence: Marwan N. Sabbagh, MD
Cleveland Clinic Lou Ruvo for Brain Health
880 W. Bonneville Rd
Las Vegas, NV 89106
Sabbagm.ccf.org

ABSTRACT

Objective: To summarize and update the status of clinical trials in patients suffering Dementia with Lewy Bodies (DLB).

Background: DLB is the second most common type of dementia after Alzheimer's disease (AD) and affect an estimated one million patients in the US alone. It is associated with many morbidities and high mortality, and it remains an area of unmet need since the majority of drug development for the dementias have been focused on AD in the past decades. Further there are currently no Food and Drug Administration (FDA) or European Medicines Agency (EMA)-approved medications to treat DLB

Methods/ Results : We reviewed all drugs in clinical development for DLB from PUBMED queries ranging between 2010 and 2019. Therapies currently under investigation or previously investigated include cholinesterase inhibitors, 5-HT6 antagonists, inverse 5-HT2A agonists, anti-psychotics, medications targeting sleep, and anti-Parkinson drugs. Careful review of the most recent literature revealed that, surprisingly, the majority of studies on DLB report the empiric treatment of medications via open label paradigms on case series with no objective measures, instead of rigorous clinical trials including randomization and placebo-control groups. The observations reported for cholinesterase inhibitors suggest they are effective for cognitive and neuropsychiatric symptoms; rivastigmine having the widest evidence base. Special care needs to be taken to avoid potentially fatal idiosyncratic reactions to neuroleptic medications; these should be used for short periods only when absolutely necessary and when alternative treatments have failed. Pimavanserin, a selective serotonin 5-HT2A inverse agonist, holds promise as an alternative therapy for synuclein-associated psychosis. Levodopa/carbidopa treatment of Parkinsonism is often limited by DOPA-induced exacerbations of neuropsychiatric and cognitive

symptoms. Autonomic symptoms are under-recognized complications of synucleinopathy. Constipation, urinary symptoms and postural hypotension respond to standard medications. Rapid eye movement sleep behavior disorder is highly specific (98 %) to the synucleinopathies and respond to long acting benzodiazines.

Conclusion: There are not drugs currently approved to specifically treat DLB. Most drugs used by clinicians are from other indications, and are not measured objectively for efficacy; rather the majority is from anecdotal case series. Measuring clinical efficacy in rigorous clinical trials remains a challenge since there are important confounders, such as fluctuations and psychomotor impairments. Future research should include not only novel therapeutic targets specific to DLB, but also new methods to thoroughly assess clinical efficacy.

Category: Therapeutics - Oral Presentation

O.13 Challenges to Improving the Management of Lewy Body dementia (the DIAMOND-Lewy Study)

Author: Claire Bamford

Additional Authors: John O'Brien, Department of Psychiatry, University of Cambridge and Institute of Neurosciences, Newcastle University

John-Paul Taylor, Institute of Neurosciences, Newcastle University

Alan Thomas, Institute of Neurosciences, Newcastle University

Louise Allan, University of Exeter

David Burn, Institute of Neurosciences, Newcastle University

Ian McKeith, Institute of Neurosciences, Newcastle University

Tracy Finch, Northumbria University

Background

Lewy body dementia (LBD) is a complex disease with profound effects on the well-being and quality of life of patients and their families. Management is often fragmented, with different symptoms being managed by different clinicians. The DIAMOND-Lewy programme investigated whether the introduction of an evidence based, standardised management toolkit could improve patient and carer outcomes. Alongside the pilot trial, we conducted a qualitative study to explore the feasibility and acceptability of the toolkit, and identify factors influencing whether and how the toolkit was implemented in practice.

Methods

We used qualitative methods (semi-structured interviews and focus groups) to obtain feedback from clinicians participating in the DIAMOND-Lewy study on the management toolkit and to understand whether and how it was integrated into their routine practice. Interviews and focus groups were audio-recorded, transcribed and checked for analysis. Data were analysed thematically and data collection continued until no new themes or insights were gained.

Results

45 clinicians (seven from movement disorder, and 38 from memory, services) were recruited. Twenty were interviewed and 25 (all from memory services) took part in focus groups. Clinicians found the layout and presentation of the management toolkit appealing and easy to navigate. Clinicians had high confidence in the content of the toolkit, but many reported that it was similar to their existing practice. Even where recommendations differed from their usual practice, clinicians seemed reluctant to change established prescribing habits. While a key benefit of the management toolkit was increasing their awareness of the wide ranging impacts of LBD, there was little evidence that clinicians became confident enough to start treating symptoms outside their immediate area of expertise.

Conclusion

Clinicians highlighted the value of the management toolkit in translating academic knowledge into a practical clinical resource. Data on the implementation of the management toolkit suggests that the main impact was to raise awareness, rather than changing prescribing habits or management strategies. Further exploration of the mechanisms through which the toolkit may have influenced practice is needed. There is considerable evidence that passive methods of disseminating guidelines result in relatively low uptake. Our findings indicate that implementation was varied; more active strategies to support clinicians to adopt and embed changes into their practice could potentially lead to more consistent uptake. Possible strategies to improve implementation suggested by participants include opportunities to discuss new treatments or hold case discussions with colleagues with some expertise in LBD.

Acknowledgements

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Category: Therapeutics - Oral Presentation

O.14 Development of holistic and comprehensive management guidelines for Lewy body dementia (the DIAMOND-Lewy Study)

Author: John-Paul Taylor

Additional Authors: Professor Ian Grant McKeith, FMedSci 1; Professor David Burn FMedSci 1, Professor Brad Boeve, M.D.2; Professor Daniel Weintraub, M.D.3,4,5; Ms Claire Bamford, MsC 6; Professor Louise Allan PhD7; Professor Alan Jeffrey Thomas1; Professor John Tiernan O'Brien FMedSci8 on behalf of the Diamond-Lewy study team.

Institute of Neuroscience, Biomedical Research Building, Campus for Ageing and Vitality,
Newcastle University, Newcastle upon Tyne NE4 5PL, UK

Department of Neurology, Mayo Clinic, Rochester, MN, USA

Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA.

Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA.

Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (PADRECC
and MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

Institute of Health and Society, Biomedical Research Building, Campus for Ageing and Vitality,
Newcastle University, Newcastle upon Tyne NE4 5PL, UK

University of Exeter Medical School, South Cloisters Building, St Luke's Campus, Heavitree
Road, Exeter, Devon EX1 2LU

Department of Psychiatry, University of Cambridge School of Clinical Medicine, Box 189, Level E4
Cambridge Biomedical Campus, Cambridge CB2 0SP, UK.

Background

Dementia with Lewy bodies and Parkinson's disease dementia, jointly known as Lewy body dementia (LBD), are common neurodegenerative conditions. Patients with LBD present with a wide range of symptoms and the expression of these symptoms varies between individual patients, and over time and treatments may benefit one symptom, but at the expense of worsening another, making the management of LBD difficult. Often symptoms are managed in isolation and by different specialists, which undermines high quality care and there is an absence of a holistic approach to management. Therefore our aim was to develop a comprehensive management guideline and toolkits for LBD.

Method

We initially conducted two formal systematic reviews (Stinton et al. 2015; Connors et al. 2017) with the aim of capturing all available, recently published information about the pharmacological and non-pharmacological management of LBD. This was coupled with two public-patient workshops. The first event focused on identifying good practice in LBD clinical management; emergent themes were then developed further in the second event. Using the systematic reviews and public-patient feedback an initial draft of the guidelines was developed by two authors (J-P.T and IGM). Specific statements, framed under symptom domains, were created and submitted to an online anonymized online platform for review by a Delphi expert panel. The Delphi panel comprised experts in the field (n=26; psychology, geriatrics, psychiatry, neurology, primary care, physiotherapy, nursing, and academic experts, as well as internationally recognized key opinion leaders) identified through consultation with relevant stakeholder groups and supported by an extensive search of the literature for their publications, or their role as keynote speakers on management of LBD at major conferences.

Results

The Delphi process was conducted over three rounds. A high level of agreement was sought across the three rounds (85% for rounds 1 and 2 and 75% for round 3). Controversial statements were modified on the basis of feedback and rerun in the subsequent round or removed. Of 252 original statements, 161 were kept, with 78 of these (48.4%) gaining full consensus panel agreement for inclusion, 52 (32.3%) with 90% to 99% consensus agreement, and 31 statements (19.3%) agreed by 75% to 89% of the panel. After this process, the guideline statements were re-collated and formulated into one document.

Conclusions

We developed a comprehensive and holistic guideline for LBD framed around cognitive, neuropsychiatric, motor, autonomic and sleep symptoms. This was complimented by one page toolkits to make the guidelines practically useful and easy to implement in busy clinics.

This guideline and toolkits were subsequently trialled to assess their real world effectiveness; these data are presented in a complementary abstract.

References

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Acknowledgements

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Category: Therapeutics - Oral Presentation

O.15 Building an Australian longitudinal cohort study of dementia with Lewy bodies

Author: Rosie Watson

Additional Authors: Authors: Lesley Vidaurre¹, Kai Sin Chin^{1,2}, Victor Villemagne^{1,3,4}, Christopher Rowe^{1,3,4}, Colin Masters⁵, Nawaf Yassi ^{1,2}, Rosie Watson ^{1,2}

Author Affiliations:

¹The Florey Institute of Neuroscience and Mental Health, Parkville, Australia

²Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Parkville, Australia.

³Department of Molecular Imaging & Therapy, Centre for PET, Austin Health, Heidelberg, Australia.

⁴Department of Medicine, Austin Health, The University of Melbourne, Melbourne, VIC, Australia.

⁵The University of Melbourne, Melbourne, VIC, Australia.

Background:

Dementia with Lewy bodies (DLB) is a common form of dementia, characterised pathologically by the accumulation of neuronal α -synuclein. While there are clear differences between Alzheimer's disease (AD) and DLB from both a clinical and neuropathological perspective, there is also significant overlap. Most cases of dementia in older age demonstrate a mixture of pathological changes; in particular changes associated with AD (deposition amyloid- β and tau), changes associated with DLB (α -synuclein) and cerebrovascular disease. The influence of comorbid pathology, particularly AD (amyloid- β and tau) and cerebrovascular disease (CVD) on clinical outcomes in DLB is unknown. Understanding the interface between AD, CVD and DLB and the influence these comorbidities have on disease progression and outcome is necessary to ensure affected individuals receive appropriate clinical care and to enable the development of effective treatments. Despite this, there are relatively few longitudinal biomarker studies of DLB. We describe a new, Australian-based, longitudinal observational biomarker study of DLB. We aim to determine the influence of amyloid- β , tau and CVD on clinical symptoms and outcome in DLB.

Method:

One-hundred people with mild to moderate probable DLB (age 50+) will be invited to complete comprehensive clinical and cognitive assessments (including MMSE, ACE-III, MoCA, CDR, NPI, GDS), function, health related quality of life (EQ-5D, DEMQOL) and carer burden. Scales targeting DLB-specific clinical features (such as fluctuations and REM-sleep behaviour disorder) will also be collected including the Clinician Assessment of Fluctuation Scale, Mayo Fluctuation Scale, and Mayo Sleep Questionnaire. Biomarker protocols incorporate blood sampling (including ApoE genotyping and systemic inflammatory markers), molecular imaging (amyloid- [18F-NAV 4694], tau [18F-MK6240], VMAT2 [18F-AV133] PET scans), 3T MRI (including high resolution structural imaging, diffusion tensor imaging, and quantitative susceptibility mapping), and CSF collection (for amyloid- β , tau and α -synuclein). Clinical assessments are completed 6 monthly and imaging 18 monthly. Participants are invited to register for brain tissue donation.

Results:

Twelve participants with probable DLB have been recruited to date (mean age 72.4 years, range 64-82, 80% male). All participants have mild to moderate cognitive impairment (mean MMSE 25, range 17-29). Half of the participants are amyloid- β positive. Study procedure tolerability has been excellent with no adverse events reported. Further biomarker and baseline assessment results will be presented.

Conclusion: Determining the influence of multimorbidity is key to the development of effective and disease modifying treatment strategies in DLB. This study supports the feasibility of intensive, longitudinal biomarker studies in dementia with Lewy bodies in the Australian Setting.

O.16 Physical therapy is associated with improvements in gait and balance in individuals with Lewy Body Dementia: A retrospective analysis

Author: Jason Longhurst

Additional Authors: Johnny Rider OTR/L-University of Nevada Las Vegas

Jason Longhurst PT DPT NCS Cleveland Clinic

Aaron Ritter MD Cleveland Clinic

Merrill Landers PT DPT PhD University of Nevada Las Vegas

Introduction: Lewy Body dementia (LBD) is a disorder characterized by cognitive and motor impairments. Together, these impairments significantly increase their fall risk and reduce daily function. Studies have demonstrated that exercise can improve strength, balance, mobility, and endurance in people with cognitive impairment and dementia. Cognitive and psychological measures, such as fear of falling activity avoidance, are rarely included in these studies. Additionally, few studies have examined these effects in individuals with LBD. The purpose of this study was to determine if physical therapy (PT) treatment with an emphasis on dual-task training would improve gait and balance as well as cognitive abilities in individuals with LBD.

Methods: Retrospective data of 35 patients diagnosed with LBD receiving outpatient PT at the Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada, USA, were extracted from electronic records from January 2016 to December 2017. PT treatment consisted of aerobic activity (20-35 minutes), strengthening (15-20 minutes), and balance training (15-20 minutes). Dual-task training was emphasized throughout all three parts. Patients were encouraged to attend PT one time per week for 2 months (average number of completed PT sessions was 6.6 ± 3.5). Additionally, each patient was provided an individualized, daily home exercise program. The following outcome measures were collected at the first and last treatment sessions: fall history, Montreal Cognitive Assessment (MoCA), miniBESTest (MBT), 5 Times Sit-To-Stand (STS), Timed Up and Go (TUG), TUG cognitive, preferred gait speed (PGS), fast gait speed (FGS), 6-Minute Walk Test (6MWT), and the Modified Fear of Falling Avoidance Behavior Questionnaire (mFFABQ). Data were analyzed using paired samples t-tests and Mann-Whitney analyses, with an intent-to-treat model and last observation carried forward imputation for any missing data (5 patients did not complete 2 months of PT).

Results: Individuals with LBD showed improvements on the MBT ($p < .001$), STS ($p < .001$), and had a reduction in the number of injurious falls ($p = .020$). They also improved on the TUG ($p = .009$), TUG Cognitive ($p = .025$), PGS ($p = .006$), FGS ($p = .005$), 6MWT ($p < .001$), and the MoCA ($p = .011$). There were no differences on the mFFABQ ($p = .527$) or number of recent falls ($p = .334$).

Discussion: Results of this retrospective study offer evidence that 2 months of PT may improve gait and balance in individuals with LBD. Improvements were demonstrated in all measures of gait and balance and this was accomplished using a one-time per week frequency. Previous studies have had reported improvements based on treatment frequencies of 3 times per week; however, our results suggest that fewer number of PT sessions may be needed to drive improvements. Our findings demonstrate an improvement in MoCA score which may suggest that the PT and/or exercise may have had a beneficial effect on cognition.

Category: Therapeutics - Oral Presentation

O.17 Neuroimaging in Parkinson's disease dementia: Connecting the dots to shed light on DLB

Author: Rimona Weil

Additional Authors:

Rimona Weil, Dementia Research Centre, UCL, UK

Joey Hsu, Berenson-Allen Center, Beth Israel Deaconess Medical Center, Harvard Medical Center, Boston

Louis Soussand, Berenson-Allen Center, Beth Israel Deaconess Medical Center, Harvard Medical Center, Boston

Ryan Darby, Department of Neurology, Vanderbilt University Medical Center, Nashville

Michael Fox, Berenson-Allen Center, Beth Israel Deaconess Medical Center, Harvard Medical Center, Boston

Neuroimaging in Parkinson's disease dementia: Connecting the dots to shed light on DLB

Weil RS1,2,3, Hsu J3, Darby R3,4,5, Soussand L3, Fox MD3,5,6

Dementia Research Centre, UCL

Wellcome Trust Centre for Neuroimaging, UCL

Berenson-Allen Center, Beth Israel Deaconess Medical Center, Harvard Medical Center, Boston

Department of Neurology, Vanderbilt University Medical Center, Nashville

Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston

Martinos Center for Biomedical Imaging, Harvard Medical School, Charlestown

Background

Dementia with Lewy Bodies (DLB) and Parkinson's disease dementia (PDD) are highly similar and are widely considered to be either end of a spectrum of one disease. They share common clinical presentations and underlying neuropathological features but the anatomical substrates of both DLB and PDD remain unclear. Uncovering the neural correlates of PDD and its earliest stages, Parkinson's disease with mild cognitive impairment (PD-MCI), will provide important insights into the earliest stages of DLB that are not easily accessed. Neuroimaging abnormalities have been reported throughout the brain in PDD and are largely inconsistent across studies. Here we test whether the heterogeneous neuroimaging findings for PDD localise to a specific brain network by using a new approach: coordinate-based network mapping.

Methods

Using a literature search, we identified studies reporting neuroimaging correlates of PDD (n=11). We restricted our search to studies of brain atrophy and hypometabolism that compared Parkinson's patients with dementia to those without cognitive involvement. We used a standard coordinate-based ALE meta-analysis to assess for consistency in neuroimaging findings. We then used coordinate-based network mapping to test whether neuroimaging findings localized to a common brain network. This approach uses resting state functional connectivity from a large cohort of normative subjects (n=1000) to identify the network of regions connected to a reported neuroimaging coordinate.

Results

The standard ALE meta-analysis failed to identify any brain regions consistently associated with PDD, showing major heterogeneity across studies. In contrast, our new approach, coordinate-based network mapping found that these heterogeneous neuroimaging findings localized to a specific brain network centred on the hippocampus (Fig. 1). Next we tested whether this network showed symptom specificity and stage specificity by performing two further analyses. We tested symptom specificity by examining studies of Parkinson's hallucinations (n=9) that are frequently comorbid with PDD and DLB. We tested for stage specificity by using studies of PD-MCI (n=15). Coordinate-based network mapping revealed that correlates of visual hallucinations fell within a network centred on bilateral lateral geniculate nucleus and

correlates of the earlier stages of PDD, PD-MCI, fell within a network centred on the posterior default mode network. In both cases, the identified networks were distinct from the hippocampal network of PDD.

Conclusion

Our results link heterogeneous neuroimaging findings in PDD to a common network centred on the hippocampus. This points to a central role for the hippocampi in established Parkinson's dementia. In contrast, our finding that posterior brain networks are involved in PD-MCI sheds light onto the earlier stages of DLB, with the potential for earlier detection and for testable hypotheses regarding therapeutic targets.

Session 7: Imaging

Category: Imaging - Oral Presentation

O.18 Cholinergic networks in dementia with Lewy bodies

Author: John-Paul Taylor

Additional Authors: Sean J. Colloby Ph.D1, Pradeep J. Nathan Ph.D2,3,, Ian G. McKeith MD1, John T. O'Brien DM3

1Institute of Neuroscience, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne. NE4 5PL. UK.

2Sosei Heptares, Steinmetz Building, Granta Park, Cambridge. CB21 6DG. UK.

3Department of Psychiatry, University of Cambridge, Level E4, Box 189, Cambridge. CB2 0QC. UK.

Background: Dementia with Lewy bodies (DLB) is characterised by fluctuating cognition, recurrent visual hallucinations, REM sleep behaviour disorder and Parkinsonism.¹ Marked cholinergic dysfunction including reduced choline acetyltransferase are key neurochemical features in DLB,²⁻⁴ and contribute to the cognitive and psychiatric disturbances.⁵ Clinically, cholinesterase inhibitors (ChEIs) have been shown to improve cognition and activities of daily living but for behavioural symptoms this is less clear⁶ although M1/M4 agonists such as Xenomeline may have benefits in Alzheimer's disease.⁷ The aim was to investigate muscarinic M1/M4 cholinergic networks in DLB and their association with changes in cognition and neuropsychiatric symptoms after 12 weeks of treatment with the cholinesterase inhibitor (ChEI) donepezil.

Methods: Thirty eight participants (14 DLB and 24 elderly controls) underwent 123I-QNB and 99mTc-exametazime SPECT scanning. We implemented voxel principal components (PC) analysis, producing a series of PC images of patterns of intercorrelated voxels across individuals. Linear regression analyses derived specific M1/M4 and perfusion spatial covariance patterns associated with DLB.

Results: We found that in ChEI naive DLB patients, a discrete M1/M4 pattern of relative decreased binding in right lateral temporal and insula, and relative preserved/increased binding in frontal, precuneus, lingual and cuneal regions that differed from controls implicating nodes of attention and dorsal visual networks. The rCBF pattern that emerged in these patients was distinct from the M1/M4 pattern, revealing deficits to the default mode network DMN. The M1/M4 pattern that correlated with change in MMSE showed relative preserved/increased uptake in prefrontal, temporal pole and anterior cingulate, regions converging on attention related networks. The M1/M4 pattern that correlated with change in neuropsychiatric symptom severity displayed relative preserved/increased uptake in inferior temporal lobes, areas within the ventral visual stream.

Conclusions: Cholinergic attention and dorsal visual networks were altered in DLB. We posit that established cholinergic maintenance of 'attentional' and ventral 'visual' networks through M1/M4 receptor modulation could be pre-requisite for cognitive and neuropsychiatric remediation, respectively, following cholinergic treatment in this condition.

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Category: Imaging - Oral Presentation

O.19 Parietal white matter hyperintensities in dementia with Lewy bodies are associated with cortical tau pathology indicating a shared mechanism with Alzheimer's disease

Author: Kirsty McAleese

Additional Authors: Dr Lauren Walker, Institute of Neuroscience, Newcastle University, UK

Dr Michael Firbank, Institute of Neuroscience, Newcastle University, UK

Professor John O'Brien, Department of Psychiatry, University of Cambridge, UK

Professor Alan Thomas, Institute of Neuroscience, Newcastle University, UK

Professor Johannes Attems, Institute of Neuroscience, Newcastle University, UK

Background: White matter hyperintensities (WMH), as seen on T2-weighted MRI scans, represent demyelination and white matter axonal loss and are often assumed to be associated with ischemia-associated damage as a result of small vessel disease (SVD). However, our previous neuropathological studies have confirmed that parietal WMH as seen in Alzheimer's disease (AD) can also be associated with degenerative axonal loss (via Wallerian degeneration) secondary to the deposition of intracellular hyperphosphorylated tau (HPT) in the overlying cortex.

Up to 55% of dementia with Lewy bodies (DLB) cases neuropathologically exhibit considerable HPT pathology (up to Braak NFT stage IV) and 28% of clinically diagnosed DLB also fulfill the neuropathological criteria for AD and are classified as mixed AD/DLB. With 85% of DLB exhibiting some form of WMH, it is unknown whether the development of WMH are associated with HPT pathology. Recent data from neuroimaging has indicated WMH in DLB may reflect AD pathology (as indicated by hippocampal atrophy) rather than cerebrovascular changes (Joki 2018) and DTI imaging has revealed microstructural changes to WM tracts in DLB that mirror those studied in AD, which have been associated with the development of HPT pathology. We aimed to determine if regional WMH were associated with the presence of SVD, HPT, A β or α -syn pathology.

Methods: The cohort was inclusive of human donated brains clinicopathologically diagnosed as DLB, n=18; mixed AD/DLB, n=16; and non-demented controls, n= 37. Prior to dissection, fixed right hemispheres were subject to a T2-weighted 4.7 scan and images assessed for WMH severity in the frontal, parieto-occipital and temporal deep WM according to the Age Related White Matter Lesion (ARWML) scale. HPT, A β and α -syn pathologic burden was quantitatively assessed in frontal, parietal, temporal, occipital and entorhinal cortices. SVD severity was semi-quantitatively assessed in the frontal, parietal, temporal and occipital deep WM. Statistical analysis was controlled for the effects of age.

Results: Frontal WMH were more severe in DLB compared to controls ($P<0.026$), but no significant difference was seen between DLB with mixed AD/DLB in any region. In the DLBs, parietal WMH were associated with parietal HPT burden (ρ 0.458, p =0.024) and parietal WMH in the mixed AD/DLB group were associated with entorhinal HPT burden (ρ 0.532, p =0.017). Only in non-demented controls was SVD associated with frontal WMH (ρ 0.448, p =0.004).

Conclusions: This study indicates that the development WMH seen in the parietal lobe of DLB and mixed AD/DLB maybe associated with the development of HPT pathology. This data is in agreement with previous studies in AD indicating WM associated with cortical areas affected early in HPT pathology development maybe affected by degenerative mechanism of axonal loss. This is in contrast to frontal WM that is not affected in the early stages of HPT development and WMH are associated with SVD. This indicates a potential shared aetiology of posterior WMH between DLB and AD, which is indicative of the presence of HPT pathology, and regional difference in WMH pathogenesis that maybe beneficial for the clinical diagnosis of patients.

O.20 The trajectory of longitudinal amyloid-beta accumulation on PiB PET and association with clinical disease progression in dementia with Lewy bodies

Author: Zuzana Nedelska

Additional Authors: Christopher G. Schwarz, PhD, Timothy G. Lesnick, MS, Scott A. Przybelski, BS, Bradley F. Boeve, MD, Val J. Lowe, MD, Walter K. Kremers, PhD, Jeffrey L. Gunter, PhD, Matthew L. Senjem, MS, Jonathan Graff-Radford, MD, Tanis J. Ferman, PhD, David S. Knopman, MD, Ronald C. Petersen, MD, PhD, Clifford R. Jack Jr., MD, Kejal Kantarci, MD, MS

Background: Patients with probable dementia with Lewy bodies (DLB) often have overlapping Alzheimer's disease (AD) pathology; approximately two thirds of DLB patients have elevated amyloid- β on PET in addition to Lewy body disease. Among normal to clinical AD dementia subjects, it has been shown that the rate of amyloid- β accumulation vs baseline standardized value uptake ratio (SUVR) follows an inverted U-shaped form; but, the nature of this relationship is unknown in DLB. Moreover, overlapping AD pathology in DLB patients has been associated with a more rapid clinical progression and shorter survival in cross-sectional studies including autopsy-confirmed observations. Therefore, understanding the influence of amyloid- β accumulation on clinical disease progression in DLB is critical for prognosis and targeting underlying neurodegenerative pathologies. In this prospective study, our objective was to determine the rate of longitudinal PiB SUVR vs baseline SUVR in DLB patients compared to cognitively unimpaired adults, and to investigate the association between amyloid- β accumulation and measures of clinical disease progression over time in DLB.

Methods: We included n=35 consecutive patients with probable DLB and n=140 age-, sex-, and APOE ϵ 4 status-matched cognitively unimpaired (CU) participants. All underwent baseline and at least one follow-up clinical evaluation and PiB PET. The trajectories of longitudinal amyloid- β accumulation for DLB and for CU were constructed from serial partial volume corrected SUVR. Rates of change in PiB SUVR by baseline PiB SUVR were compared between participant groups using generalized additive models. In DLB patients, we assessed the associations of baseline PiB SUVR and rate of change in PiB SUVR with rate of change in several clinical and cognitive measures.

Results: We demonstrated that the rates of change in PiB SUVR as a function of baseline PiB SUVR were non-linear in both participant groups; an initial acceleration at lower baseline PiB SUVR was followed by a peak and then by deceleration at higher baseline PiB SUVR, forming an inverted U-shaped curve. Rates of change in PiB SUVR did not differ between DLB patients and CU participants (p=0.59). The integral relationship of cumulative PiB SUVR as a function of time in years followed a sigmoid-shaped functional form in both participant groups. Both higher baseline PiB SUVR and increased rate of change in PiB SUVR were associated with worsening in clinical dementia rating sum of boxes (p-values <0.05) and Auditory Verbal Learning Test-delayed recall (p-values < 0.05).

Conclusion: Rate of change in PiB SUVR increases, plateaus, and then decreases in DLB, which is consistent with the trajectory observed in normal aging to AD dementia continuum. Increasing PiB SUVR is associated with clinical and cognitive decline over time in DLB. Rate of change PiB SUVR and baseline PiB SUVR may be considered in designing clinical trials targeting amyloid- β pathology in probable DLB.

Category: Imaging - Oral Presentation

0.21 DIFFERENTIAL ATROPHY OF THALAMIC SUBNUCLEI IN DEMENTIA WITH LEWY BODIES AND ALZHEIMER'S DISEASE

Author: Elijah Mak

Additional Authors: Elijah Mak, Audrey Low, Maura Malpetti, Leonidas Chouliaras, Nicolas Nicastro, Li Su, Negin Holland, Timothy Rittman, Patricia Vasquez-Rodriguez, Luca Passamonti, Richard Bevan-Jones, Simon Jones, James B Rowe, John O'Brien, University of Cambridge, United Kingdom, UK

INTRODUCTION

The thalamus has received relatively little attention in the imaging literature of dementia, despite its involvement in extensive cortical networks. Previous investigations have mainly examined the total structure. However, there is evidence that disease-related effects are not uniform throughout the thalamus. Using a novel probabilistic technique, we compared the morphology of thalamic subnuclei in dementia with Lewy bodies (DLB), Alzheimer's disease (AD) and healthy controls (HC), and studied the clinical relevance of thalamic subnuclei changes in people with DLB.

METHODS

Thalamic subnuclei were segmented using FreeSurfer in groups of DLB (n=26), AD (n=19), and HC (n=33) (Fig. 1). ANCOVA, adjusting for age, gender and intracranial volumes, was used to determine main effects of diagnosis on thalamic subnuclei. Receiver operating characteristic (ROC) analyses were performed to compare the discriminatory performance of thalamic subnuclei against that of whole thalamic volumes in terms of distinguishing HC from DLB and AD.

RESULTS

There was no main effect of diagnosis on total thalamus ($p=0.073$). However, the lateral thalamus was significantly smaller in DLB relative to HC ($p=0.027$) (Fig. 2 and Fig. 3). Relative to HC, the AD group showed more widespread atrophy encompassing the lateral ($p=0.012$), anterior ($p=0.007$), medial ($p=0.032$) and posterior thalamus ($p=0.005$). None of the thalamic subnuclei were significantly different between DLB and AD. ROC analysis revealed that the lateral thalamus (AUC = 67.1%, $p=.025$), but not the total thalamus (AUC = 56.4%, $p=.401$), was able to discriminate between HC and DLB. Similarly, the posterior thalamic subnuclei (AUC = 78.9%) was more effective than the total thalamic volume (AUC = 70.2%) at discriminating between HC and AD (Fig. 4).

DISCUSSION

Thalamic nuclei volumes were superior to the total thalamic volume at discriminating DLB from HC. The preferential vulnerability of the lateral thalamic nuclei in DLB is consistent with its rich inputs from the visual cortex and involvement in visuospatial function, one of the predominant cognitive deficits in DLB. These preliminary findings provide a better understanding of the contributions of the lateral nuclei to disease progression in DLB.

Category: Imaging - Oral Presentation

0.22 POSITIVE RELATIONSHIP BETWEEN MICROGLIAL ACTIVATION AND MICROSTRUCTURAL PRESERVATION IN DEMENTIA WITH LEWY BODIES

Author: Nicolas Nicastro

Additional Authors: Nicolas NICASTRO*1, Elijah MAK*1, Guy B. WILLIAMS2, Ajenthan SURENDRANATHAN1, William Richard BEVAN-JONES3, Luca PASSAMONTI3, Patricia VASQUEZ RODRIGUEZ3, Li SU1,4, Robert ARNOLD3, Franklin I. AIGBIRHIO2, James B. ROWE3,5+, John T. O'BRIEN1+.

1 Department of Psychiatry, University of Cambridge, UK.

2 Wolfson Brain Imaging Centre, University of Cambridge, UK.

3 Department of Clinical Neurosciences, University of Cambridge, UK.

4 China-UK Centre for Cognition and Ageing Research, Southwest University, Chongqing, China.

5 Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK.

* These authors contributed equally to the manuscript.

+ Co-Senior Authors

Our objective was to examine the relationship between central inflammation as measured with [11C]-PK11195 PET and diffusion tensor imaging (DTI) in dementia with Lewy bodies (DLB). In addition to 20 similarly-aged healthy controls, 18 clinically probable DLB underwent structural MRI with T1-weighted, 3T DTI sequences and [11C]-PK11195 PET imaging. Tract-Based Spatial Statistics (TBSS) were performed to compare DTI parameters for DLB against healthy controls and identify associations of [11C]-PK11195 binding with white matter damage. TBSS confirmed widespread changes for DLB regarding all DTI parameters (fractional anisotropy (FA), mean (MD) and radial (RD) diffusivity) in the body and splenium of corpus callosum (Threshold Free Cluster Enhancement (TFCE) corrected $p < 0.05$). In addition, we observed reduced FA and increased RD in right corona radiata, left cingulate gyrus, and right superior longitudinal fasciculus. Secondly, we performed correlations of global and lobar cortical [11C]-PK11195 binding with DTI changes, using the following covariates: age, gender, Addenbrookes Cognitive Evaluation revised (ACE-R) score, as well as time interval in months between DTI and PET. We observed that higher parietal [11C]-PK11195 binding was significantly associated with widespread increase of MD and RD in the corpus callosum, bilateral internal capsule and corona radiata, bilateral posterior thalamic radiations, external capsule and cingulate gyrus, superior longitudinal fasciculus and superior frontooccipital fasciculus (TFCE $p < 0.05$). These findings demonstrate that higher microglial activation is associated with a relative preservation of white matter, positioning central inflammation as a potential early phenomenon in DLB disease cascade.

Category: Imaging - Oral Presentation

O.23 Accuracy of the 123I-MIBG myocardial scintigraphy for the diagnosis of DLB : a multi-center three-year follow-up study

Author: Junji Komatsu

Additional Authors: Authors: Junji Komatsu, MD 1), Miharuru Samuraki, MD 1), Kenichi Nakajima, MD 2), Heii Arai, MD 3), Hiroyuki Arai, MD 4), Tetsuaki Arai, MD 5), Takashi Asada, MD 5), Hiroshige Fujishiro, MD 6), Haruo Hanyu, MD 7), Osamu Iizuka, MD 8), Eizo Iseki, MD 6), Kenichi Kashiwara, MD 9), Kenji Kosaka, MD 10), Hirotaka Maruno, MD 11), Katsuyoshi Mizukami, MD 12), Yoshikuni Mizuno, MD 13), Etsuro Mori, MD 8), Hiroyuki Nakamura, MD 14), Seigo Nakano, MD 15), Kenji Nakashima, MD 16), Yoshiyuki Nishio, MD 8), Satoshi Orimo, MD 17), Akira Takahashi, MD 18), Junichi Taki, MD 2), Takahiko Tokuda, MD 19), Katsuya Urakami, MD 20), Kumiko Utsumi, MD 21), Kenji Wada, MD 16), Yukihiro Washimi, MD 22), Shouhei Yamashina, MD 23), Junichi Yamasaki, MD 23), Mitsuhiro Yoshita, MD 1)24), *Masahito Yamada, MD 1).

(Authors are listed in alphabetical order except for the first, second, third and last.)

1 Department of Neurology and Neurobiology of Aging, Kanazawa University Graduate School of Medical Science, Kanazawa, Ishikawa 920-8640, Japan

2 Department of Nuclear Medicine, Kanazawa University Hospital, Kanazawa, Ishikawa 920-8640, Japan

3 Department of Psychiatry, Juntendo University School of Medicine, Bunkyo, Tokyo 113-8431, Japan

4 Institute of Development, Aging and Cancer, Tohoku University, Sendai, Miyagi 980-8575, Japan

5 Department of Neuropsychiatry, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaragi 305-8576, Japan

6 PET/CT Dementia Research Center, Juntendo Tokyo Koto Geriatric Medical Center, Juntendo University School of Medicine, Koto, Tokyo 136-0075, Japan

7 Department of Geriatric Medicine, Tokyo Medical University, Shinjuku, Tokyo 160-0023, Japan

8 Department of Behavioral Neurology and Cognitive Neuroscience, Tohoku University Graduate School of Medicine, Sendai, Miyagi 980-8575, Japan

9 Department of Neurology, Okayama Kyokuto Hospital, Okayama, Okayama 703-8265, Japan

10 Medical Care Court Clinic, Yokohama, Kanagawa 225-0014, Japan

11 Department of Radiology, Toranomon Hospital, Minato, Tokyo 105-8470, Japan

12 Graduate School of Comprehensive Human Sciences, Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Ibaragi 305-8576, Japan

13 Department of Neurology, Juntendo University School of Medicine, Bunkyo, Tokyo 113-8421, Japan

14 Department of Environmental and Preventive Medicine, Graduate School of Medical Science, Kanazawa University, Kanazawa, Ishikawa 920-8640, Japan

15 Center for Treatment, Care and Research of Dementia, Medical Co. LTA, Sumida, Tokyo 130-0004, Japan

16 Division of Neurology, Department of Brain and Neurosciences, Faculty of Medicine, Tottori University, Yonago, Tottori 683-8504, Japan

17 Department of Neurology Kanto Central Hospital of the Mutual Aid Association of Public School Teachers, Setagaya, Tokyo 158-8531, Japan

18 Tokai Central Hospital, Kakamigahara, Gifu 504-0816, Japan

19 Department of Molecular Pathobiology of Brain Diseases, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Kyoto 602-0841, Japan

20 Department of Biological Regulation, School of Health Science, Faculty of Medicine, Tottori University, Yonago, Tottori 683-8503, Japan

21 Department of Neuropsychiatry, Sunagawa City Medical Center, Sunagawa, Hokkaido 073-0196, Japan

22 Department for Cognitive Disorders, Hospital of National Center for Geriatrics and Gerontology, Obu, Aichi 474-8511, Japan

23 Division of Cardiovascular Medicine, Department of Internal Medicine, Ohmori Hospital, Toho University School of Medicine, Ota, Tokyo 143-8541, Japan

24 Department of Neurology, Hokuriku National Hospital, Nanto, Toyama 939-1893, Japan

Background and Purpose:

We previously reported that iodine-123-meta-iodobenzylguanidine (123I-MIBG) myocardial scintigraphy was useful for differentiation of dementia with Lewy bodies (DLB) from Alzheimer's disease (AD) in a cross-sectional multicenter study. The aim of this study was, through using reassessed diagnosis after three-year follow-up, to evaluate the diagnostic accuracy of 123I-MIBG scintigraphy in differentiation of probable DLB from probable AD.

Methods:

We conducted three-year follow-up of 133 patients with probable or possible DLB or probable AD who had undergone 123I-MIBG myocardial scintigraphy at baseline. An independent consensus panel made final diagnosis at three-year follow-up. Based on the final diagnosis, we reassessed the diagnostic accuracy of 123I-MIBG scintigraphy performed at baseline.

Results:

Sixty-five patients completed three-year follow-up assessment. The final diagnoses were probable DLB (n=30), possible DLB (n=3) and probably AD (n=31), and depression (n=1). With a receiver operating characteristic curve analysis of heart-to-mediastinum (H/M) ratios for differentiating probable DLB from probable AD, the sensitivity/specificity were 0.77/0.94 for early images using 2.51 as the threshold of early H/M ratio, and 0.77/0.97 for delayed images using 2.20 as the threshold of delayed H/M ratio. Five of six patients who were diagnosed with possible DLB at baseline and with probable DLB at follow-up had low H/M ratio at baseline. One patient who was diagnosed with possible DLB at baseline and with probable AD at follow-up had high H/M ratio at baseline.

Conclusions:

This follow-up study confirmed high correlation between abnormal cardiac sympathetic activity estimated with 123I-MIBG myocardial scintigraphy at baseline and the final clinical diagnosis of probable DLB at three-year follow-up. Its diagnostic usefulness in early stage of DLB was suggested.

Session 8: Biomarkers (Clinical, Neurophysiology & Biofluids)

Category: Biomarkers - Oral Presentation

O.24 Anterior EEG slowing in Dementia with Lewy Bodies: a multicenter European cohort study

Author: Laura Bonanni

Additional Authors: Raffaella Franciotti, PhD,¹ Flavio Nobili, MD,^{2,6} Milica G. Kramberger, MD,³ John-Paul Taylor, MD,⁴ Sara Garcia-Ptacek MD,⁵ Marco Onofri, MD,¹ N. Walter Falasca, PhD,¹ Dario Arnaldi, MD,^{6,2} Dag Aarlsand, MD⁷ on behalf of the E-DLB consortium

¹ Department of Neuroscience, Imaging and Clinical Science, and Aging Research Centre, G. d'Annunzio University of Chieti-Pescara, Chieti, Italy

² Clinical Neurology, Department of Neuroscience (DINO GMI), University of Genoa and IRCCS AOU San Martino-IST, Genoa, Italy

³ Department of Neurology, University Medical Centre, Ljubljana, Slovenia

⁴ Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, UK

⁵ Department of Neurobiology, Care Sciences and Society, Center for Alzheimer Research, Division of Clinical Geriatrics, Karolinska Institutet, and Memory Clinic Department of Geriatric Medicine, Karolinska University Hospital, Stockholm, Sweden

⁶ IRCCS Ospedale Policlinico San Martino, Genoa, Italy.

⁷ King's College of London, London, UK

Background: EEG slowing with pre-alpha dominant frequency (DF) in posterior derivations is a supportive biomarker for Dementia with Lewy Bodies (DLB) diagnosis, with high predictive value for the differential diagnosis with Alzheimer's Disease (AD).

In posterior derivations the power of alpha rhythm is maximal in controls and AD, allowing a strong differentiation with DLB where alpha in posterior derivations is much less represented, due to substitution with slower DF.

However, an intra-subject re-evaluation of original data showed that in DLB, the DF recorded on anterior derivations were constantly lower (frequency bands lower than alpha) than in posterior derivations.

The aim of the present study is to test, in a multicentre cohort, the hypothesis that EEG abnormalities are more severe in anterior than in posterior derivations of DLB patients.

Methods: We quantitatively analyzed EEGs of 122 patients from 5 Centers of the European DLB Consortium. EEG spectra values, divided into delta, theta, pre-alpha, alpha frequency bands were described by dominant frequency (DF), dominant frequency variability (DFV), frequency prevalence (FP).

Results: DF in anterior derivations resulted to be lower than in posterior derivations, thus supporting our hypothesis. Based on differences between DF values in anterior vs. posterior derivations (never higher in anterior) it was possible to allocate DLB patients into 5 groups.

Group 1: DF in alpha band in both anterior and posterior derivations.

Group 2: DF in pre-alpha band in anterior derivations and alpha band in posterior derivations.

Group 3: DF in pre-alpha band in both anterior and posterior derivations.

Group 4: DF in theta band in anterior derivations and in pre-alpha in posterior derivations.

Group 5: DF in theta band in both anterior and posterior derivations.

The majority of DLB patients belonged to group 3 (57%, $\chi^2=58$ in the comparison with group 1, which is the second for percentage of patients assigned, $p=10^{-6}$) having DF in pre-alpha band in both anterior and posterior derivations, confirming the association of the presence of pre-alpha with the diagnosis of DLB.

Significant difference among groups was found for MMSE ($F=4$, $p=0.004$). MMSE values were significantly lower for group 5 than group 1 ($p=0.004$) and 2 ($p=0.01$). For all DLB patients significant correlation was found between MMSE score and DF and FP alpha in both anterior (DF $r=0.4$, $p=3 \cdot 10^{-5}$; FP alpha $r=0.3$, $p=0.001$) and posterior derivations (DF $r=0.4$, $p=2 \cdot 10^{-5}$, FP alpha $r=0.3$, $p=2 \cdot 10^{-4}$).

Significant negative correlations were found between MMSE and FP theta in anterior ($r=-0.3$, $p=0.001$) and posterior derivations ($r=-0.3$, $p=0.001$) and FP delta in posterior derivations ($r=-0.2$, $p=0.01$).

Conclusions: EEG slowing was more severe in anterior derivations and correlated with lower MMSE scores. As fast-theta EEG rhythms have a thalamic origin, the presence of such rhythms on anterior leads

in DLB, may suggest, given the involvement of thalamic projections to anterior cortical regions, a possible pathophysiological explanation of the appearance of frontal lobe symptoms, such as attentional deficit (cognitive fluctuations) and dysexecutive symptoms. A future longitudinal study should address the possibility that the anterior EEG abnormalities appear early in the disease course.

Category: Biomarkers - Oral Presentation

O.25 Electro-encephalography as a prodromal marker of dementia with Lewy bodies

Author: Jessica van der Zande

Additional Authors: J.J. van der Zande¹, A.A. Gouw^{1,2}, I van Steenoven¹, M. vd Beek¹, Ph. Scheltens¹, C.J. Stam²

¹Department of Neurology and Alzheimer Center, Amsterdam University Medical Centers, Amsterdam Neuroscience, Amsterdam, the Netherlands

²Department of Clinical neurophysiology, Amsterdam University Medical Centers, Amsterdam, the Netherlands

Background

Early biomarkers for dementia with Lewy bodies (DLB) are still lacking. Electroencephalography (EEG) is a low-cost and non-invasive test that shows marked abnormalities in DLB. We aimed to study if EEG differentiates the prodromal phase of DLB from other causes of mild cognitive impairment (MCI) and is predictive for time to conversion from MCI to DLB.

Methods

We selected MCI-patients, who had ≥ 1 DLB core criterion (visual hallucinations, cognitive fluctuations, REM sleep behavior disorder or parkinsonism) or developed DLB during follow-up. Fifty-nine 'MCI due to DLB' (MCI-DLB) patients were compared with age-matched MCI-patients who developed Alzheimer's disease (MCI-AD) and MCI-patients who remained stable (sMCI) over ≥ 2 years. EEGs were assessed visually with a global score (ranging 1-5: normal to iso-electric) and for the presence of diffuse (slowing, decreased reactivity to eye opening) and focal (slowing, sharp elements) abnormalities. Fast Fourier Transform was performed to determine power spectrum, global peak frequency and alpha (8–13Hz) /theta (4–8Hz) ratio. We used ANOVA/Kruskal Wallis tests for group comparisons, logistic regression models to assess the diagnostic value of EEG and relations with conversion to dementia.

Results

The visual EEG-score was higher in MCI-DLB (abnormal in 86%; score >2 : 53%) compared to both MCI-AD and sMCI (score >2 : 7%, $p<0.001$). Frontal intermittent delta activity was seen in 19% of MCI-DLB, not in MCI-AD/sMCI. MCI-DLB patients had a lower peak frequency (7.56 Hz vs 8.61 in MCI-AD and 9.12 in sMCI, $p<0.001$), lower relative beta and alpha-2 power, higher theta power and theta/alpha-ratio. EEG measures showed good performance to discriminate MCI-DLB from MCI-AD/sMCI (AUCs up to 0.92). Visual EEG score, diffuse abnormalities, peak frequency, alpha2-power, and theta/alpha-ratio were related to time to progression to dementia.

Conclusions

Profound EEG abnormalities are already present in the prodromal stage of DLB and have discriminative and prognostic value.

Category: Clinical - Oral Presentation

O.26 Clinical and Pathologic Correlates of Parkinsonism in the Mild Cognitive Impairment and Dementia Stages of Lewy Body Disease

Author: Toji Miyagawa

Additional Authors: Toji Miyagawa¹, MD, PhD, Tanis J. Ferman PhD, Neill Graff-Radford MD², David S. Knopman MD¹, Jonathan Graff-Radford MD¹, Rodolfo Savica MD¹, David T Jones MD¹, Daniel A. Drubach MD¹, Julie A. Fields PhD¹, Mary M. Machulda PhD¹, John Lucas PhD², Leah K. Forsberg PhD¹, Laura Allen APRN CNP¹, Kejal Kantarci MD, MS¹, Erik K. St. Louis MD¹, MS, Michael Silber MBChB¹, Melissa E. Murray PhD², Joseph E. Parisi MD¹, Dennis W. Dickson MD², Ronald C. Petersen MD, PhD¹, Bradley F. Boeve MD¹.

1. Mayo Clinic Rochester, 2. Mayo Clinic Jacksonville

Background: The clinical and pathologic correlates of parkinsonism in the mild cognitive impairment (MCI) and dementia stages of Lewy body disease (LBD) are still being defined.

Methods: Antemortem data were analyzed from autopsied patients with either limbic-transitional LBD (TLBD) or diffuse-neocortical LBD (DLBD) who were diagnosed with mild cognitive impairment (MCI) and followed prospectively in the Mayo Alzheimer's Disease Research Center. Patients with the diagnosis of Parkinson's disease were excluded.

Results: The sample included 74 patients (34 transitional, 40 diffuse). There were no clinical or demographic differences based on distribution of Lewy-related pathology. At the first MCI evaluation, 23 patients (31%) had parkinsonism (MCI+P). The frequency of having parkinsonism increased to 54% at the initial diagnosis of dementia, and 74% at the last visit prior to death. MCI+P had more males than MCI without parkinsonism (MCI-P) (96% vs 61%, $p<0.01$). Compared to MCI-P, MCI+P had less neocortical NFT pathology (NFT Braak stage 4-6; 26% vs 63%, $p<0.01$) and less A β pathology ("moderate" or "frequent" by CERAD semiquantitative assessment of neuritic plaques; 30% vs 61%, $p=0.02$) at autopsy. Distribution of Lewy-related pathology did not differ between MCI+P and MCI-P (diffuse-neocortical; 57% vs 53%, $p=0.77$). All cases of the MCI+P had probable REM sleep behavior disorder (pRBD) at the onset of MCI, while 31% of the MCI-P had pRBD (100% vs 31%, $p<0.001$). Age at the onset of MCI (71.3 vs 73.5 years, $p=0.29$), duration from MCI to dementia (2.0 vs 2.5 years, $p=0.18$), and age at death (78.0 vs 81.9, $p=0.06$) did not differ between MCI+P and MCI-P. Years to death from the onset of MCI and from the onset of dementia were shorter with MCI+P (from MCI: 6.7 vs 8.5, $p=0.04$; from dementia; 4.7 vs 7.0, $p=0.03$).

Discussion: In this cohort, parkinsonism was infrequent at the MCI stage, increased in frequency from mild dementia to more advanced dementia, and occurred in approximately $\frac{3}{4}$ of the sample before death. The presence of parkinsonism at the time of MCI diagnosis was associated with less frequent AD pathology and shorter survival after progression to dementia. All cases who had parkinsonism at the onset of MCI also had pRBD at the time of MCI diagnosis. The presence or absence of parkinsonism was not associated with the distribution of Lewy-related pathology.

O.27 Hyposmia is Much More Severe in Neuropathologically Confirmed Dementia with Lewy Bodies as Compared with Alzheimer's Disease Dementia

Author: Thomas Beach

Additional Authors: Adler CHb, Serrano GEa, Zhang Nb, Erika Driver-Dunckleyb, Shayamal H. Mehtab, Shprecher DRa, Zamrini Ea, Sabbagh MNc, Shill HAd, Belden CMa, Davis KJa, Long KEa, Nicholson LRa, Intorcchia AJa, Glass MJa, Walker JEa, Oliver JCa, Sue LLa, Gerkin RCe.

a. Banner Sun Health Research Institute, Sun City, AZ

b. Department of Neurology, Mayo Clinic, Scottsdale, AZ

c. Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV

d. Barrow Neurological Institute, Phoenix, AZ

e. School of Life Sciences, Arizona State University, Tempe, AZ

Background

Due to the absence of core clinical features, 50% or more of subjects with neuropathologically-confirmed dementia with Lewy bodies (DLB) are never diagnosed as such during life. Most of these are diagnosed with Alzheimer's disease dementia (ADD) or dementia NOS. Unrecognized DLB therefore is a critical impediment to clinical studies and treatment trials of both ADD and DLB. There are numerous published studies that suggest that olfactory function tests may be able to differentiate some neurodegenerative conditions from each other and from normal subjects, but there are very few studies with neuropathological confirmation of diagnosis. We compared University of Pennsylvania Smell Identification Test (UPSIT) results in 30 subjects concurrently meeting intermediate or high consensus clinicopathological criteria for both DLB and ADD (no subjects with "pure" DLB were included due to low subject numbers), and 103 meeting criteria for ADD without DLB, as well as 87 control subjects that were cognitively normal and without parkinsonism at death.

Methods

Subjects were selected by database searches of the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND)/ Banner Sun Health Research Institute Brain and Body Donation Program (www.brainandbodydonationprogram.org). Most subjects had serial standardized research cognitive evaluations, done by teams of nurses, medical assistants, behavioral neurologists, neuropsychologists and psychometrists using standardized research-quality assessment batteries, including the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS). Subjects selected for this study also had one or more UPSITs done. All subjects received identical blinded neuropathological examinations by the same neuropathologist (TGB).

Results

Subjects with DLB were predominantly male (23M, 7F) while the other groups were more equally balanced (ADD: 52M, 51F; C: 42M, 49F). DLB subjects were significantly younger (85.1; $p=0.03$) than those with ADD (88.3) but not significantly different from controls (86.7). Mean MMSE score (22.2, SD 7.8 for ADD; 22.7, SD 4.6 for DLB) was not significantly different between dementia groups. Control subjects had significantly more UPSITs (mean 1.9, range 1-4; $p < 0.05$) than ADD (mean 1.6, range 1-4) or DLB subjects (mean 1.35, range 1-3) but this did not differ between ADD and DLB groups. The DLB subjects had significantly lower (one-way ANOVA $p < 0.0001$, pairwise Bonferroni $p < 0.05$) mean UPSIT scores (13.2, SD 3.9) than ADD (22.2, SD 7.9) or controls (28.9, SD 4.7). For subjects with an UPSIT score less than 20, Firth logistic regression analysis, adjusted for age, gender and mean MMSE score, conferred an odds ratio of 28.4 for predicting a DLB vs ADD diagnosis (95% CI 5.27 to 153.2).

Conclusion

To our knowledge, this is the first report of olfactory function in a large set of subjects with neuropathologically confirmed DLB and ADD. Subjects with DLB had much more severe olfactory impairment than those with ADD. Olfactory function testing may be a convenient and inexpensive strategy for enriching dementia studies or clinical trials with DLB subjects, or conversely, reducing the inclusion of DLB subjects in ADD studies or trials.

Category: Biomarkers - Oral Presentation

O.28 Plasma neurofilament light in DLB compared to other neurodegenerative disorders

Author: Abdul Hye

Additional Authors: Abdul Hye^{3,4}, Nicholas Ashton^{1,2,3,4}, Ahmad Al Khleifat³, Alberto Lleó¹⁴, Lucilla Parnetti¹⁵, Jan Lycke¹⁷, Latha Velayudhan^{3,4}, Andre Strydom³, Gil Rabinovici¹⁰, Bruce Miller¹⁰, Ammar Al-Chalabi³, Andrea L. Benedet¹⁶, Mira Chamoun¹⁶, Sulantha Mathotaarachchi¹⁶, Serge Gauthier¹⁶, Pedro Rosa-Neto¹⁶, Tharick Ali Pascoal¹⁶, Holly Green^{3,11}, Madhav Thambisetty¹³, Kaj Blennow^{1,8}, Henrik Zetterberg^{1,7,8,9}, Per Svenningsson^{3,11} and Dag Aarsland^{3,4,5}

¹ Department of Psychiatry and Neurochemistry, Institute of Neuroscience & Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden

² Wallenberg Centre for Molecular and Translational Medicine, University of Gothenburg, Gothenburg, Sweden

³ King's College London, Institute of Psychiatry, Psychology & Neuroscience, Maurice Wohl Clinical Neuroscience Institute, London, UK

⁴ NIHR Biomedical Research Centre for Mental Health & Biomedical Research Unit for Dementia at South London & Maudsley NHS Foundation, London, UK

⁵ Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway

⁶ Department of Psychiatry, University of Oxford. Warneford Hospital, Oxford, UK

⁷ Department of Neurodegenerative Disease, UCL Institute of Neurology, London, UK

⁸ Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

⁹ Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London UK

¹⁰ Memory and Aging Center, University of California, San Francisco, CA, USA

¹¹ Department of Clinical Neuroscience and Neurology, Karolinska Institutet, 17177 Stockholm, Sweden

¹² Section and Laboratory of Stress, Psychiatry and Immunology (SPI-Lab), Institute of Psychiatry, King's College London, London, UK

¹³ Clinical and Translational Neuroscience Unit, Laboratory of Behavioral Neuroscience, National Institute on Aging (NIA), National Institutes of Health (NIH), Baltimore, Maryland, United States of America

¹⁴ Memory Unit, Neurology Department. Hospital de Sant Pau. Barcelona, Spain.

¹⁵ Centre for Memory Disturbances - Lab of Clinical Neurochemistry - Section of Neurology, Dept of Medicine, University of Perugia

¹⁶ Alzheimer's Disease Research Unit, McGill Centre for Studies in Aging, McGill University, Douglas Institute, Montreal, Quebec, Canada

¹⁷ Department of Clinical Neuroscience at Institute of Neuroscience and Physiology, University of Gothenburg, Sweden

Background

Typical neurodegenerative protein markers (Amyloid, tau and α -synuclein) can be readily measured in plasma but historically the correlation with disease and/or CSF measures has been absent or weak [1-2]. However, there is a high degree of association between plasma and CSF neurofilament light (NfL) protein ($r = 0.8$) [3], another axonal neuron-specific protein. The ultra-sensitive Simoa platform for NfL has a 125-fold better analytical sensitivity than when the same anti-NFL antibodies used in other immunoassay-based platforms (Meso Scale Diagnostics [MSD] or ELISA) [4]. This is significant improvement now means that NFL can be accurately measured in blood samples from normal individuals, which are below the level for accurate quantification when using other methods. Using the Simoa NFL assay, a recent ADNI study showed a marked increase in plasma NFL in AD and MCI patients as compared with controls, with a diagnostic performance comparable to the core AD CSF biomarkers [5]. Furthermore, plasma NFL has been shown to be increased in several other atypical parkinsonian disorder [6] but normal in Parkinson's disease. Yet, to date, there has been no study that compares the levels plasma NfL across several neurodegenerative diseases within the same study.

Methods

Plasma samples were obtained covering a range of neurodegenerative conditions from multiple international cohorts such as European Medical Information Framework (EMIF), European DLB (eDLB),

Baltimore Longitudinal Study of Aging (BLSA). The cohorts comprised of mild cognitive impairment (MCI; n=86), Alzheimer's disease (AD; n=89), frontotemporal dementia (FTD; n=49), Amyotrophic lateral sclerosis (ALS; n=50), dementia with Lewy bodies (DLB; n=139), Parkinson's disease (PD; n=64), primary tauopathies (n=63) and healthy elderly controls (n=74).

Plasma NfL concentration was measured using the single molecule array (Simoa) platform at the Maurice Wohl Clinical Neuroscience Institute, London, UK. Samples were randomised, blinded and measured in duplicate using a batch of reagents from the same lot.

Results

Control individuals had the lowest mean NfL concentrations (30 pg/mL). Highest was observed in ALS (143.9 pg/mL), Down syndrome with dementia (DS-D; 80 pg/mL) and DLB (79.6 pg/mL). However, statistically significant differences ($p < 0.05$) were observed in five neurodegenerative conditions (FTD, corticobasal syndrome (CBS), DS-D, DLB and ALS) when compared to controls.

Conclusion

NfL has shown to be the most reliable marker of axonal damage in the brain. Here for the first time we have shown that NfL on its own is able to distinguish several neurodegenerative conditions when compared to healthy controls. These results hold promise for the use of NfL as a clinical tool and in clinical trials.

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Category: Biomarkers - Oral Presentation

O.29 Dementia with Lewy Bodies and Alzheimer's Disease Cerebrospinal Biomarkers

Author: Lynn Bekris

Additional Authors: L. Bekris 1, M. Khrestian 1, S. Berman², D. Galasko 3, J. Galvin 4, J. Goldman 5, D. Irwin 6, D. Kaufer 7, C. Lippa 8, I. Litvan 3, O. Lopez 2, I. Mata 1, A. Sturtevant 1, D. Tsuang 9, C. Zabetian 10, J. Leverenz 11.

Cleveland Clinic, Genomic Medicine Institute, Cleveland, USA.

University of Pittsburgh School of Medicine, Department of Neurology, Pittsburgh, USA.

University of California San Diego, Department of Neurology, San Diego, USA.

Florida Atlantic University, Department of Neurology, Boca Raton, USA.

Shirley Ryan AbilityLab and Department of Neurology and Physical Medicine and Rehabilitation, Northwestern University, Chicago, USA.

University of Pennsylvania, Department of Neurology, Philadelphia, USA.

University of North Carolina, Department of Neurology, Chapel Hill, USA.

Thomas Jefferson University, Department of Neurology, Philadelphia, USA.

VA Puget Sound Health Care System, Geriatric Research Education and Clinical Center
Department of Psychiatry, University of Washington, Seattle, USA.

VA Puget Sound Health Care System, Geriatric Research Education and Clinical Center
Department of Neurology, University of Washington, Seattle, USA.

Cleveland Clinic, Lou Ruvo Center for Brain Health, Neurological Institute, Cleveland, USA.

Background:

Co-existent Alzheimer's disease (AD) neuropathologic changes are observed in most autopsy confirmed cases of DLB, but of variable severity and frequency. To understand the characteristics of AD-associated biomarkers in the cerebrospinal fluid (CSF) of DLB, we examined the relationship between AD-associated CSF biomarkers (and other biomarkers) in the highly characterized DLB cases from the U.S. based Dementia with Lewy Bodies Consortium (DLBC).

Methods:

DLBC subjects undergo evaluation at enrollment, six months, and annually for the duration of the study. At each annual visit, blood and CSF are collected and stored. Baseline and two-year follow up visits include DaTscan and ADNI-3 compatible MRI scans. All subjects agree to autopsy. CSF AD biomarkers and alpha-synuclein were evaluated using the Luminex platform and Millipore multiplex assays.

Results:

DLBC cases were mostly male (~85%). The mean age at enrollment was 71.2 years and the mean MoCA score was 20.1. Significant parkinsonism was observed with an average UPDRS Part III score of 27.9. CSF A β 42 levels were low in virtually all cases, while CSF phosphorylated-tau levels ranged from normal to abnormally high. There was a positive correlation between alpha-synuclein and AD-associated biomarkers CSF A β 42, total-tau, and phosphorylated-tau in DLB.

Conclusion:

These CSF AD-associated biomarker results appear to be consistent with the neuropathologic literature, suggesting near universal amyloid deposition, but variable severity of neurofibrillary tangle pathology as well as a relationship with alpha-synuclein in DLB. Additional data will be reported as further DLBC recruitment and analysis is achieved.

Session 9: Genetics and Epigenetics

Category: Genetics & Epidemiology - Oral Presentation

O.30 Lewy Body Dementia Genome Sequencing Initiative: an Update

Author: Sonja Scholz

Additional Authors: Marya S. Sabir, Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

Coralie Viollet, The American Genome Center, Collaborative Health Initiative Research Program, Uniformed Services University, Bethesda, MD, USA

Sarah Ahmed, Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA

Elisa Martinez-McGrath, The American Genome Center, Collaborative Health Initiative Research Program, Uniformed Services University, Bethesda, MD, USA

Camille Alba, The American Genome Center, Collaborative Health Initiative Research Program, Uniformed Services University, Bethesda, MD, USA

John A. Hardy, Department of Molecular Neuroscience, University College London, London, UK

Mike Nalls, DataTecnica International, Glen Burnie, MD, USA

Toshiko Tanaka, National Institute on Aging, Baltimore, MD, USA

Susan M. Resnick, National Institute on Aging, Baltimore, MD, USA

Adriano Chio, Rita Levi Montalcini Department of Neuroscience, University of Torino, Torino, Italy

Walter Kukull, National Alzheimer's Coordinating Center (NACC), University of Washington, Seattle, WA, USA

J. Raphael Gibbs, Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA

Andrew B. Singleton, Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA

Owen Ross, Mayo Clinic Jacksonville, Jacksonville, FL, USA

Clifton L. Dalgard, The American Genome Center, Collaborative Health Initiative Research Program, Uniformed Services University, Bethesda, MD, USA

Bryan J. Traynor, Laboratory of Neurogenetics, National Institute on Aging, Bethesda, MD, USA

On behalf of the International Lewy Body Dementia Genomics Consortium

Background: Lewy body dementia (LBD) is a common, underserved form of dementia with complex clinical and pathological features. A genetic contribution to the disease pathogenesis is increasingly recognized. Recent advances in genome sequencing technologies provide unprecedented opportunities to decode the molecular genetic underpinnings of complex neurodegenerative syndromes. To extend modern gene discovery efforts to LBD and to generate a unique genomic resource for the research community, we undertook a genome sequencing study, including a large cohort of LBD cases and neurologically healthy controls. Here, we provide an update of the LBD genome sequencing initiative. **Methods:** A total of 2,983 LBD cases, and 2,173 neurologically healthy controls were included in the study. All subjects were from individuals of European ancestry. Short-read, paired-end genome sequencing at an average depth of 35x was performed on the Illumina HiSeq X Ten sequencing platform. The resulting FASTQ-files were transferred to the Google Cloud platform for alignment to the human reference genome (build 38) and for variant calling using the Centers for Common Disease Genomics standardized pipeline. Next, we applied stringent quality control metrics, such as screening for within- and cross-sample contamination, determination of the heterozygous/homozygous SNV ratio, sex chromosome SNV ratio, duplicate sample assessment, and determination of population outliers.

Results: The aligned genome sequence data have been assembled on the Google Cloud Platform. Analyses are currently ongoing and include common and rare variant testing, pathway analysis as well as comparative analyses between LBD and related neurodegenerative diseases. All genome data will be made available to the scientific community via the AMP-PD and NIAGADS knowledge platforms without embargo.

Conclusion: We anticipate that the analysis of these genomes together with access to this resource in publicly accessible knowledge platforms will accelerate the pace of genetic discovery within the LBD research field.

Category: Genetics & Epidemiology - Oral Presentation

O.31 A meta-analysis of genome-wide association studies in dementia with Lewy bodies

Author: Jose Bras

Additional Authors: Jose Bras and Rita Guerreiro for the International DLB Genetics Consortium, Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids Michigan

Dag Aarsland and Arvid Rongve for the European Dementia with Lewy Bodies consortium, Department of Old Age Psychiatry, Institute of Psychiatry and Neuroscience, King's College, London, UK

Ole Andreassen for the Norwegian Dementia Genetics Network (DemGene), Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Carla Abdelnour for the Dementia Genetics Spanish Consortium (DEGESCO) and Genomic Research at Fundació ACE (GR@ACE) Consortium, Fundació ACE, Institut Català de Neurociències Aplicades, Universitat Internacional de Catalunya, Barcelona, Spain

Introduction

Dementia with Lewy bodies is the second most common form of dementia in elderly people but has been largely overshadowed in the genetic research field, partly because of similarities between dementia with Lewy bodies, Parkinson's disease, and Alzheimer's disease. We have conducted the first genome-wide association study that identified genetic variants associated with the disease, conclusively showing that genetics plays a role in this disease and suggesting the association profile is unique when compared with Alzheimer's and Parkinson's diseases. These data suggest that increasing the sample size in this type of study will yield novel loci associated with this disease.

Materials and Methods

We performed a meta-analysis of three datasets from the USA and Europe to identify loci associated with DLB. Summary statistics for each study were generated using logistic regression and correcting for sex and principal components. These datasets were then meta-analyzed using fixed-effects.

Results

A total of 2,414 DLB cases and 10,281 controls were included, with imputed or genotyped data at 7,554,262 SNPs. We identified four loci that surpassed the threshold for genome-wide significance (GBA, SNCA, BCL7C and APOE). Additionally, we identified several loci that although not surpassing our significance threshold, show suggestive levels of association.

Discussion

These data provide further insight into the genetics of DLB and represent the largest genome-wide association study conducted in this disease.

O.32 Replication analysis of genetic risk factors for cognitive impairment in Parkinson's disease

Author: Ignacio Fernandez Mata

Additional Authors: Ignacio F. Mata^{1,2}, James B. Leverenz³, Hubert H. Fernandez², Lynn Bekris¹, Daniel Weintraub⁴⁻⁶, John Q. Trojanowski^{7,8}, Vivianna M. Van Deerlin⁷, Joseph F. Quinn^{9,10}, Kathryn A. Chung^{9,10}, Amie L. Peterson-Hiller^{9,10}, Liana S. Rosenthal^{11,12}, Ted M. Dawson¹¹⁻¹⁴, Marilyn S. Albert^{11,12}, Nico Bohnen¹⁵⁻¹⁸, Martijn Muller^{15,18}, Roger Albin¹⁵⁻¹⁹, Zbigniew K. Wszolek²⁰, Owen A. Ross²¹, Dennis W. Dickson²¹, Jennifer G. Goldman^{22,23}, Glenn T. Stebbins²³, Bryan Bernard²³, Kathleen Poston^{24,25}, Laurice Yang^{24,25}, Alberto J. Espay²⁶, Fredy J. Revilla²⁷, Johnna Devoto²⁶, Tanya Simuni²⁸, Steven Lubbe²⁸, Niccolo Mencacci²⁸, David Eidelberg^{29,30}, Paul J. Mattis^{29,30}, Martin Niethammer²⁹, Oswaldo Lorenzo-Betancor^{31,32}, Brenna A. Cholerton^{31,33}, Thomas J. Montine³³, Karen L. Edwards³⁴, Cyrus P. Zabetian^{31,32}

¹Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio

²Center for Neurological Restoration, Neurological institute, Cleveland Clinic, Cleveland, Ohio

³Lou Ruvo Center for Brain Health, Neurological Institute, Cleveland Clinic, Cleveland, Ohio

⁴Department of Psychiatry, University of Pennsylvania, Philadelphia

⁵Parkinson's Disease and Movement Disorders Center (PDMDC), Hospital of the University of Pennsylvania, Philadelphia, PA

⁶Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

⁷Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia

⁸Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia

⁹Portland Veterans Affairs Medical Center, Portland, Oregon

¹⁰Department of Neurology, Oregon Health and Science University, Portland

¹¹Johns Hopkins University School of Medicine, Baltimore, Maryland

¹²Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland

¹³Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

¹⁴Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland

¹⁵Division of Nuclear Medicine, Department of Radiology, University of Michigan, Ann Arbor

¹⁶Department of Neurology, University of Michigan, Ann Arbor

¹⁷Neurology Service and Geriatric Research Education and Clinical Center, Veterans Administration Ann Arbor Healthcare System, Ann Arbor Michigan

¹⁸University of Michigan Udall Center of Excellence for Parkinson's Disease Research, University of Michigan, Ann Arbor

¹⁹Michigan Alzheimer Disease Center, Ann Arbor

²⁰Department of Neurology, Mayo Clinic, Jacksonville, Florida

²¹Department of Neuroscience, Mayo Clinic, Jacksonville, Florida

²²Departments of Physical Medicine and Rehabilitation and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

²³Department of Neurological Sciences, Rush University Medical Center, Chicago, Illinois

²⁴Department of Neurology and Neurological Sciences, Stanford University, Stanford, CA

²⁵Department of Neurosurgery, Stanford University, Stanford, CA

²⁶Department of Neurology and Rehabilitation Medicine, University of Cincinnati, Cincinnati, OH

²⁷Division of Neurology at Greenville Health System and the University of South Carolina Medical School-Greenville, Greenville, SC

²⁸Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL

²⁹Center for Neurosciences, Feinstein Institute for Medical Research, Manhasset, New York

³⁰Department of Neurology, Northwell Health, Manhasset, New York

³¹Veterans Affairs Puget Sound Health Care System, Seattle, Washington

³²Department of Neurology, University of Washington School of Medicine, Seattle

³³Department of Pathology, Stanford University, Stanford, CA

³⁴Department of Epidemiology, School of Medicine, University of California Irvine, Irvine, CA

Background: Cognitive impairment is a common and disabling problem in Parkinson's disease (PD). Identification of genetic variants that influence the risk or severity of cognitive deficits in PD might provide a clearer understanding of the pathophysiology underlying this important non-motor feature. We recently performed the first large-scale analysis of genetic risk factors for cognitive impairment in PD in a multisite cohort from the PD Cognitive Genetics Consortium (PDCGC). In this "discovery" cohort we identified 29 common variants that had a false discovery rate (FDR) corrected p-value of < 0.1 . Our goal was to replicate these findings in an independent "replication" cohort from the PDCGC.

Methods: We genotyped 814 PD patients enrolled at 12 PDCGC sites using the NeuroX array and extracted genotypes for the 29 variants of interest. The following 9 cognitive variables were used for analysis: Montreal Cognitive Assessment (MoCA), Letter-Number Sequencing Test (LNST), Trail Making Test (TMT) B-A, semantic and phonemic verbal fluency, Benton Judgment of Line Orientation (JoLO), and Hopkins Verbal Learning Test-Revised (HVLT-R) total recall, delayed recall, and recognition discrimination index. We used linear regression to test for association between genotype and cognitive performance with adjustment for important covariates (age, sex, disease duration, years of education, and site).

Results: In the replication cohort, 9 variants were associated with one or more of the 9 cognitive variables (uncorrected p-value < 0.05). However, only 3 variants survived correction for multiple testing (FDR corrected p-value < 0.05) and displayed the same direction of effect as was observed in the discovery sample. The first, GBA rs2230288 (E326K), is well-established risk factor for cognitive dysfunction in PD. The others, MPHOSPH10 rs3732240 and FETUB rs34522046, represent novel findings of the discovery cohort.

Conclusions: We have successfully replicated two new susceptibility genes (MPHOSPH10 and FETUB) for cognitive impairment in PD. MPHOSPH10 is of particular interest because it is expressed at high levels in the hippocampus and basal ganglia, and a rare variant in the gene was recently nominated as a risk factor for early-onset PD in a case-control study. Further work will be necessary to understand the effect of these genes on cognition in PD.

O.33 SNCA variants are not associated with cognitive decline in Parkinson's disease

Author: Oswaldo Betancor

Additional Authors: Oswaldo Lorenzo-Betancor^{1,2}, Kimmy G. Su^{1,2}, Steven P. Millard¹, James B. Leverenz³, Daniel Weintraub^{4,5,6}, John Q. Trojanowski^{7,8}, Vivianna M. Van Deerlin⁷, Joseph F. Quinn^{9,15}, Kathryn A. Chung^{9,10}, Amie L. Peterson-Hiller^{9,10}, Liana S. Rosenthal^{11,12}, Ted M. Dawson^{11,12,13,14}, Marilyn S. Albert¹², Stewart A. Factor¹⁵, Cathy Wood-Siverio¹⁵, Zbigniew K. Wszolek¹⁶, Owen A. Ross¹⁷, Dennis W. Dickson¹⁷, Jennifer G. Goldman^{18,19}, Glenn T. Stebbins¹⁸, Bryan Bernard¹⁸, Brenna A. Cholerton^{1,20}, Thomas J. Montine²⁰, Ignacio F. Mata²¹, Karen L. Edwards²², Cyrus P. Zabetian^{1,2}

¹Veterans Affairs Puget Sound Health Care System, Seattle, WA

²Department of Neurology, University of Washington School of Medicine, Seattle, WA

³Lou Ruvo Center for Brain Health, Neurological Institute, Cleveland Clinic, Cleveland, OH

⁴Department of Neurology, University of Pennsylvania, Philadelphia, PA

⁵Department of Psychiatry, University of Pennsylvania, Philadelphia, PA

⁶Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

⁷Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA

⁸Institute on Aging, University of Pennsylvania, Philadelphia, PA

⁹Portland Veterans Affairs Medical Center, Portland, OR

¹⁰Department of Neurology, Oregon Health and Science University, Portland, OR

¹¹Neurodegeneration and Stem Cell Programs, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, MD

¹²Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD

¹³Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD

¹⁴Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD

¹⁵Department of Neurology, Emory University School of Medicine, Atlanta, GA

¹⁶Department of Neurology, Mayo Clinic, Jacksonville, FL

¹⁷Department of Neuroscience, Mayo Clinic, Jacksonville, FL

¹⁸Department of Neurological Sciences, Rush University Medical Center, Chicago, IL

¹⁹Departments of Physical Medicine and Rehabilitation and Neurology, Northwestern University Feinberg School of Medicine, and Shirley Ryan AbilityLab, Chicago, IL

²⁰Department of Pathology, Stanford University, Stanford, CA

²¹Lerner Research Institute, Genomic Medicine, Cleveland Clinic Foundation, Cleveland, OH

²²Department of Epidemiology, University of California, Irvine, School of Medicine, Irvine, CA

Background

Cognitive impairment is a common non-motor problem of Parkinson's disease (PD) that affects more than 20% of patients at initial diagnosis and progresses to dementia in approximately 80% of patients over time. Common variation within the SNCA gene (encoding α -synuclein) is a well-established risk factor for PD, and a recent study proposed distinct SNCA association signals for PD, PD with dementia, and dementia with Lewy bodies. However, there have been no comprehensive studies to date addressing whether SNCA variants predict progression of cognitive decline in PD. Our study aimed to address this issue in a large multi-site PD cohort with extensive longitudinal neuropsychological data.

Methods

The study population was comprised of 1,019 PD patients enrolled at seven sites from the PD Cognitive Genetics Consortium (PDCGC). All patients met UK PD Society Brain Bank clinical diagnostic criteria for PD and underwent at least two neuropsychological evaluations. The following 9 cognitive variables were used for analysis: Montreal Cognitive Assessment (MoCA), Letter-Number Sequencing Test (LNST), Trail Making Test (TMT) B-A, semantic and phonemic verbal fluency, Benton Judgment of Line Orientation (JoLO), and Hopkins Verbal Learning Test-Revised (HVLT-R) total recall, delayed recall, and recognition discrimination index. We selected 48 variants across the SNCA locus ± 10 kb that were genotyped using

the Illumina NeuroX array. Forty-six of the 48 variants had a minor allele frequency > 0.01. Linear mixed models were used to test for association between each variant and change in cognitive test scores across visits. The analyses included the following covariates: sex, site, age and disease duration at first evaluation, and years of education.

Results

The mean age at enrollment of the cohort was 66.9 ± 8.9 years and disease duration at enrollment was 8.2 ± 5.6 years. The mean duration of follow-up was 4.1 ± 2.4 years (range, 0.7 – 14 years). In the fully adjusted model 12 of the 48 SNCA variants were associated with change in the MoCA score over time (uncorrected p-values 0.004 – 0.009). However, none of these findings survived correction for multiple testing (Holm procedure), with all p-values > 0.19. No variants were associated with changes in scores for the other 8 cognitive variables.

Conclusions

We found that SNCA variants did not modify the rate of cognitive decline in a large and well-characterized PD cohort. Thus, while SNCA is a susceptibility locus for PD itself, it is unlikely to represent a biomarker for dementia in PD.

O.34 Prevalence of REM Sleep Behavior Disorder in Sun City, Arizona

Author: David Shprecher

Additional Authors: David R. Shprecher, DO MSci;¹ Anthony Intorcia, BS2; Michael Glass, BS2; Jasmine Curry, BS2; Jessica Walker, BS2; Brett, Cutler, BS2; Michael Callan, BS2; Geidy Serrano², PhD; Nan Zhang, MS; ³Lucia I. Sue, BS;² Kathryn J. Davis, BA2, and Thomas G. Beach, MD, PhD²
¹Cleo Roberts Center, Banner Sun Health Research Institute, Sun City, AZ, United States
²Civin Laboratory for Neuropathology, Banner Sun Health Research Institute, Sun City, AZ, United States
³Department of Biostatistics, Mayo Clinic College of Medicine, Scottsdale, AZ, United State

Background: REM sleep behavior disorder (RBD) is the strongest known clinical risk factor for Lewy body disorders including Parkinson disease (PD) and dementia with Lewy bodies, however prevalence data necessary to guide design of prevention trials are limited.

Methods: In order to determine the prevalence of RBD in Sun City, Arizona; we designed a survey using the RBD single item question (RBD1Q) for probable RBD (pRBD), "have you ever been told, or suspected yourself, that you act out your dreams while asleep (for example, punching; flailing your arms; making running movements; shouting out loud; knocking things over; jumping out of bed)?" and the Innsbruck RBD Inventory for high-likelihood RBD (HL-RBD).¹ Four out of 5 "yes" responses to these more specific questions have been shown to increase specificity of RBD1Q in a community-based sample.² Attempts by telephone and mail were made to administer it to 1000 individuals in the Sun City, Arizona zip code. Individuals who answered "yes" to 4/5 Inventory questions were considered to have HL-RBD.

Results: Of 3,000 individuals contacted, there were 484 respondents (response rate 16%), who were 96.7% Caucasian, mean age 78 (SD 8.5.) A total of 48 (9.9%) had pRBD as indicated by positive response to the RBD1Q and 16 (3.3%) HL-RBD as indicated by "yes" response to 4 out of 5 responses to the Innsbruck RBD inventory. By gender, pRBD prevalence was 26/201 (12.9%) of men and 22/274 (8.0%) of women and HL-RBD prevalence 8 (4.0%) of men and 8 (2.9%) of women. Overall prevalence of idiopathic cases (excluding those with a co-existing neurodegenerative disease) was 8.8% pRBD and 2.8% HL-RBD.

Conclusions: Previous research suggests that 66% of HL-pRBD respondents will have polysomnogram confirmed RBD.² Along these lines, the prevalence of definite idiopathic RBD (iRBD) in Sun City, Arizona is estimated to be at least 1/3 of HL-RBD cases: 1.1% overall, 1.1% of men and 1.1% of women. This rate is quite similar to that reported in a recent community based studies using PSG confirmation. An overall iRBD prevalence rate of 1% appears useful in guiding feasibility and recruitment strategies for purposes of observational and interventional trials in a population with prodromal synucleinopathy, at high risk for Lewy body dementia.

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O.35 Causes & Outcomes of Hospitalization in Lewy Body Dementia

Author: Melissa Armstrong

Additional Authors: C. Chauncey Spears (University of Florida College of Medicine)

Amir Besharat (University of Florida College of Medicine)

Erin Hastings Monari (University of Florida College of Medicine)

Daniel Martinez-Ramirez (Tecnologico de Monterrey, Escuela de Medicina y Ciencias de la Salud)

Leonardo Almeida (University of Florida College of Medicine)

Melissa J. Armstrong (University of Florida College of Medicine)

Background: Understanding hospitalization in Lewy body dementia (LBD) is a known knowledge gap. We aimed to identify common causes, medication profiles, complications, and outcomes of hospitalization in LBD.

Methods: A retrospective cohort study investigated details of academic medical center hospitalizations over a two-year period for patients with LBD (ICD-9 331.82, ICD-10 G31.83). Data collected included demographics, home medications, pre-hospital living status, reason for admission, admission service, inpatient medications, complications, and discharge status. Non-parametric statistics assessed associations between variables and length of stay. Odds of a change in living situation based on admission variables was calculated.

Results: The study included 178 hospitalizations (117 individuals). At the time of the first hospitalization within the two-year study period, mean age of included individuals was 78 years (SD 8 years); 59% of the cohort was male. At baseline, 35% of patients were taking antipsychotic medications, 58% were taking dopaminergic medication, and 38.5% were taking cholinesterase inhibitors. Neuropsychiatric symptoms were the most common admission reason (40%), followed by falls (24%) and infection (23%). Patients were usually admitted to medicine services; neurology or psychiatric consultations occurred less than 40% of the time. Hospital complications included delirium (50%), pneumonia, (17%), falls (4.5%), and death (4.5%). Antipsychotics were administered during 38% of hospitalizations. Length of stay was longer for individuals with delirium present at admission (median 6 days vs 3 days, $p=0.002$) and those experiencing complications including delirium (6 vs 3 days, $p<0.001$), in-hospital pneumonia (6 vs 4 days, $p=0.007$), and in-hospital falls (8 vs 4 days, $p=0.011$). Use of antipsychotics other than quetiapine or clozapine was associated with longer length of stay (7.5 vs 4 days, $p=0.001$) and increased odds of discharge to a higher level of care (OR 2.41, 95% CI 1.06–5.47). One-third of hospitalizations resulted in transition to a higher level of care; 15% ended in hospice care or death. Study limitations include its retrospective approach, reliance on ICD codes and chart documentation, single center experience, and relatively small sample size, limiting the ability to perform multivariable regressions. Statistics reflect associations and do not imply causation; it may be that inpatient antipsychotic use reflected higher dementia severity or more complicated inpatient courses.

Conclusions: These findings support prior studies suggesting that neuropsychiatric symptoms are a major driver of hospitalization in dementia in general and LBD in particular. The most common reasons for hospitalization in LBD are potentially modifiable, but emphasize the need for improved therapies targeting neuropsychiatric symptoms and fall prevention. Opportunities for improved hospital care include increased involvement of neurological and psychiatric services, delirium prevention strategies, and reduced antipsychotic use. Clinicians should counsel patients and families that hospitalizations in LBD can be associated with end of life. Research is needed to identify strategies to prevent hospitalization and optimal standards for inpatient care.

Session 10: Neuropathology & Biology

Category: Neuropathology & Biology - Oral Presentation

O.36 A novel staging system for the neuropathological diagnosis of Lewy body disease

Author: Jon Toledo

Additional Authors: Jon Toledo, University of Pennsylvania

Lauren Walker, Newcastle University

John Q. Trojanowski, University of Pennsylvania

Ian McKeith, Newcastle University

Current staging systems for the neuropathological diagnosis of Lewy body disease (LBD) include the Braak Lewy body (LB) stages, Newcastle-McKeith criteria (NM), Leverenz modification of the NM (LNM), and the Unified Staging System (USS). To assign a diagnosis according to the respective system the severity of LBs and Lewy neurites (LN) is semi-quantitatively scored in defined neuroanatomical regions using 4 or 5 tiered scales. Since the assignment of semi-quantitative scores is partly subjective the inter-rater agreement on the resulting diagnostic category is low in a subset of cases. Moreover, some cases do not fit into any while others fit into more than one category, respectively.

We have therefore developed and tested a novel staging system (NSS) which is based on dichotomous scoring, i.e. absence or presence of LBs/LNs in olfactory bulb, medulla oblongata, substantia nigra, amygdala, mediotemporal lobe, and cingulate, frontal and parietal cortices. Sections of 34 cases were stained with alpha-synuclein antibody, scanned, and photomicrographs were uploaded on a server. The scanned slides were then assessed by 16 experts and semi-quantitative scores were assigned for each slide. Neuropathological diagnoses were stated according to Braak LB stages, NM, LNM, USS, and NSS. The inter-rater agreement was highest using NSS followed by NM, LNM, USS, and Braak LB stages. Using USS or NSS allowed to classify all cases while the percentage of unclassified cases was over a third when using Braak LB stages. We conclude that the proposed NSS should be widely used for the basic diagnostic neuropathological assessment of post mortem brains from elderly individuals as it allows to classify all cases and can be applied in large multi-centre studies.

Category: Neuropathology & Biology - Oral Presentation

O.37 Age-related neurochemical and behavioural changes in D409V/WT GBA mouse: relevance to Lewy body dementias

Author: Paul Francis

Additional Authors: Clarke, E1.; Jantrachotechatchawan, C1.; Buhidma, Y.; Broadstock, M1.; Howlett, D1.; Aarsland, D2; Ballard, C3.; Francis, P.T.1,3

1King's College London, Wolfson Centre for Age-Related Diseases

2King's College London, Department of Old Age Psychiatry

3University of Exeter, College of Medicine and Health

Background

Heterozygous mutations in GBA1, the gene which encodes the lysosomal enzyme glucocerebrosidase (GCase), are a strong genetic risk factor for the development of Lewy body dementia (LBD). Until this point however, recapitulation of the symptoms and pathology of LBD has been limited to a homozygous GBA1 mouse model which genetically and enzymatically reflects the lysosomal storage disorder Gaucher's disease. The aim of this study was to characterise a heterozygous GBA1 mutant mice (D409V/WT) with respect to age in relation to activity of key glycosphingolipid enzymes together with behaviour and neuropathological features.

Methods

D409V/D409V GBA1 mice were crossed with C57Bl/6 wild type mice to generate D409V/WT GBA1 heterozygotes. Glucocerebrosidase (GCase) enzyme activity was measured as described previously using the artificial substrate 4-methylumbelliferone- β -glucopyranoside (4-MUP). Activated GBA1 derived GCase activity and GBA2 activity were also assessed by standard procedures.

Mice were subject to behavioural testing at 3,6,9 and 12 months of age - open field, Morris water maze and Y-maze. Paraffin embedded sections underwent immunohistochemistry using anti-GFAP, anti-Iba1 and anti- α -synuclein.

Results

Activated GBA1 derived GCase enzyme activity was significantly reduced by 72% in the hippocampus of D409V/WT mice compared with wild type and activated GBA1 activity by 71% at 12 months of age. In addition, GBA2 derived GCase activity was reduced by 91%. Mutant mice demonstrated a progressive decline in cognitive ability by both the Morris water maze and Y-maze, showing a significant deficit at 12 months of age. Mutant mice exhibited signs of inflammation in the hippocampus through significantly increased expression of both astrocytes and microglia (% area stained increased 3-fold for both markers). Although there was no evidence for deposition of α -synuclein, soluble α -synuclein was increased to 245% compared to wild type.

Conclusions

This study reports for the first time progressive cognitive impairment by two independent behavioural tests in heterozygous GBA1 mutant mice (D409V/WT) which demonstrate significant cognitive impairment by the age of 12. Furthermore, reductions in GBA1 GCase enzyme activity within the brain reflect levels seen in sporadic and GBA1 mutant LBD patients. While there is no overt deposition of α -synuclein, alterations to neuroinflammation were evident that have been described in LBD.

Overall, this study presents evidence to suggest that some pathological hallmarks associated with Lewy body dementia, affecting brain regions intrinsically associated with cognition, are present in D409V/WT mice. In the absence of overt α -synuclein deposition, the D409V/WT mice could be considered an early pre-clinical model of Lewy body dementias with potential for drug discovery. Since few robust pre-clinical models of Lewy body dementia currently exist, with further characterisation, the mouse model described here may contribute significantly to understanding of the pathophysiology of Lewy body dementias the development of new symptomatic and disease-modifying treatments.

O.38 Central and Peripheral Inflammation in Dementia with Lewy Bodies

Author: Ajenthnan Surendranathan
Additional Authors: A. Surendranathan - University of Cambridge
J. Kane - Newcastle University
A. Bentley - University of Cambridge
S. Barker - Newcastle University
J-P. Taylor - Newcastle University
A. Thomas - Newcastle University
I. McKeith - Newcastle University
D. Burn - Newcastle University
J. O'Brien - University of Cambridge

Background: Diagnostic rates for dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD) in clinical practice in the UK were recently found to be 4.6% and 9.7% respectively (Kane et al. 2018). The rate of DLB was below that found in pathological studies, which report a rate of more than 15%. The proportion of Parkinson's disease (PD) cases with dementia was also below that expected, with the majority of clinical studies revealing a prevalence of between 20% and 30%. Here we assess whether diagnostic rates of both PDD and DLB could be increased by the introduction of a structured assessment toolkit for clinicians.

Methods: An assessment toolkit was produced based on the established diagnostic criteria for DLB and PDD, with the aim of providing a structured framework for clinicians to assess patients suspected of either condition (Thomas et al. 2017; Thomas et al. 2018).

The toolkits were introduced to clinicians working in services within the North East and East Anglia within the UK, the same two regions we previously sampled. Teaching sessions on using the toolkits were provided to clinicians by the investigators. In total, four memory clinics and three movement disorder/PD clinics were then reassessed for the rate of diagnosis of DLB and PDD, respectively, using exactly the same methodology previously used to ascertain baseline diagnostic rates.

Results: For DLB, 2058 case notes were reviewed from memory clinics and DLB was diagnosed in 6.2% of dementia cases (see Figure 1). This is an absolute rise of 1.6%, equal to a 35% increase in the cases diagnosed, compared to the previously reported rate of 4.6% prior to the introduction of the DLB toolkit ($P=0.021$).

With respect to PDD, 3405 case notes were reviewed from movement disorder or PD clinics across the two regions. The number of PD patients diagnosed with PDD was not found overall to be significantly different after the introduction of the toolkit: 8.2% compared to the prior rate of 9.7%, $P=0.09$, though with some variation between regions.

Conclusion: Introduction of the assessment toolkit significantly increased the rate of DLB diagnosis, suggesting that a structured means of assessing patients for DLB could assist clinicians and improve rates of diagnosis.

The assessment toolkit did not alter the overall rate of PDD diagnosis, meaning alternate means may be required to improve the rate of diagnosis of dementia in Parkinson's disease.

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O.39 Inflammation in Dementia with Lewy bodies and Alzheimer's disease

Author: Jay Amin

Additional Authors: Dr Jay Amin, Associate Professor in Psychiatry of Older Age, University of Southampton;

Dr Tony Williams, Reader in Clinical Immunology, University of Southampton;

Prof Jessica Teeling, Professor of Experimental Neuroimmunology, University of Southampton;

Prof Delphine Boche, Professor of Neuroimmunopathology, University of Southampton;

Prof Clive Holmes, Professor of Biological Psychiatry, University of Southampton

Introduction

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative cause of dementia. The clinical features and neuropathology of DLB overlap with Alzheimer's disease (AD) and Parkinson's disease (PD), with timely diagnosis of DLB often delayed. There is mounting evidence supporting a role for inflammation in the aetiology of AD and PD, with the innate immune cells of the brain, microglia, being key players. In addition, alterations in the peripheral immune profile have been identified in both AD and PD. In contrast, our understanding of the role of inflammation in DLB is much less well developed.

Aims

To investigate cerebral and peripheral inflammatory processes in DLB and AD. Our hypothesis was that inflammatory processes would show a profile unique to DLB and be significantly associated with the neuropathological and clinical features of the disease.

Methods

Clinical study: 95 participants (32 DLB, 31 AD, 32 controls) entered an observational, cross-sectional clinical study and underwent assessments for cognitive, mood, behavioural and motor symptoms. Blood samples were analysed for peripheral immune cell populations and cytokine concentrations, using flow cytometry and multiplex immunoassay respectively.

Post-mortem study: Human brain sections from the middle temporal gyrus of 59 cases (30 DLB, 29 controls) were immunostained for neuropathology (alpha-synuclein, amyloid-beta, p-tau), microglial activation (Iba1, HLA-DR, CD68) and Fc-gamma receptors (CD64, CD32a, CD32b and CD16).

Quantification was performed to obtain protein load (%) using Image J.

Results

The clinical study revealed increased serum concentrations of two pro-inflammatory cytokines (IL1 β and IL6) in DLB compared with controls. In addition, flow cytometry showed a decline in cell populations associated with adaptive immunity (helper T cells and activated B cells) in DLB compared to AD. These data demonstrate senescence of the peripheral adaptive immune system in DLB compared with AD, possibly driving a chronic pro-inflammatory state.

The post-mortem study confirmed increased alpha-synuclein, amyloid-beta and p-tau protein load in DLB. However, there was no difference in the protein load of microglial activation markers Iba1, HLA-DR or CD68 in DLB compared with controls. Examination of Fc-gamma receptor markers did show significantly decreased CD32a and increased CD16 load in DLB compared to controls, but there was no difference in CD64 or CD32b load. This contrasts with previous work in AD that has shown a strong phagocytic phenotype of microglia. These differences may be associated with the divergent profiles of the peripheral adaptive immune system, with AD characterised by increased antibody-mediated microglial activation compared with DLB.

No significant correlations were identified when data were tested for associations between inflammatory markers and neuropathology, or clinical features of DLB.

Conclusions

Data from the clinical and post-mortem studies appear to show that the immunophenotype of DLB is distinct from that of AD, with cerebral inflammation not a primary feature of DLB as it is in AD. This has therapeutic implications in that the exploration of anti-inflammatory therapy may not indicated late in DLB.

Furthermore, identification of a unique peripheral immune profile in DLB warrants further exploration to understand the interaction between disease progression and inflammation.

Category: Neuropathology & Biology - Oral Presentation

O.40 Cingulate Lewy Body Density and Age of Onset of Disease in DLB and Parkinson's Disease with and without Dementia

Author: Daniel Erskine

Additional Authors: Daniel Erskine, Institute of Neuroscience, Newcastle University, UK

Ian McKeith, Institute of Neuroscience, Newcastle University, UK

Garry Blessed, Institute of Neuroscience, Newcastle University, UK

Robert Perry, Institute of Neuroscience, Newcastle University, UK

Background

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative disorder and histopathologically shares features also found in Parkinson's disease (PD) with dementia, and PD without dementia. The degree to which cortical Lewy body (LB) formation determines the clinical presentation in individual cases, or evolves as the disease(s) progress, and the emergence of subsidiary features such as DOC (disturbance of consciousness) and extent of cognitive impairment is not yet established.

Methods

The relationship between the age of onset of Lewy body disease to cortical LB density was investigated using data reanalysed from previous clinical pathological studies (Perry, Irving and Brown, 1990 unpublished). Neo- and archicortical tissue blocks from patients with DLB (16 cases including 3 of Diffuse Lewy body disease & 1 of mixed DLB/AD), PD without dementia (12 cases, including 2 with DOC) and PD with dementia (10 cases) were used to establish the cortical Lewy body density in the anterior cingulate gyrus (expressed as LB density/sq cm. taken from coronal level 13). Cortical LB density was established using immunohistochemistry.

Results

Age of presentation of dementia symptoms was significantly different between all diagnostic groups, with DLB>PDD>PD. In the cingulate gyrus the cortical LB density ranged from 0/mm sq to above 80/sq cm, and was significantly different between DLB in comparison to PDD and PD combined, but only PD in isolation.

Conclusions

The present findings indicate that despite the putative view that cortical Lewy body deposition is progressive over time in a stereotyped sequence, cortical Lewy body severity is not associated with disease duration in Lewy body diseases. PD cases without dementia exhibited remarkably earlier ages of onset than both PD cases with dementia and DLB, yet lower burdens of Lewy body pathology in the cingulate gyrus. - These findings suggest that the rate or occurrence of "spreading" of Lewy body pathology is remarkably different between individuals and different patient groups, with some exhibiting resilience to the genesis of cognitive symptoms, concomitant with slower spreading or extension of Lewy body pathology.

O.41 TDP-43 pathology in Lewy body disease is not associated with Lewy-related pathology or Parkinsonism

Author: Dennis Dickson

Additional Authors: Shunsuke Koga, M.D., Ph.D.

Naoya Aoki, M.D, Ph.D.

Joshua Menke, M.D.

Brittany Dugger, Ph.D.

Naomi Kouri, Ph.D.

Owen A. Ross, Ph.D.

Rosa Rademakers, Ph.D.

Melissa E. Murray, Ph.D.

Tanis J. Ferman, Ph.D.

Neill Graff-Radford, M.D.

Bradley F. Boeve, M.D.

Keith A. Josephs, M.D.

Mayo Clinic, Jacksonville, Florida and Mayo Clinic, Rochester, MN

In the brain bank for neurodegenerative disorders at Mayo Clinic in Jacksonville, 1051 brains with Lewy-related pathology have been screened for TDP-43 pathology. The Lewy body disease (LBD) cases include amygdala predominant (ALB, n=174), brainstem predominant (BLBD, n=125), transitional (TLBD, n=330) and diffuse (DLBD, n=422). Advanced Alzheimer pathology (Braak stage >IV, Thal phase>3) was present in 98% of ALB, 14% of BLBD, 46% of TLBD and 44% of DLBD. Other neurodegenerative pathologies included 74 primary tauopathies [progressive supranuclear palsy (n=58), corticobasal degeneration (n=12), Pick's disease (n=2) and argyrophilic grain disease (n=2)]. In addition there were 122 cases with frontotemporal lobar degeneration (n=19) and/or hippocampal sclerosis (n=139). TDP-43 pathology was detected in 315 (30%) cases with Lewy-related pathology. The factors most associated with TDP-43 pathology in LBD were age ($r=0.23$, $p=1.3E-17$), brain weight ($r=-0.25$, $p=2.2E-16$), Braak neurofibrillary tangle stage ($p=0.21$, $p=6.7E-12$), Thal amyloid phase ($r=0.13$, $p=3E-05$), disease duration ($r=1.8$, $p<0.001$), and female sex ($p=0.12$, $p<0.001$). TDP-43 was inversely related to Consortium for Dementia with Lewy bodies classification ($r=-0.20$, $p=3.4E-11$). Of genetic factors evaluated (APOE, TMEM106B and GRN), only APOE4 was associated with TDP-43 pathology ($r=0.14$, $p=3.4E-05$). Cases with clinical parkinsonism were less likely to have TDP-43 pathology ($r=-0.22$, $p=1.4E-12$). Frontotemporal lobar degeneration and hippocampal sclerosis with Lewy-related pathology were more likely to have TDP-43 pathology ($p<0.001$), and there was also a trend for primary tauopathies to have more frequent TDP-43 pathology ($p=0.011$). This observational study suggests that there is not a strong association of TDP-43 pathology with Lewy-related pathology, but it is more often related to factors known to increase risk for TDP-43 pathology, including advanced age, Alzheimer's disease, hippocampal sclerosis, frontotemporal degeneration and primary tauopathies.

Poster Presentations

Section: Biomarker

Category: Biomarkers - Poster Presentation

P.1 CSF Abeta42 and tau biomarkers are associated with regional brain atrophy in DLB patients

Author: Carla Abdelnour

Additional Authors: Abdelnour C1, Ferreira D2, Oppedal K3,4, Cavallin L2, Blanc F5, Bousiges O6, Wahlund L-O4, Hort J7, Nedelska Z7, Padovani A8, Pilotto A8, Bonanni L9, Kramberger M10, Boada M1, Westman E4,11, Pagonabarraga J12, Kulisevsky J12 and Aarsland D3,13.

Research Center and Memory Clinic, Fundació ACE, Institut Català de Neurociències Aplicades, Universitat Internacional de Catalunya-Barcelona. Centro de Investigación en Red-Enfermedades Neurodegenerativas (CIBERNED), Spain.

Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden.

Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway.

Department of Radiology, Stavanger University Hospital, Stavanger, Norway.

Hôpitaux Universitaire de Strasbourg, CMRR (Centre Mémoire de Ressource et de Recherche), Hôpital de jour, pôle de Gériatrie, et CNRS, laboratoire ICube UMR 7357 et FMTS (Fédération de Médecine Translationnelle de Strasbourg), équipe IMIS/Neurocrypto, Strasbourg, France.

Hôpitaux Universitaire de Strasbourg, Laboratoire de Biochimie et Biologie Moléculaire, et CNRS, Laboratoire de Neurosciences Cognitives et Adaptatives (LNCA), UMR7364 Strasbourg, France.

Department of Neurology, Charles University, 2nd Faculty of Medicine and Motol University Hospital, Prague, Czech Republic, International Clinical Research Center, Brno, Czech Republic.

Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy.

Department of Neuroscience Imaging and Clinical Sciences and CESI, University G d'Annunzio of Chieti-Pescara, Chieti, Italy.

Department of Neurology, University Medical Centre Ljubljana, Medical faculty, University of Ljubljana, Slovenia.

Department of Neuroimaging, Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.

Movement Disorders Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; Biomedical Research Institute (IIB-Sant Pau), Barcelona, Spain; Centro de Investigación en Red-Enfermedades Neurodegenerativas (CIBERNED), Spain.

Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK.

Background

Alzheimer's disease (AD)-related pathology is frequently found in patients with dementia with Lewy bodies (DLB), and the combination of α -synuclein, amyloid- β and tau-related pathologies is likely to be associated with the clinical expression of DLB core features, disease progression, survival and cognitive performance, although it is yet not known how amyloid- β and tau-related pathologies influence neurodegeneration in DLB.

Understanding the mechanisms underlying brain atrophy in DLB is important to improve our knowledge about the disease progression, differential diagnosis, and development and testing of anti-amyloid and anti-tau therapies in DLB.

Thus, we aimed at investigating the association between amyloid- β and tau-related pathologies and brain atrophy in DLB by analysing the relationship between CSF biomarkers and regional atrophy measured with visual rating scales on MRI in the European DLB Consortium (E-DLB) cohort.

Methods

87 DLB patients from the E-DLB cohort who had data on AD-related CSF biomarkers and MRI were included in this study. Random forest was used to analyze the association of CSF Ab42, total tau and phosphorylated tau (p-tau) (predictors) with scales for medial temporal lobe atrophy (MTA), posterior atrophy (PA) and global cortical atrophy scale-frontal subscale (GCA-F) (outcomes). Age, sex, education and disease duration were also included as predictors.

Results

DLB patients with abnormal MTA scores had shorter disease duration, abnormal CSF Ab42 levels and older age. Similarly, individuals with abnormal PA scores had older age, lower education level, and abnormal CSF Ab42 and p-tau levels. In contrast, abnormal GCA-F scores were not associated with any AD-related CSF biomarker, but with lower education level, male sex and older age.

Conclusions

In DLB patients, abnormal levels of CSF Ab42 used as a surrogate marker of amyloid- β pathology, were associated with atrophy in the medial temporal and posterior cortices. Abnormal CSF levels of p-tau, a marker of tau pathology, were related to the atrophy in the posterior cortex. Interestingly, CSF T-tau levels (a marker of neurodegeneration) were not associated with DLB-related regional brain atrophy. Future studies should include α -synuclein biomarkers to further understand the interaction between α -synuclein, amyloid- β and tau-related pathologies with regional brain atrophy and clinical phenotype in DLB patients

Category: Biomarkers - Poster Presentation

P.2 Regional [18F]-Flortaucipir Uptake in Lewy Body Disorders and Correlation with Cerebrospinal Fluid and Neuropathological Tau

Author: David Coughlin

Additional Authors: David G. Coughlin MD 1,2,3, Jeffrey Phillips PhD 1,4 , Emily Roll BS1,4, Claire

Peterson BS2, Rebecca Lobrovich MS2, David A. Wolk MD1,5, Sandhitsu Das PhD 1,5, Daniel

Weintraub MD 1,6, Sanjeev Vaishnavi MD 1,3, Andrew Siderowf MD MSCE 1,3, Ilya Nasrallah MD PhD

7, David Irwin MD MSTR 1,2,3 Corey T. McMillan PhD 1,4

1 Department of Neurology,

2 Digital Neuropathology Laboratory,

3 Lewy Body Disease Center of Excellence,

4 Frontotemporal Dementia Center

5 Alzheimer's Disease Center, at Perelman School of Medicine at the University of Pennsylvania

6 Michael J. Crescenzi VA Medical Center, Parkinson's Disease Research, Education, and Clinical Center,

7 Department of Radiology, Hospital of the University of Pennsylvania, in Philadelphia PA, USA 19104

Objective: To examine regional uptake of [18F]-flortaucipir (formerly [18F]-AV1451) in Lewy body disorders (LBD: dementia with Lewy bodies (DLB) and Parkinson's disease (PD)) and its association with cerebrospinal fluid (CSF) total tau (t-tau) and phospho-tau (p-tau), and digital histologic measurements of tau pathology at autopsy.

Background: Half of LBD patients have moderate to severe Alzheimer's disease (AD) pathology at autopsy which is associated with decreased overall survival and faster time to dementia. In vivo detection of tau pathology by [18F]-flortaucipir may provide regional specificity to compliment CSF tau biomarkers in LBD.

Design/Methods: Twenty patients with LBD and cognitive impairment (DLB=15, PD with MCI/Dementia=5) underwent [18F]-flortaucipir PET imaging with accompanying high resolution MR imaging. CSF Aβ42, p-tau and t-tau were analyzed using a Luminex platform and AlzBio3 immunoassay reagents. The LBD cohort was divided using an established Aβ42 cut-off of 191pg/ml (LBD+Aβ=11, LBD-Aβ=9). Fifteen amyloid-PET-negative healthy controls (HC-Aβ) and 12 age-, sex- and MMSE-matched amyloid-PET-positive patients from ADNI (AD/ MCI+Aβ) were comparators. PET images were registered to MR images, regions were assigned using MindBoggle atlas, and data were corrected for partial-volume effects. Regional standardized uptake value ratios (SUVRs) using whole cerebellum as reference and voxel-wise t-tests (uncorrected, $p < 0.005$, $k=0$) were compared across groups. SUVR values in LBD was correlated with CSF t-tau and p-tau using linear regression, co-varying for sex and age. Post mortem tissue in 23 regions from two LBD cases that went to autopsy underwent digital histologic analysis for tau pathology using AT8 staining

Results: LBD+Aβ had elevated [18F]-flortaucipir uptake compared with HC-Aβ in 5 temporo-occipital regions, whereas LBD-Aβ had no regional elevations. In voxel-wise analysis, AD/ MCI+Aβ had clusters of higher uptake than LBD+Aβ in all lobes, whereas LBD+Aβ had higher uptake than AD/MCI+AB in areas of the precentral gyrus. In the total LBD cohort, CSF t-tau was associated with mean cortical SUVR ($t=2.49, p=0.049$) as well as 17 regions from frontal and temporal lobes. CSF p-tau was associated with amygdala uptake ($t=2.35, p=0.03$) but not mean cortical SUVR ($t=1.27, p=0.22$). Two LBD patients that went to autopsy had diffuse neocortical Lewy body pathology. One had Braak tau stage II/VI, whereas the other had Braak tau stage V/VI pathology. Digital histologic measures of tau pathology were significantly associated with regional [18F]-flortaucipir uptake ($t=2.64, p=0.015$).

Conclusion: In LBD, patients with amyloid-positive CSF have [18F]-flortaucipir uptake that is elevated compared to controls but generally less than AD/MCI+Aβ, except for unique areas of elevated precentral gyrus uptake. In LBD, [18F]-flortaucipir uptake in several regions correlates with CSF t-tau, is significantly associated with neuropathological tau at autopsy, and adds important information about the regional distribution of potential tau pathology during life.

Category: Biomarkers - Poster Presentation

P.3 Cognitive and Cerebrospinal fluid biomarkers in prodromal Lewybody Disease

Author: Arvid Rongve

Additional Authors: Bjørn-Eivind Kirsebom, Department of Neurology, University Hospital of North Norway, UNN, 9037 Tromsø, Norway.

Luiza Chwiszczuk Helse-Fonna, Haugesund Hospital, Department of Research and Innovation, Box 2170, 5504 Haugesund, Norway.

Dag Aarsland, Stavanger University Hospital Norway and Kings College London, UK.

Lene Pålhaugen, Department of Neurology, Akershus University Hospital, Lørenskog, Norway

Erik Hessen, Department of Psychology, University of Oslo, Oslo, Norway and Department of Neurology, Akershus University Hospital, Lørenskog, Norway

Tormod Fladby, Department of Neurology, Akershus University Hospital, Lørenskog, Norway and Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway

Background

Dementia with Lewy bodies (DLB) is prevalent with rapid progression with no effective treatment available. DLB overlaps both clinically and pathologically with Alzheimer's disease (AD) and Parkinson's disease (PD). MCI stages in both AD and PD have been defined and multiple studies presented. A definition for the MCI stage in DLB was only recently proposed [1] and probable DLB-MCI defined as MCI based on the NIA-AA MCI criteria plus two DLB core symptoms like visual hallucinations, parkinsonism, fluctuations, REM sleep behaviour disorder or with one core symptom and a positive indicative biomarker like CIT-SPECT /DaTSCAN. Here we studied the concentrations of established and new dementia biomarkers in CSF and cognitive tests in DLB-MCI and compared to in AD-MCI and in normal controls.

Methods

The Norwegian Dementia Disease Initiation (DDI) study included persons with subjective cognitive decline, mild cognitive impairment (MCI) and cognitively normal controls in all Norwegian Health regions. The goal is to find new markers for different pre-dementia diseases from blood and cerebrospinal fluid (CSF), radiology or from cognitive measures. Biomarkers in CSF were measured applying commercial enzyme-linked immunosorbent assays based on monoclonal antibodies to measure CSF levels of the following protein biomarkers: Abeta1–42, t-tau, and p-tau were determined using Innostest Abeta (1–42), Innostest h-Tau Ag, and Innostest Phospho-Tau (181P) (Fujirebio, Ghent, Belgium), respectively. BACE1 and neurogranin (trunc P75) levels were determined using kits from EUROIMMUN AG (Lübeck, Germany). A battery of cognitive tests were administered to all participants [2].

Results

We found significantly lower concentration of CSF Abeta 1-42 for persons classified as having DLB-MCI as compared to cognitively normal controls. Additionally the level of the CSF biomarkers Abeta 1-42, t-tau, p-tau, Neurogranin, BACE1 and the Neurogranin/BACE1 ratio differed significantly between healthy controls and those classified as having AD-MCI. We found the time needed to complete the Trail-making test A to differ significantly between individuals diagnosed with DLB-MCI and AD-MCI, see table 1 for details.

Conclusions

The identification of persons living with DLB-MCI is based on clinical signs and neuropsychological test and proposed new indicative biomarkers. Here we show that lower CSF Abeta 1-42 and the results from one specific cognitive test measuring sustained attention and psychomotor tempo may be putative markers for DLB-MCI in the absence of other pathological CSF AD markers.

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Poster Presentations

Section: Clinical

Category: Clinical - Poster Presentation

P.4 Impaired sensory integration underlies Lewy body disease-associated visual hallucinations

Author: Angeliki Zarkali

Additional Authors: Authors:

Angeliki Zarkali¹, Rick A. Adams^{2,3}, Louise-Ann Leyland¹, Geraint Rees^{2,4}, Rimona S Weil^{1,4}

Institutions:

Dementia Research Centre, University College London

Institute of Cognitive Neuroscience, University College London

Department of Computer Science, University College London

Wellcome Centre for Human Neuroimaging, University College London

Background

Visual hallucinations are a distressing and common symptom of Lewy body disease (LBD: Dementia with Lewy bodies and Parkinson's disease). Their mechanisms remain unknown in LBD but models of hallucinations in psychosis suggest disruption of sensory integration with a shift towards prior knowledge and away from sensory evidence. We used an image-based learning paradigm to test how knowledge is used differently in people with LBD-associated visual hallucinations, specifically whether they show higher dependence on prior knowledge.

Methods

To test the effect of prior knowledge, we used two-tone images generated from colour figures of people or animals. These are difficult to disambiguate without prior information but generate a strong percept once the original colour figure is seen. On each trial, participants indicated whether a person was present in the image. Firstly, participants were presented with black-and-white images, secondly with original colour images and finally the black-and-white images were repeated. Order of presentation was randomised in each block. We examined performance before and after viewing the colour images in people with LBD-associated hallucinations (LBD/VH), LBD without hallucinations and healthy controls. All assessments were performed with participants in the ON state.

Results

37 individuals with LBD took part, 17 habitual hallucinators and 20 without hallucinations, and 20 age-matched unaffected individuals. Mean age was 68.9 years (range 50-83). Groups did not significantly differ in age, gender, time in education, low level vision (visual acuity, colour vision and contrast sensitivity), or general cognitive measures (MMSE and MOCA), $p > 0.05$. LBD/VH had lower performance in one visuospatial task (Hooper visual organisation test) compared to controls ($p = 0.026$) but not compared to LBD without hallucinations; two additional visuo-perceptual tasks were equivalent between all three groups. People with LBD with and without hallucinations did not significantly differ in disease duration, motor examination scores or levodopa equivalent doses.

People with LBD-associated hallucinations showed a significantly greater improvement performance in percentage correct after seeing the original colour images: 6.9% improvement (from 74.1% to 81.5%, $SD = 4.4$), compared with 2.7% in LBD without hallucinations (82% to 84.8%, $SD = 4.4$), and 4.7% in controls (79.3% to 84%, $SD = 3.5$), $F = 4.902$, $p = 0.011$; post-hoc analysis showed that this difference was between LBD/VH and LBD without hallucinations ($t = 2.93$, $p = 0.006$).

Conclusion

People with LBD and visual hallucinations showed improved performance in an image-based learning task, implying a higher reliance on prior knowledge over sensory evidence. This sheds light onto the processes underlying LBD hallucinations and could provide insights for future therapeutic targets.

Category: Clinical - Poster Presentation

P.5 Quantifying the tendency to hallucinate in Lewy body disease

Author: Angeliki Zarkali

Additional Authors: Angeliki Zarkali¹, Rick A. Adams^{2,3}, Stamatios Psarras⁴, Louise-Ann Leyland¹, John-Paul Taylor⁵, Geraint Rees^{2,6}, Rimona S Weil^{1,6}

Dementia Research Centre, University College London

Institute of Cognitive Neuroscience, University College London

Department of Computer Science, University College London

Space Syntax Laboratory, University College London

Institute of Neuroscience, Newcastle University

Wellcome Trust Centre for Human Neuroimaging, UCL, London

Background

Visual hallucinations are a characteristic and often distressing symptom of Lewy body disease (LBD: Dementia with Lewy bodies and Parkinson's disease). But they are transient in nature, making them difficult to study and hard to quantify. Pareidolia, or seeing meaningful objects within ambiguous visual scenes, has been proposed as a surrogate marker of hallucinations but its relationship with hallucination severity and other visual deficits remains unclear. We tested whether worsening pareidolias accompanied worsening visual hallucinations in LBD.

Methods

We used the standardised pareidolia test which contains 40 black and white images of visual noise. Eight of these images contain an embedded black and white human face. Participants were presented with each image for 30 seconds and asked whether the image contained a face. They were then asked to point at the observed face. Three training trials were performed prior to the experiment. Responses where patients identified a face outside of the embedded faces were classified as pareidolias. We examined performance in the pareidolia task in people with LBD-associated hallucinations (LBD/VH), LBD without hallucinations and unaffected controls. All assessments were performed with participants in the ON state.

Results

35 individuals with LBD were included: 17 habitual hallucinators and 18 without hallucinations, as well as 18 age-matched controls. Mean age was 68.9 years (range 50-83). Four patients were receiving acetylcholinesterase inhibitors: 2 LBD/VH (11.8%) and 2 LBD without hallucinations (11.1%). Our two clinical groups did not differ in age, disease duration, time in education, visual acuity, general cognitive measures (MMSE and MOCA) or domain specific tasks for attention, memory or language. LBD/VH had worse contrast sensitivity than those without hallucinations ($p=0.034$) and lower performance in a visuospatial task (Judgement of line orientation: $p=0.020$).

People with LBD-associated hallucinations reported significantly more pareidolias: mean \pm SD = 5.3 ± 5.9 , compared to 2.3 ± 3 for LBD without hallucinations and 2.5 ± 4.6 for controls ($p=0.011$). Hallucination severity on a standardised clinical scale was associated with worse pareidolias ($F=23.65$, $r^2=0.400$, $p<0.001$).

Conclusion

In an independent European dataset, we have validated that people with LBD and visual hallucinations reported significantly more pareidolias than patients with LBD without hallucinations or age-matched controls. Importantly, the number of pareidolias predicted hallucination severity. Pareidolia testing has the potential to be a biomarker for hallucinations in LBD with potential use in clinical trials for treatments to prevent visual hallucinations.

Category: Clinical - Poster Presentation

P.6 Longitudinal progression of mild cognitive impairment with Lewy bodies

Author: Calum A. Hamilton

Additional Authors: Calum A. Hamilton, Institute of Neuroscience, Newcastle University

Fiona E. Matthews, Institute of Health and Society, Newcastle University

Paul C. Donaghy, Institute of Neuroscience, Newcastle University

John-Paul Taylor, Institute of Neuroscience, Newcastle University

John T. O'Brien, Department of Psychiatry, University of Cambridge School of Clinical Medicine

Nicola Barnett, Institute of Neuroscience, Newcastle University

Kirsty Olsen, Institute of Neuroscience, Newcastle University

Sean J. Colloby, Institute of Neuroscience, Newcastle University

Jim Lloyd, Nuclear Medicine Department, Newcastle upon Tyne Hospitals NHS Foundation Trust

George Petrides, Nuclear Medicine Department, Newcastle upon Tyne Hospitals NHS Foundation Trust

Ian G. McKeith, Institute of Neuroscience, Newcastle University

Alan J. Thomas, Institute of Neuroscience, Newcastle University

Background

In comparison with the more common Alzheimer's disease (AD), dementia with Lewy bodies (DLB) features greater early attention, executive and visuospatial dysfunctions, less memory impairment, and a faster progression. It is unclear whether these different cognitive profiles are already evident in the respective mild cognitive impairment (MCI) stages, or only become apparent at the dementia stage, and whether MCI with Lewy bodies (MCI-LB) progresses more rapidly to dementia than MCI in AD (MCI-AD), in line with the faster decline in DLB. We present longitudinal data on domain-specific cognitive function and progression in an MCI cohort classified as MCI-LB or MCI-AD.

Methods

We followed 76 MCI patients (age ≥ 60) annually with repeated cognitive testing, and review of clinical diagnosis and symptomology, including presence of core features of DLB. MCI was diagnosed by application of NIA-AA criteria by an expert three-rater panel given the presence of cognitive impairment without loss of independent functioning.

The presence of core Lewy body symptoms was assessed by the same panel and dopaminergic imaging (^{123}I -N-fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl) single-photon emission computed tomography, FP-CIT SPECT) was rated as normal or abnormal by a separate expert imaging panel, blind to clinical information.

Patients were classified as either possible MCI-LB (with either one core symptom, or abnormal FP-CIT SPECT), probable MCI-LB (either two or more core Lewy body symptoms, or one core symptom with abnormal FP-CIT SPECT), or MCI-AD (no core Lewy body symptoms and normal FP-CIT SPECT). At annual reviews diagnoses were re-evaluated by the diagnostic panel and NIA-AA AD dementia and Fourth Consensus DLB criteria were applied where subjects had progressed to dementia.

At each assessment, subjects completed the Addenbrooke's Cognitive Examination-Revised (ACE-R), Trail Making Test parts A and B, as well as a computerised battery of simple, choice and digit-vigilance reaction time tasks, and a line angle judgement test.

Results

Full and up to date findings will be presented at the meeting but so far after a mean of about two years (maximum follow-up five years) preliminary findings are that global cognition, language, and attention declined over time in MCI, without clear diagnostic group differences. Visuospatial function progressively declined in probable MCI-LB, but not in MCI-AD. Trajectories of memory impairment did not significantly differ between groups. Verbal fluency was more impaired initially in probable MCI-LB; this did not significantly decline in any diagnostic group.

Conclusion

These preliminary findings suggest that decline in visuospatial impairments may help differentiate MCI-LB from MCI-AD and add to the evidence of the importance of thoroughly assessing this cognitive domain in Lewy body disease. Further follow-up may clarify whether MCI-LB and MCI-AD continue to progress at comparable rates, and whether baseline differences in memory, attention, and executive functions change longitudinally.

Category: Clinical - Poster Presentation

P.7 An artificial neural network model of visual hallucinations in dementia with Lewy bodies

Author: Li Su

Additional Authors: Li Su^{1,2}, Vlad-Petru Moroza¹, Hiromichi Tsukada³, John-Paul Taylor⁴, Daniel Collerton⁴, John O'Brien¹

1. Department of Psychiatry, University of Cambridge, UK

2. Sino-Britain Centre for Cognition and Ageing Research, Southwest University, China

3. Neural Computation Unit, Okinawa Institute of Science and Technology, Japan

4. Institute of Neuroscience, Newcastle University, UK

Introduction

Neural networks have not only become the standard for artificial intelligence (AI) but also have the potential to help define mechanisms underlying normal and disordered neurocognitive functions such as learning and perception. Currently, in mental health, there is a conceptual and experimental gap between clinical studies, aimed at quantifying symptoms and syndromes, and those at the molecular level, aimed at studying the signaling pathways and the interactions between different cellular components to provide insights into pathophysiological mechanisms. Hence, how pathological changes at the molecular level explain symptomatology remains largely unresolved (Mavritsaki et al., 2019).

Methods

We developed a neural network model to bring these together by generating new hypotheses about particular disease mechanisms. Here, we apply the model to dementia with Lewy bodies (DLB), focusing on understanding the neuro-computational basis of the distressing recurrent complex visual hallucinations which are a core clinical feature of the disease, seen in over 80% of cases. Building upon an existing model (Tsukada et al., 2015), we developed a multilayered neural network model with biologically plausible units and biologically motivated learning algorithms. The layers in the model are intended to imitate different neural networks or regions of the brain; see Fig 1.

Results

By using the parameters derived from normal individuals we were able to simulate normal object recognition. By altering the network parameters based on DLB patients, the model was then able to produce “computational hallucinations”, in which the output of the network in the absence of an object input matches with the output of the network when the object was presented. In other words, false object representations were activated in the network without the corresponding visual inputs; see Fig 2.

Discussion

In conclusion, we have illustrated a computational model that serves as a candidate explanation for the visual hallucinations in DLB. Future research will validate our “in-silicon” model predictions with in vivo human neuroimaging and behavioral data. We believe that this computational psychiatry approach can provide insight into the cognitive mechanisms responsible for this symptom, and further lead to improvements in diagnosis and treatment of DLB.

Category: Clinical - Poster Presentation

P.8 Altered interval timing as a novel marker of cognitive fluctuations in Lewy Body Dementia

Author: Elie Matar

Additional Authors: Elie Matar 1, Joseph R Phillips 2, Kaylena A Ehgoetz Martens 1, Glenda M Halliday 1, Simon JG Lewis 1

Brain and Mind Centre, University of Sydney, Camperdown, NSW, Australia

MARCS Institute for Brain, Behaviour and Development, Western Sydney University, Sydney, New South Wales, Australia

Introduction: Cognitive fluctuations are characterized by spontaneous marked variations in cognitive abilities and alertness and are considered a core clinical feature of Dementia with Lewy Bodies (DLB). There is a paucity of objective measurements of fluctuations in the clinical setting. Altered time awareness has been reported by patients and represents a potential clinical marker of fluctuations and/or their severity. In this study we aimed to investigate qualities of interval timing in patients with DLB.

Methods: 25 patients with probable DLB and 16 healthy age-matched older controls underwent testing using a simple time perception paradigm testing probing different aspects of interval timing including time estimation (retrospective estimation of interval length), time production (prospective determination of an interval) and time pacing (explicit timing of an interval). Intervals of 10, 30, 60 and 90 seconds were utilized and randomized between groups. Presence and severity of fluctuations in DLB patients was measured using the clinician assessment of fluctuation (CAF) and one-day fluctuation (OFS) scales respectively.

Results: We found significant differences in interval timing between controls and DLB for time estimation and time production only. Specifically, DLB patients estimated less time which was significant at 90 seconds (proportion of interval 0.92 vs 0.69; $p=0.03$). Likewise DLB produced less time (proportion of 90s interval 0.58 vs 1.0; $p<0.001$). Absolute deviation in time estimation at 90 seconds correlated with fluctuation presence according to the CAF ($r_s=0.47$; $p=0.009$) whilst errors in time pacing at 90s correlated strongest with fluctuation severity according to the OFS ($r_s=0.65$, $p<0.001$). Receiver operating characteristic analysis identified time production at 90 seconds to be a valid test to distinguish controls and DLB (AUC=0.87; 95% CI: 0.75 – 0.98).

Conclusion: We demonstrate objective evidence for altered temporal processing in DLB and show utility of time perception tasks as a potential novel means of exploring the neural basis of cognitive fluctuations as well as a feasible marker of fluctuations in the clinical setting.

Category: Clinical - Poster Presentation

P.9 How to diagnose DLB: Characterizing the prevalence and underlying relationships between core and supportive clinical features in Dementia with Lewy Bodies

Author: Elie Matar

Additional Authors: Elie Matar 1, Kaylena A Ehgoetz Martens 1, Glenda M Halliday 1, Simon JG Lewis 1
Brain and Mind Centre, University of Sydney, Camperdown, NSW, Australia

Introduction: The recent consensus criteria for DLB distinguish between key core and supportive clinical features to aid diagnosis, yet the relationship between all these variables and optimal methods for detecting them has not been addressed. In this study we assess all core and supportive features in a single cohort. We evaluate the suitability of our assessment battery with respect to core variables and expose latent symptom clusters to guide future diagnostic approaches in the clinic.

Methods: The clinical and neuropsychological profile of 27 prospectively recruited participants diagnosed with probable DLB and 25 age-matched controls was characterized according to the most recent consensus criteria. Symptoms were scored using a novel combination of established clinical and research instruments.

Results: Prevalence and characteristics of all core and supportive features were obtained. Factor analysis between all core and supportive features revealed six independent factors accounting for 81.3% of the total variance. Factors identified unique relationships including between hallucinations, fluctuations and excessive daytime somnolence, between REM sleep behaviour disorder and postural hypotension, and Parkinsonism and urinary disturbance. Predominantly 'prodromal' symptoms including mood, early neuropsychiatric and autonomic features were represented in the remaining factors. Receiver operator characteristic analysis of cognitive and clinical assessment tools reinforced MOCA (AUC=0.96; 95%CI: 0.91-1.00) as a suitable screening tool for cognitive impairment with subsections correlating strongly ($p<0.001$) to formal cognitive domains on neuropsychometric testing. Utility of UPDRS and RBDSQ scales for detecting core features is discussed and a novel DLB-Parkinsonism scale is proposed to aid diagnosis (sensitivity = 92%, specificity=50%).

Conclusion: Expansion of clinical criteria for DLB necessitates changes to routine diagnostic practices. Findings in relation to clinical screening instruments and identified symptom clusters shed light on the present phenotype of DLB and may inform future diagnostic algorithms.

Category: Clinical - Poster Presentation

P.10 Does the cardiac autonomic nerve affect the DLB fluctuating alertness?

Author: MIYUKI MATSUMURA

Additional Authors: no other author

Background and Objective

In DLB, fluctuating alertness is one of the core symptoms. In PD, there is not much fluctuating alertness. Both PD and DLB are diseases in which Lewy bodies accumulate in the brain in the same way, but why this difference occurs? To examine the difference in alertness fluctuation of both diseases, we compared the cardiac autonomic function of PD and DLB in this study.

Patients and Methods

Forteen patients with DLB and 11 with PD were examined. All patients were not taking drugs that influence the cardiac conduction system, nor medications for arrhythmia, or cardiac disease. Electrocardiography was performed and HR, PR time, QRS time, and QTc time were measured. And compared between two groups. Student's dependent t test was used for the statistical analysis.

Result

In the DLB group, there were episodes of consciousness variation close to syncope or syncope in 7 of 14 cases. Compared with PD, HR of DLB was statistically significantly decreased.

Discussion and conclusion

There was no statistically significant difference, but the value of CVr-r tended to be lower in the DLB group than in the PD group, and the H / M ratio of MIBG myocardial scintigraphy was lower in both the early stage and the delay stage in the DLB group, and WR Was higher in the DLB group.

In DLB, cardiac sympathetic nervous function is decreased more than PD, and it is suspected that arousal variation occurs.

Category: Clinical - Poster Presentation

P.11 *Faster Cognitive Decline in Dementia due to Alzheimer Disease with Clinically Undiagnosed Lewy Body Disease*

Author: Michael Malek-Ahmadi

Additional Authors: Thomas G. Beach², Edward Zamrini², Charles H. Adler³, Marwan N. Sabbagh⁴, Holly A. Shill⁵, Sandra A. Jacobson², Christine M. Belden², Richard J. Caselli³, Brian K. Woodruff³, Steven Z. Rapsack⁶, Geoffrey L. Ahern⁶, Jong Shi⁷, John N. Caviness³, Erika Driver-Dunckley³, Shayamal H. Mehta³, David R. Shprecher², Spann BM², Pierre Tariot¹, Kathryn J. Davis², Kathy E. Long², Lisa R. Nicholson², Anthony Intorcio², Michael J. Glass², Jessica E. Walker², Michael Callan², Jasmine Curry², Brett Cutler², Javon Oliver², Richard Arce², Douglas G. Walker⁷, Lih-Fen Lue², Geidy E. Serrano², Lucia I. Sue², Kewei Chen^{1,8,9,10,11} and Eric M. Reiman¹

1. Banner Alzheimer Institute, Phoenix, AZ

2. Banner Sun Health Research Institute, Sun City, AZ

3. Department of Neurology, Mayo Clinic, Scottsdale, AZ

4. Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV

5. Barrow Neurological Institute, Phoenix, AZ

6. Department of Neurology, University of Arizona, Tucson, AZ

7. Molecular Neuroscience Research Center, Shiga University of Medical Science, Otsu, Japan

8. Shanghai Green Valley Pharmaceutical

9. Arizona State University School of Mathematics and Statistics

10. College of Medicine-Phoenix, University of Arizona

11. Beijing Normal University

Background

Neuropathology has demonstrated a high rate of comorbid pathology in dementia due to Alzheimer's disease (ADD). The most common major comorbidity is Lewy body disease (LBD), either as dementia with Lewy bodies (AD-DLB) or Alzheimer's disease with Lewy bodies (AD-LB), the latter representing subjects with ADD and LBD not meeting neuropathological distribution and density thresholds for DLB. Although it has been established that ADD subjects with undifferentiated LBD have a more rapid cognitive decline than those with ADD alone, it is still unknown whether AD-LB subjects, who represent the majority of LBD and approximately one-third of all those with ADD, have a different clinical course.

Methods

Subjects with dementia included those with "pure" ADD (n = 137), AD-DLB (n = 64) and AD-LB (n = 114), all with two or more complete Mini Mental State Examinations (MMSE) and a full neuropathological examination.

Results

Linear mixed models assessing MMSE change showed that the AD-LB group had significantly greater decline compared to the ADD group ($\beta = -0.69$, 95% CI: -1.05, -0.33, $p < 0.001$) while the AD-DLB group did not ($\beta = -0.30$, 95% CI: -0.73, 0.14, $p = 0.18$). Of those with AD-DLB and AD-LB, only 66% and 2.1%, respectively, had been diagnosed with LBD at any point during their clinical course. Compared with clinically-diagnosed AD-DLB subjects, those that were clinically undetected had significantly lower prevalences of parkinsonism ($p = 0.046$), visual hallucinations ($p = 0.0008$) and dream enactment behavior (0.013).

Conclusions

The probable cause of LBD clinical detection failure is the lack of a sufficient set of characteristic core clinical features. Core DLB clinical features were not more common in AD-LB as compared to ADD. Clinical identification of ADD with LBD would allow stratified analyses of ADD clinical trials, potentially improving the probability of trial success.

Category: Clinical - Poster Presentation

P.12 Neuropsychiatric symptoms correlate with disability trajectories among people living with Alzheimer disease and Dementia with Lewy Bodies

Author: Miguel Germán Borda

Additional Authors:

Miguel Germán Borda^{1,2,3}, Kolbjørn Brønnick^{1,3}, Guido Alves⁴, Audun Osland Vik-Mo^{1,5}, Ketil Oppedal^{1,6,7}, Carlos Alberto Cano-Gutierrez², Dag Aarsland^{1,8}

Centre for Age-Related Medicine (SESAM), Stavanger University Hospital. Stavanger, Norway.
Semillero de Neurociencias y Envejecimiento, Ageing Institute, Medical School, Pontificia Universidad Javeriana. Bogotá, Colombia.

Faculty of Health Sciences, University of Stavanger, Stavanger, Norway.

Norwegian Center for Movement Disorders, Stavanger University Hospital, Stavanger, Norway.

Department of Clinical Science, University of Bergen. Bergen, Norway.

Department of Radiology, Stavanger University Hospital, Stavanger, Norway.

Department of Electrical Engineering and Computer Science, University of Stavanger. Stavanger, Norway.

Department of Old Age Psychiatry, King's College. London, United Kingdom.

Corresponding author

Full name: Miguel Germán Borda

Institute: Stavanger University Hospital. Stavanger, Norway.

Department: Centre for Age-Related Medicine (SESAM)

Address: Centre for Age-Related Medicine (SESAM), Stavanger University Hospital, PB 8100, N-4068. Stavanger, Norway. Tel: +47 51515619 E-mail address: mmborda@gmail.com

Abstract:

Introduction:

Neuropsychiatric symptoms (NPS) are common in persons living with dementia. The negative impacts of NPS lead to loss of functionality. We aim to assess the effect of NPS at diagnosis in a 7-year functional trajectory in persons living with dementia.

Methods:

This is a secondary analysis of the Dementia Study of Western Norway (Demvest) including a total of 186 patients with AD (n=116) and DLB (n=70) with mild dementia at baseline (mean age 76.10 ± 7.59 years; 62.90% females). Functionality was assessed annually using the RDRS-21 scale and NPS were evaluated using the Neuropsychiatric Inventory (NPI). The longitudinal functional trajectory was analyzed using linear mixed modelling adjusted by age, sex, cognition and comorbidity.

Results:

The age mean at baseline was 76.10 ± 7.59 . There were more women (62.90; n=117) than men (37.10; n=69) in the sample. The sample consisted of 116 patients with AD 70 patients with DLB. The 7-year total functional decline was significantly more severe in DLB than AD, but the trajectories did not differ (figure 1). Depression (Coef. 0.022 (IC95% 0.007-0.036) p 0.003), apathy (Coef. 0.017 (IC95% 0.006-0.028) p 0.002) and loss of appetite (Coef. 0.018 (IC95% 0.007-0.037) p 0.001) were significantly correlated with functional loss in AD. Similarly, depression was correlated with functional decline in DLB (Coef. 0.034 (IC95% 0.0061-0.0062) p 0.017). Association between psychotic symptoms and aggression was not found.

Conclusion:

Negative NPS such as apathy, depression and loss of appetite independently of age, global cognition and comorbidities play an important role in the progression of the studied dementias. These results highlight the importance of detection and treatment of these related important targets for preventing functional loss.

Category: Clinical - Poster Presentation

P.13 A possible case of prodromal DLB with prominent hallucinations, autonomic dysfunction, and REM behavior disorder but absence of cognitive impairment: Case Report

Author: Katherine Amodeo

Additional Authors: Katherine Amodeo, MD University of Rochester, Rochester N.Y. USA

Dementia with Lewy bodies (DLB) is the second most common cause of neurodegenerative dementia, after Alzheimer's disease (AD). While mild cognitive impairment (MCI) is widely recognized as the key prodromal syndrome for AD, the prodrome for DLB is likely more broad with syndromes other than MCI. Rapid eye movement sleep behavior disorder (RBD) is strongly associated with neurodegenerative synucleinopathies, like DLB, and can present years prior to the onset of cognitive impairment. Here, we present a case of spontaneous psychosis, RBD, autonomic dysfunction (characterized by excessive diaphoresis), and fluctuations in level of alertness in a 47 years old man with no objective cognitive impairment. At the time of presentation to our Movement disorders center, the patient had been experiencing visual and auditory hallucinations for 5 years in the absence of a mood or other primary psychiatric disorder. He had no prior history of psychosis. He had been experiencing symptoms of RBD (diagnosis confirmed with polysomnogram) for 4 years. He had been evaluated by Psychiatry, Neuroimmunology, Epilepsy, and Memory Care specialists with no clear diagnosis in the setting of an unrevealing, extensive work-up, which included a normal brain MRI, long-term monitoring EEG, paraneoplastic CSF and plasma panels, 24 urine collection for catecholamines and porphobilinogens, CT scans of the chest, abdomen, and pelvis, HIV, ceruloplasmin, and syphilis testing. In addition to hallucinations and RBD, he had been experiencing excessive night-sweats for 5 years and underwent tilt-table testing on one occasion with evidence of increased sympathetic tone in the supine position. Despite self-reports of cognitive impairment, extensive neuropsychological testing failed to detect deficits with normal to high-normal performance across all domains. EMG/NCS was done with no evidence of polyneuropathy, generalized peripheral nerve hyperexcitability, fasciculations, myokymia or neuromyotonia. On exam, there was slight parkinsonism in his right upper extremity. DaTscan was subsequently obtained and demonstrated asymmetrically decreased radiotracer in the left basal ganglia. I proposed that this case may represent a psychiatric prodrome/pre-dementia subtype of DLB1 with disproportionate limbic involvement over other areas of the brain.

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Category: Clinical - Poster Presentation

P.14 Mild cognitive impairment in Dementia with Lewy bodies - Frequency and cognitive profiles in the Norwegian Dementia Disease Initiation Study

Author: Arvid Rongve

Additional Authors: Bjørn-Eivind Kirsebom, Department of Neurology, University Hospital of North Norway, UNN, 9037 Tromsø, Norway.

Luiza Chwiszczuk Helse-Fonna, Haugesund Hospital, Department of Research and Innovation, Box 2170, 5504 Haugesund, Norway.

Dag Aarsland, Stavanger University Hospital Norway and Kings College London, UK.

Lene Pålhaugen, Department of Neurology, Akershus University Hospital, Lørenskog, Norway

Erik Hessen, Department of Psychology, University of Oslo, Oslo, Norway | [i] Department of Neurology, Akershus University Hospital, Lørenskog, Norway

Tormod Fladby, Department of Neurology, Akershus University Hospital, Lørenskog, Norway | [j] Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway

Background

Dementia with Lewy bodies (DLB) is prevalent with rapid progression and no effective treatment available. DLB overlaps both clinically and pathologically with Alzheimer's disease (AD) and Parkinson's disease (PD). In both AD and PD the Mild Cognitive Impairment (MCI) stages of the diseases have been defined and multiple studies presented. In DLB however, a definition of the MCI stage were only very recently proposed with probable DLB-MCI defined as MCI based on the NIA-AA MCI criteria plus two DLB core symptoms including visual hallucinations, parkinsonism, fluctuations, REM sleep behavior disorder or with one core symptom and a positive indicative biomarker like CIT-SPECT /DaTSCAN (1). A previous study found the non-amnesic subtype of MCI to convert to DLB over time (2). Here we describe the frequency of possible and probable DLB-MCI in three different cognitive subgroups.

Materials and Methods

The Norwegian Dementia Disease Initiation (DDI) study included 658 persons diagnosed with subjective cognitive decline, mild cognitive impairment (MCI) and cognitively normal controls from all Norwegian Health regions from 2013 with follow-ups after 2 years. Cognition was assessed with a battery of cognitive tests and participants were classified as having pure amnesic, non-amnesic or multidomain cognitive failure.

Results

Nine persons (4%) were diagnosed with probable DLB-MCI and 57 (25 %) with possible DLB-MCI, in total 66 persons (29%) of those diagnosed with MCI fulfilled criteria for DLB-MCI. In the group with DLB-MCI 21/66 (32%) were classified as having the non-amnesic subtype, 13/66 (20%) had pure amnesic MCI and 32/66 (49 %) had multidomain MCI. 160 (71%) were classified as having non-DLB subtypes of MCI, and of these about one third had each of the three cognitive subtypes.

Discussion

In a Norwegian Memory Clinics sample of SCD, MCI and NC's the frequency of DLB-MCI among individuals classified with MCI was 29%, of these 80% had the non-amnesic or multidomain subtypes of MCI. The frequency of probable and possible DLB-MCI in the MCI group is corresponding to the prevalence of DLB among persons admitted to Memory clinics for dementia. Follow-up of these individuals classified as having DLB-MCI will be important to find out if they will develop dementia and Dementia with Lewy bodies (DLB). Identifying new biomarkers for disease progression in DLB-MCI will also be equally important to identify persons most likely to benefit from disease modifying therapy available now or in the near future like amroxol.

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Category: Clinical - Poster Presentation

P.15 The mild cognitive impairment stage of Dementia with Lewy bodies -conversion to dementia during two years in the Norwegian Dementia Disease Initiation Study

Author: Arvid Rongve

Additional Authors: Bjørn-Eivind Kirsebom, Department of Neurology, University Hospital of North Norway, UNN, 9037 Tromsø, Norway.

Luiza Chwiszczuk Helse-Fonna, Haugesund Hospital, Department of Research and Innovation, Box 2170, 5504 Haugesund, Norway.

Dag Aarsland, Stavanger University Hospital Norway and Kings College London, UK.

Lene Pålhaugen, Department of Neurology, Akershus University Hospital, Lørenskog, Norway

Erik Hessen, Department of Psychology, University of Oslo, Oslo, Norway | [i] Department of Neurology, Akershus University Hospital, Lørenskog, Norway

Tormod Fladby, Department of Neurology, Akershus University Hospital, Lørenskog, Norway | [j] Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway

Background

A definition for the MCI stages in Dementia with Lewy bodies was recently proposed and probable DLB-MCI was defined as MCI based on the NIA-AA MCI criteria plus two DLB core symptoms; visual hallucinations, parkinsonism, fluctuations and REM sleep behavior disorder, or with one core symptom and a positive indicative biomarker like CIT-SPECT /DaTSCAN (1). Here we studied the rate of progression from DLB-MCI to dementia after two years of follow-ups.

Materials and Methods

The Norwegian Dementia Disease Initiation (DDI) study included 658 persons classified as having subjective cognitive decline, mild cognitive impairment (MCI) or cognitively normal controls including cognitive assessments and lumbar puncture with follow-ups after 2 years. A main purpose with the DDI study was to find new markers for disease progression, and for differentiation between pre-dementia diseases using CSF and cognitive measures. Based on reported cognitive symptoms, the MCI subjects were categorized as amnesic, non-amnesic or multidomain MCI, and we counted the frequencies of MCI subjects converting to dementia in subgroups with none, one, two or more than one DLB core symptoms, also stratified on cerebrospinal fluid amyloid beta 1-42 pathology using an amyloid PET verified cutoff (Ab+/Ab-) (2).

Results

Six hundred fifty eight persons were included at baseline and 382 completed follow-up at 2 years. Two hundred twenty nine persons were diagnosed with MCI at baseline and data from 143 of these (62%) were available from follow up after two years. 46 (20 %) were diagnosed with probable or possible DLB-MCI and 97 were classified as having a non DLB MCI-subtype. During two years of follow-ups 17/143 (11.8 %) developed dementia, four of the 46 (8.7 %) persons diagnosed with probable and possible DLB-MCI at baseline developed dementia and 13/97 (13.4 %) of those having non DLB-MCI developed dementia after two years. Both in the DLB and non DLB MCI subtypes the conversion rate to dementia was higher in the A-beta positive subjects with 30% conversion after two years. Although the numbers here are small, we found the group including both probable and possible DLB-MCI with multidomain MCI and positive A-beta to have the highest conversion rate to dementia with 3 of 7 (42.9 %) developing dementia after only two years.

Discussion

In the Norwegian Dementia Disease Initiation Study we followed persons living with MCI after 2 years and based on core diagnostic criteria for DLB, cognitive subtypes and AD biomarkers like A-beta we were able to sort out subtypes of individuals classified as having MCI with a particular high conversion rate to dementia after only 2 years of observation. In future studies it will be highly important to tailor effective interventions specifically to these high-risk individuals.

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Category: Clinical - Poster Presentation

P.16 *Orthostatic hypotension may be associated with a distinct cognitive profile in Lewy body dementia: Preliminary results from an on-going cross-sectional study*

Author: Katherine Amodeo

Additional Authors: 1. Katherine Amodeo, MD- University of Rochester

2. Miriam Weber, PhD- University of Rochester

Introduction: Autonomic dysfunction is common in Lewy body dementia (LBD), often manifesting as orthostatic hypotension (OH). Untreated OH causes cerebral hypoperfusion, which may result in immediate syncope and falls. In addition to these transient symptoms, chronic OH and cerebral hypoperfusion may impact cognition. Studies to date have yielded conflicting results both supporting and failing to support an association.¹ This may be due to measures, such as the MMSE, that may fail to detect subtle impairment or assess a range of cognitive domains. We aim to determine the relationship between OH and cognition using a comprehensive neuropsychological test (NPT) battery.

Materials and Methods: In our ongoing cross-sectional study, we recruited nine ≥ 60 y.o. participants with LBD (6 with and 3 without OH). Participants have mild to moderate dementia, as defined by Clinical Dementia Rating scores 1 and 2. We obtained orthostatic vitals and administered the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). We compared group performance on the total score, index scores, and subtest raw scores. Here, we only report trends observed given small N and that results are still preliminary. We administered the MDS-UPDRS and questionnaires on falls and fluctuations (results not reported here).

Results: The groups did not differ in age and education. The OH group had longer disease duration (12 ± 14.4 y.) than the non-OH group (4 ± 3.46 y.). Total scores did not differ between groups and both groups performed in the impaired range on measures of immediate memory, language, and delayed memory. However, the non-OH group performed in the borderline range for visuospatial construction and attention, while the OH group performed in the impaired ranges. Furthermore, the OH group performed worse than the non-OH group on measures of processing speed (Coding subtest: 5 ± 9.1 and 31 ± 2.83 in OH and non-OH group, respectively), visuospatial construction (Figure copy: 3.8 ± 4.4 and 13.5 ± 2.1 ; Line orientation: 1.2 ± 1.6 and 16 ± 2.8), and visual memory (Figure recall: 1.3 ± 2.0 and 13 ± 1.4).

Discussion: Although preliminary, our findings suggest that the presence of OH may contribute to slower processing speed and visuospatial dysfunction in LBD. However, this finding may reflect longer disease duration among OH group. Additional work is needed to determine if our findings hold-up in a larger sample and to clarify if OH leads to worse cognitive function or is a marker of advanced disease. Clarifying the relationship between OH and cognition in LBD is important because OH may be a modifiable condition for worse cognition.

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Category: Clinical - Poster Presentation

P.17 Effects of comorbid Alzheimer's disease and Lewy-related pathology on survival and time until severe dementia in neurodegenerative dementia

Author: Ragnhild Eide Skogseth

Additional Authors: 1. Ragnhild Eide Skogseth, Haraldsplass Deaconess Hospital and Department of Clinical Medicine, University of Bergen, Norway.

2. Tibor Hortobagyi; MTA-DE Cerebrovascular and Neurodegenerative Research Group, University of Debrecen, Debrecen, Hungary and Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, Kings College, UK.

3. Arvid Rongve; Department of Research and Innovation, Helse Fonna HF Haugesund Hospital, Old Age Department, Clinic of Psychiatry, Helse-Fonna HF Haugesund Hospital, Haugesund, Norway and Department of Clinical Medicine, University of Bergen, Norway.

4. Luiza Jadwiga Chwiszczuk, Department of Research and Innovation, Helse Fonna HF Haugesund Hospital, Haugesund, Norway, Neurological Department, Clinic of Medicine, Helse-Fonna HF Haugesund Hospital and Department of Clinical Medicine, University of Bergen, Norway.

5. Audun Osland Vik-Mo; Center for Age-Related Diseases (SESAM), Stavanger University Hospital, Norway and Department of Clinical Medicine, University of Bergen, Norway.

6. Dag Aarsland; Center for Age-Related Diseases (SESAM), Stavanger University Hospital, Norway and Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, Kings College, UK.

Effects of comorbid Alzheimer's disease and Lewy-related pathology on survival and time until severe dementia in neurodegenerative dementia

Skogseth RE, Hortobagyi T, Rongve A, Chwiszczuk L, Vik-Mo AO, Aarsland D.

Objectives: To examine the effect of comorbid Alzheimer's disease (AD) and Lewy-related pathology on survival and time to severe dementia in patients with neurodegenerative dementia.

Materials and methods: Patients with mild dementia (Mini-Mental State Examination (MMSE) ≥ 20 and/or Clinical Dementia Rating (CDR) ≤ 1) were followed with annual assessments from diagnosis to death.

Post mortem brain dissection, immunohistochemistry and neuropathological diagnosis were conducted according to the appropriate protocols. Patients with a neuropathological diagnosis of AD or Lewy body dementia (LBD) were included ($n=51$), of these 31 had a pathological diagnosis of AD and 20 LBD (15 DLB and 5 PDD). In the LBD group, 11 patients with severe AD (Braak tau stage V-VI) and diffuse neocortical Lewy-related pathology were classified as mixed AD and LBD, whereas 9 were LBD. Time to reach severe dementia (CDR=3) and to death were recorded. Groups were compared using Chi-Square-, Mann-Whitney U-, the Kruskal-Wallis- and the Log Rank (Mantel-Cox) tests.

Results: There were no significant differences between baseline age, MMSE score, gender, CDR global or CDR sum of boxes between the three groups. 16 patients died before reaching severe dementia.

There were significant differences in survival ($p=0.021$) and duration from baseline to CDR score 3 ($p=0.008$) between groups. Both the LBD group and the mixed AD-LBD group had significantly shorter survival than the AD group, ($p=0.013$ and $p=0.011$ respectively), while there were no differences in survival or time to severe dementia between the LBD and the mixed group.

Discussion: In prospectively followed, newly diagnosed patients, mixed AD-LBD and LBD patients had significantly shorter survival and time to severe dementia compared with AD patients. Thus our findings adds to other evidence of decreased survival and faster progression in LBD. Survival and time to severe dementia were similar in the mixed and LBD group, thus we were not able to replicate previous findings of a poorer prognosis in mixed AD-LBD patients than more pure LBD patients. However, the Kaplan-Meier curve suggest that the mixed group have a faster decline to severe dementia than the LBD group. Due to small sample size, our study was at risk for type II errors. Also, most of the LBD patients had significant AD pathology, 7 of the 9 LBD patients had Braak tau stage IV. In contrast, only 7 of the 31 AD patients had any Lewy-body related pathology, including 3 patients with affection the amygdala only. Most of our LBD patients were DLB, others have found severe AD pathology to be more common in DLB than PDD. In summary; patients with LBD pathology have a poorer prognosis than AD patients, patients with mixed AD/LBD had shorter time to reach severe dementia than the pure LBD group, but the difference did not reach statistical significance.

Category: Clinical - Poster Presentation

P.18 DLB Stupor or (semi-) Coma – Description of three cases of Dementia with Lewy bodies (DLB) showing a protracted period of unresponsiveness

Author: Robert Perry

Additional Authors: Daniel Erskine, Institute of Neuroscience, Newcastle University, UK

Ian McKeith, Institute of Neuroscience, Newcastle University, UK

David Mendelow, Institute of Neuroscience, Newcastle University, UK

Robert Perry, Institute of Neuroscience, Newcastle University, UK

Background

Dementia with Lewy bodies (DLB) is the second most common neurodegenerative disorder, for which one of the core clinical criteria is transient periods of reduced awareness and arousal - termed cognitive fluctuations. Although DLB has been well clinically and neuropathologically characterized, little is known about whether there are clinical or neuropathological sub-types of this disorder. Here we describe three neuropathologically-confirmed DLB cases who exhibited protracted periods of decreased consciousness lasting days or weeks in the terminal phase of their illness.

Methods

We describe clinical and neuropathology findings in three patients who exhibited a state of stupor or coma in the terminal phase of DLB.

Results

Three elderly patients (two with established dementia, and one a history of confusion and cognitive decline) had a prolonged period of decreased consciousness lasting days or weeks (range 7 to 17days). Clinically, the decreased consciousness was sufficient to suggest a state of stupor or coma at or prior to admission and no cases had received neuroleptic therapy. In these three cases dementia/features of DLB had been diagnosed in life in two female patients: AB (66y) & CD (75y). The third case (EF, male 80y) was initially admitted to a peripheral hospital with a suspected head injury following a collapse or fall at home; however It later emerged that confusion and cognitive decline had been noted for a year prior to hospital admission, and he was prone to falls. Referral to a Neurosurgical unit did not reveal neurological or brain imaging features to account for the stupor. Clinically and pathologically these three patients did not show features of illnesses known to cause stupor or coma such as liver failure, diabetes, drug overdose, gross sepsis, seizures, or stroke/brain stem herniation,. After autopsy neuropathological features of DLB were observed in all cases.

Conclusions

The authors acknowledge that clinical observations during the terminal phase of dementia lack the precision of prospective studies. Nevertheless these findings from case-note, ward, & neuropathology observations indicate a potential clinical sub-type of DLB characterized by a state of stupor or coma in at least the terminal phase of the illness. Importantly in such cases, clinical assessment of cognitive and conscious status and the integrity of neurologic brain stem reflexes (supplemented by neuroimaging) may provide mechanistic and therapeutic insights into the disturbances of attention and arousal that are known to occur in approximately 75% of DLB cases.

Category: Clinical - Poster Presentation

P.19 Newcastle Studies in DLB: Identification of the first case in 1980 following Acetylcholinesterase Histochemistry and the demonstration of a Cholinergic Neurotransmitter Deficit

Author: Robert Perry

Additional Authors: Robert Perry, Institute of Neuroscience, Newcastle University, UK

Garry Blessed, Institute of Neuroscience, Newcastle University, UK

Elaine Perry, Institute of Neuroscience, Newcastle University, UK

Andrew Fairbairn, Institute of Neuroscience, Newcastle University, UK

In the 1960s Newcastle research by Blessed, Tomlinson and Roth applied quantitative methods to correlate clinical psychiatric features with brain morphological abnormalities in the elderly.

In 1974 following a Lancet report of a GABA defect in dementia the Newcastle Brain Bank was formed to investigate the neurochemistry of Alzheimer's disease (AD). Within two years Elaine Perry (EP) established a cholinergic neurotransmitter deficit in AD and Robert Perry (RP) introduced acetylcholinesterase (AChE) histochemistry to demonstrate cholinergic histopathology in AD.

In the spring of 1980 AChE histochemistry was used as a faster diagnostic test for AD in the lab. A patient with dementia died, and the brain sampled for both neuro- and histochemistry. Within three days AChE histochemistry showed absent hippocampal reactivity, indicating a cholinergic neurotransmitter deficit. The patient was assumed (RP) to have AD.

Two months later Robert and Dorothy (Dorothy Irvine Laboratory Scientist = LS) assessed the brain microscopic sections. Senile plaques were present in all four cortical lobes (compatible with AD) but neurofibrillary tangles (NFT) were almost entirely restricted to the temporal lobe and hippocampus. In frontal, parietal and occipital lobes NFTs were rare – a feature not typical of AD. In the brain stem mid brain sections showed a further unexpected feature: an intraneuronal Lewy body - the “hallmark” of Parkinson's disease (PD). But Substantia Nigral neurone loss was minimal – so clinical PD was unlikely. Clinical case notes were routinely retained by Neuropathology and when examined (RP) the patient's notes showed several clinical features unusual for AD:

The Mental Test Scores were variable (fluctuating at routine clinic assessments) and contrasted with the inexorable decline characteristic of AD; but the Dementia Score was raised – so dementia was highly likely

Curious episodes of “inaccessibility” were recorded in the notes

Visual hallucinations had been noted on the ward and in outpatients

The case notes recorded no PD features – which were familiar to Brighton Clinic clinicians

The diagnostic AChE histochemical test had apparently failed, and a curious enigma had emerged. It stood out as a solitary “jigsaw” piece but with intriguing neuropathology links to both AD and PD, and also a cholinergic neurotransmitter deficit - previously reported in AD but not in PD. The case didn't fit standard clinical and neuropathology diagnostic “pigeon holes”. RP discussed the details with DI, and classified the case as “Atypical Dementia” - a new diagnostic pigeon hole.

The larger jigsaw picture, incorporating elements of Alzheimer's and Parkinson's disease, with additional diagnostic, treatment, epidemiological, and ageing implications, would emerge in the 1980s decade. The pigeon hole diagnostic category “Atypical Dementia” morphed into SDLT (Senile Dementia of Lewy Body Type) in 1989/90 as distinctions from PD (with and without dementia, both now shown to have a cholinergic deficit), Diffuse Lewy body disease, and AD with “incidental Lewy body disease” were established. In 1992 Garry Blessed retired and Ian McKeith joined the studies; SDLT terminology changed to DLB (Dementia with Lewy bodies) at the first DLB international meeting in Newcastle in 1995.

Category: Clinical - Poster Presentation

P.20 Clinical and Pathologic Correlates of Excessive Daytime Somnolence in the Mild Cognitive Impairment and Dementia Stages of Lewy Body Disease Pathology

Author: Leah Forsberg

Additional Authors: Tanis J. Ferman PhD2, Bradley F. Boeve MD1, Toji Miyagawa MD PhD1, Neill Graff-Radford MD2, David S. Knopman MD1, Jonathan Graff-Radford MD1, Rodolfo Savica MD,1 David T Jones MD1, Daniel A. Drubach MD1, Julie A. Fields PhD1, Mary Machulda PhD1, John Lucas PhD2, Laura Allen APRN CNP,1 Kejal Kantarci MD1, MS, Erik St.Louis MD1, MS, Michael Silber MBChB,1 Melissa E. Murray PhD2, Joseph E. Parisi MD1, Dennis W. Dickson MD2, Ronald C. Petersen MD, PhD1.

1Mayo Clinic, Rochester, MN, USA

2Mayo Clinic, Jacksonville, FL, USA

Background: The clinical and pathologic correlates of excessive daytime somnolence (EDS) in the mild cognitive impairment (MCI) and dementia stages of Lewy body disease are poorly understood. We hypothesized that 1) the frequency and severity of EDS would increase from MCI to dementia, 2) the presence of EDS in MCI would be associated with shorter survival, and 3) EDS would be correlated with the topography of LBD pathology as well as Alzheimer's disease (AD)-associated pathology - Braak neurofibrillary (NFT) stage and neuritic amyloid plaque (NP) density.

Methods: Antemortem data were analyzed from autopsied patients with either limbic-transitional or diffuse-neocortical LBD diagnosed with mild cognitive impairment (MCI) and followed prospectively through the Mayo Alzheimer's Disease Research Center. Clinical and pathologic features were compared based on presence vs absence of EDS as defined by an Epworth Sleepiness Scale (ESS) score ≥ 10 as rated by an informant.

Results: The sample included 54 patients [25 (20 male) transitional, 29 (25 male) diffuse] with at least 1 antemortem ESS score. Comorbid AD pathology was present in 19 (35%; 5 of transitional and 14 of diffuse). At the first MCI evaluation, the mean ESS was 10 ± 5 with 51% having EDS. At the evaluation when dementia was initially diagnosed ($n=50$), the mean ESS was 11 ± 5 with 66% having EDS. At the evaluation closest to death, the mean ESS was 13 with 68% having EDS. The presence of EDS at the diagnosis of MCI had a worse prognosis than those who did not have EDS at the time of diagnosis (5.0 years vs 7.3 years, $p=0.01$). Those with MCI and EDS had more frequent parkinsonism than MCI without EDS (67% vs 26%, $p=0.02$). There were no statistically significant differences in EDS frequency or severity at MCI diagnosis comparing transitional vs diffuse LBD (transitional-neocortical; 61% with EDS vs 45% without EDS, $p=0.91$), neocortical NFT stage (NFT Braak stage 4-6; 34% with EDS vs 36% without EDS, $p=0.30$), or NP density ("moderate" or "frequent" by CERAD semiquantitative assessment of neuritic plaques; 39% with EDS vs 36% without EDS, $p=0.84$).

Discussion:

These findings suggest that EDS is relatively frequent and severe in MCI associated with LBD pathology, and the frequency and severity of EDS increases from MCI to mild dementia to more advanced dementia. The presence of EDS at MCI diagnosis was associated with shorter survival. EDS was also correlated with parkinsonism, but EDS does not appear to be correlated with the topography of LBD pathology, nor with features of comorbid Alzheimer's disease pathology. Further prospective longitudinal research with subjective and objective markers of sleepiness are needed to determine its prognostic implications at presentation in Lewy body diseases.

Category: Clinical - Poster Presentation

P.21 *The Phenomenology of Dementia with Lewy Bodies: A descriptive observational study*

Author: MING ZHANG

Additional Authors: Ming Zhang^{1,2,3}, Lingchuan Xiong^{1,2}, Xin Yu^{1,2}, Huali Wang^{1,2,*}

1. Dementia Care and Research Center, Clinical Research Division, Peking University Institute of Mental Health (Sixth Hospital), No. 51 Huayuanbei Road, Haidian District, Beijing 100191, China.

2. Beijing Dementia Key Lab, National Clinical Research Center for Mental Disorders, NHC Key Laboratory of Mental Health (Peking University), Beijing, China.

3. Department of Psychiatry, the Third Affiliated Hospital of Sun Yat-sen University, No.600 Tianhe Road, Tianhe District, Guangzhou 510000, China

Abstract

Background: Dementia with Lewy Bodies (DLB) is common, but often underdiagnosed and misdiagnosed in clinical practice. The phenomenology may provide clues to aid timely detection and diagnosis in clinical practice. Therefore, we designed the observational study to describe the common symptoms, neuropsychological profiles and imaging presentations in DLB in a memory.

Materials and Methods: From January 2008 to March 2019, forty people meeting with the revised consensus criteria of probable DLB were registered in the memory clinic of Peking University Sixth Hospital. The demographic and clinical presentation were documented with the unified data set. The Mayo Fluctuation Scale (MFS-19) was used to evaluate the fluctuation of the clinical presentations. In addition, the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were used to assess the cognitive function. All participants completed the brain magnetic resonance imaging (MRI) to examine the severity of cerebral atrophy and white matter lesions.

Results: Twenty-six (65.0%) were men and fourteen (35.0%) were women. The average onset age was 70.24 ± 9.09 (38-83) years and the age of the first visit to memory clinic was 76.95 ± 8.16 (52-91) years. The duration from the onset to being diagnosed was 3.75 ± 3.25 (1-15) years. The most common initial symptoms included memory loss (47.5%), delusions (15.0%), rapid eye movement sleep behavior disorder (RBD, 12.5%) and hallucinations (12.5%). During the course of the disease, 25 participants (62.5%) experienced visual hallucinations, 21 (52.5%) with fluctuating cognition, 20 (50.0%) with Parkinson's symptoms, 13 (32.5%) with delusions (e.g., misidentification, paranoid, jealousy, poverty, reference, guilt), 9 (22.5%) with irritability, 7 (17.5%) with RBD, 4 (10.0%) with severe autonomic dysfunction, 2 participants (5.0%) with severe sensitivity to antipsychotic agents, 2 (5.0%) with significant anxiety and depression. The score of MFS-19 averaged 9.00 ± 5.10 (range: 3-21). Concerning the cognitive function, the average global score of MMSE was 17.9 ± 8.3 and MoCA was 13.3 ± 6.1 . Specifically, the visuospatial and executive function scored 2.0 ± 1.4 , abstract thinking ability 0.7 ± 0.8 , and delayed recall was 0.2 ± 0.5 . The global cortical atrophy averaged 1.0 ± 0.7 . The visual rating of the medial temporal lobe atrophy was 1.4 ± 0.8 in left hemisphere and 1.5 ± 0.7 in right hemisphere. The Fazekas score averaged 1.5 ± 0.7 .

Conclusions: Dementia with Lewy bodies is characterized by variable and fluctuating clinical presentations covering cognitive, motor and perceptual function, and preserved brain volume. The clinical phenotype may aid timely diagnosis in clinical settings.

Keywords: Dementia with Lewy bodies; clinical phenotype; observational study

Category: Clinical - Poster Presentation

P.22 *The individual long-term course of neuropsychiatric symptoms in Lewy-body dementia*

Author: Dag Aarsland

Additional Authors: Audun Osland Vik-Mo, Lasse Melvaer Giil, Miguel Borda

Introduction:

Understanding the natural course of Neuropsychiatric symptoms (NPS) in dementia is important for planning patient care and trial design, but few studies have described the long-term course of NPS in individual patients. Here we describe the course of NPS in patients with Lewy-body dementia (LBD) compared to Alzheimer's disease (AD) from time of diagnosis until death.

Methods:

After the primary screening of 667 suspected mild dementia patients from general practice, 223 were included (113 ADs, 86 LBDs) and followed annually with the Neuropsychiatric Inventory (NPI) for up to 12 years. NPS were classified as persistent, re-occurring, or single episode.

Results:

Nearly all patients had NPS, which were mostly relapsing or single episodic. DLB patients had more often mild and moderate NPS, but rarely severe and persistent high NPI total score. 84% of LBD and 57 % of AD patients had re-occurring psychotic symptoms. Hallucinations were more frequent and persistent in LBD, while aggression were more persistent in AD ($p<0.05$). Forty-seven (55 %) of LBD patients had delusions, usually single episodes (24 patients) while re-occurrence was less common (7 patients). Similarly, affective symptoms were usually single episode in LBD. Anxiety, irritability and aberrant motor behaviour were more stable in AD than LBD.

Conclusion:

NPS have highly individual course in LBD and AD. Most patients have single episodes or relapsing course, while persistent NPS was rare. These findings demonstrate the need for individualized approach towards managing NPS in LBD, with relevance also for clinical trial design.

Category: Clinical - Poster Presentation

P.23 *Greater variability in cognitive decline in Lewy body dementia compared to Alzheimer's disease*

Author: Dag Aarsland

Additional Authors: Lasse Melvaer Giila, Arvid Rongveb,

a) Department of Internal Medicine, Haraldsplass Deaconess Hospital, Bergen, Norway.

b) Haugesund Hospital, Haugesund, Norway

Background

Studies indicate a higher annual decline in cognitive test performance in patients with Lewy Body Dementia (LBD) compared to Alzheimer's disease (AD). However, there are indications that the inter-individual variation is particularly high in LBD but there are few systematic studies of the variability of cognitive decline.

Methods

We assessed Mini-Mental State (MMSE) test performance in 222 patients with mild dementia in the DemVest study who had either AD (137) or LBD (85) and had been followed over 5 years with annual assessments. We first assessed a homoscedastic random coefficient model. We compared this to an identical heteroscedastic random coefficient model, but where intercepts and slopes varied according to diagnosis.

Results

The heteroscedastic model had lower Bayesian (-9.6) and Akaike Information Criteria (-24.3) and a significant Likelihood ratio test of the nested models ($X^2 = 30.3$, $p < 0.001$). The MMSE intercept variance, slope variance and intercept-slope covariance were all higher in LBD than in AD patients, indicating a greater variability in rate of cognitive decline in LBD.

Conclusions

Patients with LBD have a higher variability in MMSE decline compared to AD, with some having a slow rate of decline whereas others have a very high rate of cognitive decline. Identifying mechanisms and predictors of DLB patients with rapid cognitive decline is a future research priority.

Category: Clinical - Poster Presentation

P.24 Primary manifestations of autopsy-confirmed DLB patients in psychiatric hospitals

Author: Hiroshige Fujishiro

Additional Authors: 1,2,3Hiroshige Fujishiro, MD, PhD, 1,4Hirotaka Sekiguchi, MD, PhD, 1,3Youta Torii, MD, PhD, 1,5Chikako Habuchi, MD, PhD, 5Aizawa Tasuku, MD, 1,6Mitsuaki Hirano, MD, 3Ayako Miwa, MD, 1Norio Ozaki, MD, PhD, 6Mari Yoshida, MD, PhD, and 1,3,4Shuji Iritani, MD, PhD

1Departments of Psychiatry, Graduate School of Medicine, Nagoya University, Nagoya, Japan

2Departments of Psychiatry, Kawasaki Memorial Hospital, Kawasaki, Japan

3Departments of Psychiatry, Moriyama Integrated Mental Care Hospital, Nagoya, Japan

4Department of Psychiatry, Okehazama Hospital Fujita Mental Care Center, Toyoake, Japan

5Department of Psychiatry, Aichi Psychiatric Medical Center, Nagoya, Japan

6Institute for Medical Science of Ageing, Aichi Medical University, Nagakute, Japan

Correspondence: Dr Hiroshige Fujishiro MD PhD, Department of Psychiatry, Kawasaki Memorial Hospital, 20-1 Shiomidai, Miyamae, Kawasaki, Kanagawa 216-0013 Japan.

Introduction: Dementia with Lewy bodies (DLB) is the second most common neurodegenerative dementing disorder after Alzheimer's disease (AD). Although there is limited information regarding the prodromal manifestation of DLB, there are considered to be several prototypical forms, including a mild cognitive impairment (MCI) onset, a delirium onset, and a psychiatric onset. Previous studies identified the clinical characteristics of MCI in the prodromal DLB state. Recent studies have reported that delirium precedes the onset of cognitive decline in a subset of patients with DLB. Moreover, although DLB patients with a psychiatric onset are described in many clinicopathological studies, the characteristics of their primary presentation are not widely recognized. The aim of this study is to investigate the primary manifestation of pathologically confirmed DLB patients who were admitted to psychiatric hospitals and underwent autopsy.

Materials and Methods: We retrospectively reviewed the clinical charts of 42 consecutive patients who first visited a psychiatric outpatient service at the age of 50 years and older, and underwent autopsy at psychiatric hospitals. All patients had standardized pathological evaluations.

Results: Fourteen patients were pathologically defined as having Lewy body disease (LBD) subtypes. Two patients with diffuse neocortical LBD and four patients with transitional LBD corresponded to the high-likelihood DLB category based on the pathological criteria of the fourth consensus report of the DLB Consortium. One patient with transitional LBD corresponded to the intermediate-likelihood DLB category. One with brainstem-predominant LBD and six patients with amygdala-predominant LBD corresponded to the low-likelihood DLB category. In the context of pathologically advanced AD in the high-likelihood AD category, all patients with amygdala-predominant LBD were identified as previously reported. Although six with amygdala predominant LBD did not exhibit overt neuronal loss in the substantia nigra, the degree of loss varied from mild to severe in the other LBD subtypes. The presence or absence of parkinsonism broadly corresponded to the degree of nigra degeneration. In terms of primary manifestation, the seven high- or intermediate-likelihood DLB category patients were classified as follows: 3 MCI onset, 2 delirium onset, and 2 psychiatric onset. In contrast, all patients with amygdala-predominant LBD in the low-likelihood DLB category were classified as MCI onset. All but two of these patients had progressive cognitive decline, and one patient developed overt parkinsonism in the early stage.

Discussion: In this autopsy series, the delirium onset and psychiatric onset subtypes were not uncommon in high- or intermediate-likelihood DLB category. Considering that preceding REM sleep behavior disorder (RBD) symptoms might be underestimated in the retrospective survey, the prodromal presentation of one patient with a delirium onset suggests RBD episodes. Two patients exhibited psychotic symptoms in their fifties as primary manifestations. Their psychotic symptoms without overt cognitive decline continued for a long time. Further clinicopathological studies in psychiatric populations are needed to identify the clinical characteristics of the delirium onset and psychiatric onset subtypes in the early stage.

P.25 *The majority of NACC subjects with nonamnesic MCI progress to Alzheimer's disease*

Author: Debby Tsuang

Additional Authors: Debby Tsuang, MD, MSc Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA; GRECC, VA Puget Sound, Seattle, WA

Jane Shofer, MSc. Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA; GRECC, VA Puget Sound, Seattle, WA

Ge Li, MD, PhD. Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA; GRECC, VA Puget Sound, Seattle, WA

Introduction: Dementia with Lewy bodies (DLB) is difficult to diagnose early in its disease course due to the overlap in initial symptoms with Alzheimer's disease (AD) and psychiatric disorders. Moreover, the three biomarker tests in the consensus diagnostic criteria for DLB require radioligand imaging and sleep laboratory assessments that are primarily limited to specialty-care centers. Many individuals with DLB therefore experience long delays before receiving a diagnosis or intervention. Some investigators have suggested that the presence of nonamnesic mild cognitive impairment (MCI) rather than amnesic MCI may be helpful in identifying prodromal DLB. However, few studies have been conducted to directly compare conversion rates to DLB among patients with based on MCI subtypes alone.

Methods: This study sought to compare conversion rates to dementia in subjects with MCI from the National Institute on Aging funded Alzheimer's Disease Centers (ADCs) of the National Alzheimer's Coordinating Center (NACC). We selected 1299 subjects with MCI at baseline with at least three assessments. Conversion rates were evaluated for a range of 1 to 11 years following the baseline appointment.

Results: We found that after a median 2 years of follow-up (interquartile range 1-3 yrs), 78% of MCI subjects in the NACC (n=1,011) converted to some form of dementia with no significant difference in time to diagnosis by dementia subtype (DLB, AD or mixed etiology, two sample t-test, p=.59). Of the subjects who converted to dementia, 90 had nonamnesic MCI at the baseline assessment (9%), and 921 had amnesic MCI at the baseline assessment (91%). As expected, subjects with nonamnesic MCI were more likely to convert to DLB (n=15; 12%) than subjects with amnesic MCI (n=35; 3%), and subjects with amnesic MCI were more likely to convert to AD (n=830; 70%) than subjects with nonamnesic MCI (n=65; 53%; overall chi square = 33.3, p < 0.00001, see Table 1). However, it was unexpected that over half of the nonamnesic MCI subjects would convert to AD. At baseline, 20 of the subjects with nonamnesic MCI also demonstrated the presence of parkinsonism, as defined by a Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale score of > 10, or hallucinations, which are two of the core features of the consensus diagnosis of DLB. Of these 20 nonamnesic MCI subjects, 6 converted to LBD (30%).

Discussion: It is important to identify clinical indicators of prodromal DLB that do not require assessments at specialty-care centers. However, our analysis found that, contrary to our expectations, the majority of nonamnesic MCI subjects converted to AD. This suggests that the diagnosis of nonamnesic MCI alone is not a good indicator of prodromal DLB. However, given that AD specialty centers recruit mainly subjects with memory impairment, these findings do not generalize to subjects who are evaluated at movement disorders centers. The assessment of other core DLB features (e.g., parkinsonism and hallucinations) may increase the likelihood that nonamnesic MCI will progress to DLB, but further improvement in the diagnostic criteria for prodromal DLB is necessary.

Category: Clinical - Poster Presentation

P.26 Trajectories of cognitive and functional decline in Parkinson's disease

Author: Jennifer Goldman

Additional Authors: Jennifer G. Goldman, MD, MS, Shirley Ryan Abilitylab and Departments of Physical Medicine and Neurology, Northwestern University Feinberg School of Medicine

Doug Merkitch, BA, Shirley Ryan Abilitylab

Bryan Bernard, PhD, Department of Neurological Sciences, Rush University Medical Center

Alice Negron, Department of Neurological Sciences, Rush University Medical Center

Glenn Stebbins, PhD, Department of Neurological Sciences, Rush University Medical Center

Objective: To examine cognitive and functional decline in Parkinson's disease (PD)

Background: Cognitive impairment in PD as manifested by mild cognitive impairment (PD-MCI) or dementia (PDD) remains frequent and disabling complication in the disease. The stability of cognitive status vs. progression to PD-MCI or PDD is not fully elucidated, and markers of progression would facilitate earlier identification and treatments. Moreover, diagnosing PDD depends on functional decline, though this remains controversial in PD-MCI and challenging in PD.

Methods: We conducted clinical and comprehensive neuropsychological evaluations in a 3-year longitudinal study of PD participants (Time1, n=51; Time 2, n=47; Time 3, n=31). We examined change in cognitive and functional abilities over time comparing non-demented cognitively "stable" (no change PD normal cognition, PD-NC or PD-MCI), "converters" (decline to PD-MCI or PDD), and "stable PDD."

Assessments included global cognitive tests (MMSE, MoCA), Clinical Dementia Rating scale (CDR) Sum of Boxes (SOB) and Global score), and functional measures (FAQ, PDAQ, PD-CFRS, ADCS-ADL).

Baseline measures were compared using ANOVAs. Repeated measures ANOVA was used for group comparisons over time, with Scheffe for multiple comparisons.

Results: Baseline cohort included 23 PD-NC, 16 PD-MCI, and 12 PDD (mean disease duration 12y, education 16y), with significant differences in age ($p=0.021$) and cognitive, functional, and motor scores ($p's < 0.0005$), but not levodopa equivalents or PD years). Over time, 22 remained non-demented stable, 7 converted, and 6 were stable PDD. There were significant overall effects for global cognitive measures, CDR-SOB, and CDR-Global over time (Hotelling's trace max $F=9.35$, CDR-SOB); post-hoc analyses indicated significant differences between non-demented stable and converters vs. stable PDD, but not between non-demented stable and converters. Functional measures showed overall significance for change across time, with significant post-hoc's between non-demented stable vs. converters and stable PDD, and converters vs. stable PDD.

Conclusion: Global cognitive measures in our PD cohort lacked significant change over time between non-demented stable and converters, whereas in contrast, the functional measures were more sensitive to change over time. Greater decline occurred between time points 2 and 3.

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Poster Presentations

Section: Genetics & Epidemiology

Category: Genetics - Poster Presentation

P.27 APOE, GBA and three potential novel genetic loci associate with dementia with Lewy-bodies in a genome-wide association

Author: Inger van Steenoven

Additional Authors: Inger van Steenoven¹, Sven J. van der Lee^{1,2}, Marleen van de Beek¹, Niccolo Tesi^{1,2}, Iris Jansen^{1,3}, Natasja M. van Schoor⁴, Marcel J.T. Reinders⁵, Martijn A. Huisman^{4,6}, Philip Scheltens¹, Charlotte E. Teunissen⁷, Henne Holstege^{1,2}, Wiesje M. van der Flier^{1,4}, Afina W. Lemstra¹.

Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands.

Department of Clinical Genetics, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands.

Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije University, Amsterdam, The Netherlands.

Department of Epidemiology and Biostatistics, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, the Netherlands.

Pattern Recognition & Bioinformatics, Delft University of Technology, Delft, The Netherlands.

Department of Sociology, VU University, Amsterdam, the Netherlands.

Neurochemistry Laboratory and Biobank, Department of Clinical Chemistry, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

Introduction

Dementia with Lewy bodies (DLB) is the second most common form of dementia in elderly people. Large-scale genetic study of dementia with Lewy bodies have begun to dissect the genetics underlying this disease. Here, we performed a genome-wide association study with the aim of identifying novel genetic risk factors for DLB in the Dutch population.

Methods

We collected 189 patients (age = 69.4±7 years) with probable DLB from the Amsterdam Dementia cohort (ADC). Diagnostic workup included physical and neurological examinations, neuropsychological examination, MRI, EEG, and laboratory tests for all patients and an 123I-FP-CIT SPECT scan was performed in 46% of the DLB patients (90% rated as abnormal). We compared the patients with 2572 controls (age = 62.1±7.9 years). All samples were genotyped on the Illumina Genome Screening Array (GSA) 24v1-0_A1. We performed standard quality control and imputed to the Haplotype reference consortium reference panel. We fitted logistic regression models adjusting for population stratification (principal components 1-5) and excluded variants with a low imputation quality ($R^2 < 0.5$), minor allele frequency (MAF) < 0.005 and extreme effect estimates ($-3 > \beta > 3$). In total 8725291 variants were analyzed. Of the DLB patients with CSF (N=150), 33% have abnormal cerebrospinal fluid (CSF) biomarkers compatible with Alzheimer's disease (AD) (CSF Tau/Amyloid- β 1-42 > 0.52). For significant variants ($P < 5 \times 10^{-10}$) we explored if the variants were associated with an AD CSF profile.

Results

We found genome-wide significant associations in five different loci (Table 1, Figure 1). No genomic inflation was observed (Figure 2). The most significant variant was in Apolipoprotein E (APOE), associated with a 2.6-times increased risk of DLB ($P = 4.2 \times 10^{-16}$). Followed by an exonic variant (p.E365K) in the beta-glucocerebrosidase (GBA) gene associated with a 4.4-times increased risk of DLB ($P = 1.8 \times 10^{-13}$). We further found rare variants in three loci to associate with increased risk of DLB; variants in 3q28 ($OR = 8.9$, $P = 8.6 \times 10^{-9}$), in the locus 11q14.1 ($OR = 7.3$, $P = 4.2 \times 10^{-8}$) and an intronic variant in the gene Tau Tubulin Kinase 2 (TTBK2) ($OR = 5.4$, $P = 1.0 \times 10^{-8}$). APOE associated stronger with DLB patients with an AD CSF profile ($OR = 4.3$, $P = 1.7 \times 10^{-12}$) than with DLB patients with a normal CSF profile ($OR = 1.9$, $P = 1.6 \times 10^{-4}$). GBA only associated with DLB patients with a normal CSF profile ($OR = 7.6$, $P = 2.9 \times 10^{-19}$) and not with DLB patients with an AD CSF profile ($OR = 1.3$, $P = 0.63$).

Conclusions

We replicated the association of genetic variants in APOE and GBA with DLB and identified three novel variants associated with an increased risk of DLB. The novel variants will require replication in independent datasets. APOE is a major risk factor for DLB patients with concomitant AD pathology, whereas GBA is only a major risk factor for 'pure' DLB.

Category: Genetics - Poster Presentation

P.28 Polygenic risk scores from Alzheimer's disease and Parkinson's disease applied on Dementia with Lewy bodies

Author: Arvid Rongve

Additional Authors: Lene Pålhaugen, Department of Neurology, Akershus University Hospital, Lørenskog, Norway

Francesco Bettella, NORMENT, Oslo University Hospital, Oslo, Norway

Aree Witoelar, NORMENT, Oslo University Hospital, Oslo, Norway

Lavinia Athanasiu, NORMENT, Oslo University Hospital, Oslo, Norway

Tormod Fladby, Department of Neurology, Akershus University Hospital, Lørenskog, Norway and Institute of Clinical Medicine, Campus Ahus, University of Oslo, Oslo, Norway

Dag Aarsland, Stavanger University Hospital Norway and Kings College London, UK.

Ole A Andreassen, NORMENT, Oslo University Hospital, Oslo, Norway

On behalf of the DemGene and the APGem Networks, the DDI-study and the E-DLB Consortium.

Background

Dementia with Lewy bodies (DLB) is prevalent and with rapid progression and no effective treatment available. DLB overlaps both clinically and pathologically with Alzheimer's disease (AD) and Parkinson's disease (PD). Genetically DLB is associated to variants in APOE ϵ 4, GBA and SNCA. In a previous study, DLB was found to overlap genetically with both AD and PD [1].

Methods

We calculated polygenic risk scores (PGRS) from IGAP for AD [2] and from the International PD genetics consortium for PD [3]. We applied the scores on genotyped cases diagnosed with DLB from the Dementia Genetics Network in Norway and the European DLB Consortium (E-DLB). Polygenic risk scores (PGRS) were computed for PD (PD-PGRS) and AD with (AD-PGRSw/APOE) and without APOE (AD-PGRSwo/APOE) based on summary statistics from the respective GWAS studies for a set of p-values. The PD-PGRS score that performed best in logistic regression of PD (n=626) vs controls (n=6429) was for p=5.0 E-08, and the best AD-PGRSw/APOE in logistic regression of AD (n=1537) vs controls was for p=0.01. These scores were used in further analyses. PGRS scores were z-transformed based on means and standard deviations in the control group. Logistic regression models were used with DLB (n=394) vs. controls, AD vs. controls and DLB vs. AD as dependent variables and the PGRS scores as independent variables.

Results

The AD-PGRSw/APOE, PD-PGRS and AD-PGRSwo/APOE were all significantly associated with the diagnosis of DLB, with OR 1.373 (p<0.001), 1.149 (p=0.011) and 1.120 (p=0.029), respectively. Both the PD-PGRS and the AD-PGRSw/APOE were also significantly different between DLB and AD, with OR 0.835 (p=0.001) and 1.353 (p<0.001), respectively.

Conclusion

These findings indicate some common genetic contributions to the pathogenesis of DLB with both AD and PD. We will further explore genetic overlap applying LD score regression analysis for presentation at the conference.

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Category: Genetics - Poster Presentation

P.29 *The genetic heritability of dementia with Lewy bodies*

Author: Jose Bras

Additional Authors: First name Last name Institution

Rita Guerreiro Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, Michigan, USA

Valentina Escott-Price MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK

Celia Kun-Rodrigues Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, Michigan, USA

Owen A. Ross Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

Susana Carmona Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, Michigan, USA

Nadia Deghani Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, Michigan, USA

John D. Eicher Genetics and Pharmacogenomics, Merck Research Laboratories, Boston, MA, USA

Claire Shepherd Neuroscience Research Australia, Sydney, Australia and School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia

Laura Parkkinen Nuffield Department of Clinical Neurosciences, Oxford Parkinsons Disease Centre, Oxford, UK

Michael G. Heckman Division of Biomedical Statistics and Informatics, Mayo Clinic, Jacksonville, FL, USA

Sonja W. Scholz Neurodegenerative Diseases Research Unit, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, Maryland, USA

Juan C. Troncoso Department of Pathology (Neuropathology), Johns Hopkins University School of Medicine, Baltimore, MD, USA

Olga Pletnikova Department of Pathology (Neuropathology), Johns Hopkins University School of Medicine, Baltimore, MD, USA

Ted Dawson Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA

Liana Rosenthal Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD, USA

Olaf Ansorge Nuffield Department of Clinical Neurosciences, Oxford Parkinsons Disease Centre, Oxford, UK

Jordi Clarimon Memory Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Alberto Lleó Memory Unit, Department of Neurology, IIB Sant Pau, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Lorraine Clark Taub Institute for Alzheimer Disease and the Aging Brain and Department of Pathology and Cell Biology, Columbia University, New York, NY, USA

Lawrence S Honig Taub Institute for Alzheimer Disease and the Aging Brain and Department of Pathology and Cell Biology, Columbia University, New York, NY, USA

Karen Marder Taub Institute for Alzheimer Disease and the Aging Brain and Department of Pathology and Cell Biology, Columbia University, New York, NY, USA

Afina Lemstra Department of Neurology and Alzheimer Center, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, the Netherlands

Ekaterina Rogaeva Tanz Centre for Research in Neurodegenerative Diseases and department of Medicine, University of Toronto, Ontario, Canada

Peter St. George-Hyslop Tanz Centre for Research in Neurodegenerative Diseases and department of Medicine, University of Toronto, Ontario, Canada

Elisabet Londos Clinical Memory Research Unit, Institution of Clinical Sciences Malmö, Lund University, Sweden

Henrik Zetterberg UK DRI, London UK, UCL, London, UK and Clinical Neurochemistry Laboratory, University of Gothenburg, Mölndal, Sweden

Kevin Morgan Human Genetics, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, UK

Claire Troakes Department of Basic and Clinical Neuroscience and Institute of Psychiatry, Kings College London, London, UK

Safa Al-Sarraj Department of Basic and Clinical Neuroscience and Institute of Psychiatry, Kings College London, London, UK

Tammarn Lashley Queen Square Brain Bank, UCL, London, UK

Janice Holton Queen Square Brain Bank, UCL, London, UK

Yaroslau Compta Queen Square Brain Bank, UCL, London, UK

Vivianna Van Deerlin Department of Pathology and Laboratory Medicine, Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, USA

Geidy E Serrano Banner Sun Health Research Institute, 10515 W Santa Fe Drive, Sun City, AZ 85351, USA

Thomas G Beach Banner Sun Health Research Institute, 10515 W Santa Fe Drive, Sun City, AZ 85351, USA

Suzanne Lesage Inserm U1127, CNRS UMR7225, Sorbonne Universites, UPMC Univ Paris 06, UMR and S1127, Institut du Cerveau et de la Moelle epiniere, Paris, France

Douglas Galasko Department of Neurosciences, University of California, San Diego, La Jolla, CA, United States; Veterans Affairs San Diego Healthcare System, La Jolla, CA, United States

Eliezer Masliah Department of Neurosciences, University of California, San Diego, La Jolla, CA, United States; Department of Pathology, University of California, San Diego, La Jolla, CA, United States

Isabel Santana Neurology Service, University of Coimbra Hospital, Coimbra, Portugal

Pau Pastor Memory Unit, Department of Neurology, University Hospital Mutua de Terrassa, University of Barcelona, and Fundacio de Docencia I Recerca Mutua de Terrassa, Terrassa, Barcelona, Spain. Centro de Investigacion Biomedica en Red Enfermedades Neurdegenerativas (CIBERNED), Madrid, Spain

Pentti J. Tienari Molecular Neurology, Research Programs Unit, University of Helsinki, Department of Neurology, Helsinki University Hospital, Helsinki, Finland

Liisa Myllykangas Department of Pathology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Minna Oinas Department of Neuropathology and Neurosurgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

Tamas Revesz Queen Square Brain Bank, UCL, London, UK

Andrew Lees Queen Square Brain Bank, UCL, London, UK

Brad F Boeve Neurology Department, Mayo Clinic, Rochester, MN, USA

Ronald C. Petersen Neurology Department, Mayo Clinic, Rochester, MN, USA

Tanis J Ferman Department of Psychiatry and Department of Psychology, Mayo Clinic, Jacksonville, FL, USA

Neill Graff-Radford Department of Neurology, Mayo Clinic, Jacksonville, FL, USA

Nigel J. Cairns Knight Alzheimers Disease Research Center, Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA

John C. Morris Knight Alzheimers Disease Research Center, Department of Neurology, Washington University School of Medicine, Saint Louis, MO, USA

Stuart Pickering-Brown Institute of Brain, Behaviour and Mental Health, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK

Glenda M. Halliday Neuroscience Research Australia, Sydney, Australia and School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sydney, Australia

John Hardy Department of Neurodegenerative Diseases, UCL, London, UK

John Q. Trojanowski Department of Pathology and Laboratory Medicine, Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, USA

Dennis W. Dickson Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA

Andrew Singleton Laboratory of Neurogenetics, National Institutes on Aging, NIH, Bethesda, MD, USA

David J. Stone Genetics and Pharmacogenomics, Merck Research Laboratories, West Point, Pennsylvania, USA

Jose Bras Center for Neurodegenerative Science, Van Andel Research Instiute, Grand Rapids, Michigan, USA

Background: To overcome the fact that a substantial portion of the genetic heritable component of complex traits is not captured by genome-wide significant SNPs, we have estimated the proportion of phenotypic variance explained by genetic variability (SNP heritability) in dementia with Lewy bodies (DLB) using a method that is unbiased by allele frequency or linkage disequilibrium properties of the underlying variants. We also aimed to determine the proportion of variance explained by PRSs from Parkinson's (PD) and Alzheimer's disease (AD) in DLB.

Methods: we applied the GCTA-LDMS method to estimate heritability based on imputed data. Additionally, we used PRSice to calculate the polygenic risk scores on base phenotypes (PD and AD), and used these as predictors of the target phenotype (DLB) in a regression test.

Results: These data show that the heritability of DLB is nearly twice as high as previous estimates based on common variants only (31% vs 59.9%). We also determine the amount of phenotypic variance in DLB that can be explained by recent polygenic risk scores from either Parkinson's disease (PD) or Alzheimer's disease (AD), and show that, despite being highly significant, they explain a low amount of variance.

Conclusion: Our data suggests that novel genetic risk factors for DLB should be identified by larger GWAS and these are likely to be independent from known AD and PD risk variants.

Category: Genetics - Poster Presentation

P.30 Latin American and Caribbean Consortium on dementia (LAC-CD): Towards a common voice across the region

Author: Ignacio Fernandez Mata

Additional Authors: Ignacio F. Mata a, Agustin Ibanez b,c,d,e,f Mario A Parra e,g, on behalf of the Latin American and Caribbean Consortium on dementia (LAC-CD).

a. Department of Genomic Medicine, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, USA

b. Institute of Cognitive and Translational Neuroscience (INCYT), INECO Foundation, Favaloro University, Buenos Aires, Argentina.

c. National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina.

d. Center for Social and Cognitive Neuroscience (CSCN), Universidad Adolfo Ibáñez, Santiago, Chile.

e. Universidad Autónoma del Caribe, Barranquilla, Colombia.

f. Australian Research Council (ACR) Centre of Excellence in Cognition and its Disorders, Sydney, New South Wales, Australia

g. Psychology Department. School of Psychological Sciences & Health, University of Strathclyde, Glasgow, UK

Dementia poses manifold challenges for Latin American and Caribbean countries (LAC). Critical and unique challenges in the region include heterogeneity, diversity, genetic isolates, insufficient governmental support, environmental factors, lack of non-pharmacological interventions, and absence of a regional clinical trial program, among others. This complex scenario prompted the establishment of the Latin American and Caribbean Consortium on Dementia (LAC-CD). The LAC-CD involved +130 member across 18 countries and proposes a framework to implement specific actions identified as priorities in the context of global and rapidly changing dementia challenges. We operationalized these key actions and aligned them to global strategies, including a biomarker framework, a genetics and epidemiology workgroup, a dementia platform, a clinical trial program, non-pharmacological interventions and a LAC network for translational research. Our short and long-term goals are 1) to promote a regional dementia culture in each LAC country (creating key alliances, increasing communication among regional dementia leaders and providing quality training, etc.), 2) characterized dementia and related disorders in LAC countries and investigate the specific risk factors affecting incidence, age at onset, etc., 3) improve health systems increasing support for patients and caregivers and using new technologies such as telemedicine, 4) seek and secure governmental support and oversee their implementation of dementia plans, 5) The development of strategies for the generation, characterization and distribution of animal models and for funding brain bank platforms for dementia research, and creating platforms for sharing all these resources and 6) The development of valid and affordable biomarkers based on cognitive assessment, eye-tracking, noninvasive peripheral markers and neuroimaging (EEG and multiple MRI modalities) combined with machine- and deep-learning algorithms. Efforts carried out by the LAC-CD into a comprehensive, integrative, and harmonized framework can transform barriers into unprecedented opportunities for LAC.

Category: Genetics & Epidemiology - Poster Presentation

P.31 Survival time and differences between dementia with Lewy bodies and Alzheimer's disease following diagnosis: A meta-analysis of longitudinal studies

Author: Christoph Mueller

Additional Authors: Christoph Mueller, King's College London, London, UK

Pinar Soysal, Bezmialem Vakif University, Istanbul, Turkey

Arvid Rongve, University of Bergen, Bergen, Norway

Robert Stewart, King's College London, London, UK

Clive Ballard, University of Exeter Medical School, Exeter, UK

John T. O'Brien, University of Cambridge, Cambridge, UK

Dag Aarsland, King's College London, London, UK

Brendon Stubbs, King's College London, London, UK

Nicola Veronese, National Research Council, Padova, Italy

Background: Survival in dementia with Lewy bodies (DLB) has been a matter of considerable clinical and academic debate. Greater awareness among clinicians, further revisions of the diagnostic criteria, the inclusion of DLB in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, and the increased use of naturalistic data from electronic health records has led to an expanding number of publications on survival in DLB. The majority of observational studies, but not all, report shorter survival in DLB than Alzheimer's disease (AD). Aim of this study was to synthesize the evidence available from longitudinal studies investigating survival in DLB and compare findings to AD.

Methods: We conducted a systematic review and meta-analysis of studies comparing survival in clinically diagnosed dementia with Lewy bodies (DLB) to Alzheimer's disease. Longitudinal cohort studies were identified through a systematic search of major electronic databases from inception to May 2018. A random effects meta-analysis was performed to calculate survival time and relative risk of death.

Results: Overall, 11 studies were identified meeting the inclusion criteria including 22,952 patients with dementia: 2,029 with DLB (mean diagnosis age 76.3; 47% female) compared with 20,923 with AD (mean diagnosis age 77.2; 65.1% female). Average survival time in DLB from diagnosis was 4.11 years (SD ± 4.10) and in AD 5.66 (SD ± 5.32) years, equating to a 1.60 (95% CI: -2.44 to -0.77 years) shorter in DLB ($p < 0.01$). Relative risk of death was increased to 1.35 in DLB compared to AD ($p < 0.01$). Differences in survival were not explained by follow-up time, age at diagnosis, gender, or cognitive score.

Conclusions: There is consistent evidence that DLB has higher and earlier mortality than AD, which is important for all stakeholders. Future research should focus on modifiable risk factors which could prolong survival in this condition.

Category: Genetics & Epidemiology - Poster Presentation

P.32 Determining the predictors and outcomes of people with Dementia with Lewy Bodies (DLB) using the CPFT Research Database (CRATE) to improve diagnosis and management: The Lewy-CRATE Study

Author: Sinéad Moylett

Additional Authors: Sinéad Moylett^{1,2}, Annabel Price^{1,2}, Rudolf N Cardinal^{1,2}, and John T O'Brien^{1,2}

¹Department of Psychiatry, University of Cambridge School of Clinical Medicine, Level E4, Cambridge Biomedical Campus, Cambridge, CB2 0SP

²Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK

Determining the predictors and outcomes of people with Dementia with Lewy Bodies (DLB) using the CPFT Research Database (CRATE) to improve diagnosis and management: The Lewy-CRATE Study

Introduction: Despite being the second most common degenerative dementia in older people, rates of misdiagnosis for Dementia with Lewy bodies (DLB) are high, and little is known of its natural history and outcomes. Very few previous studies have been able to access routine clinical information for large, unbiased DLB cohorts in order to examine presentation, neuropsychological profile and mortality in depth.

Materials and methods: Using the Cambridgeshire and Peterborough NHS Foundation Trust (CPFT) Research Database (CRATE), a de-identified copy of electronic clinical records, the Lewy-CRATE project is identifying a cohort of ~700 DLB cases and several thousand non-DLB disease dementia controls to allow a detailed examination of their predictors, symptoms and outcomes. We aim also to link to UK national hospital episode databases to incorporate predictors and outcomes relating to acute healthcare. We have already identified a DLB cohort (N = 251) diagnosed between 2005 and 2012 and we are currently in the process of extending this cohort to include diagnoses between 2012 and 2018. We will include a large comparator cohort of several thousand non-DLB disease dementia controls.

Results: In a comparison of 251 DLB individuals to 222 individuals with Alzheimer's Disease (AD), we have found that survival times following diagnosis among individuals with DLB are markedly shorter (by 3 years on average) than in AD individuals, and that individuals with DLB present to NHS care settings with a range of complaints, including memory loss, hallucinations and low mood. Rates of REM sleep disorder among our cohort were considerably lower (8.4%) than would be expected. Among the DLB cohort deficits in non-amnesic cognitive domains were associated with reduced mortality compared to amnesic-only presentations. Further planned analyses will examine initial presentation, disease progression and outcomes from a larger cohort, representing one of the largest DLB cohorts drawn in unbiased fashion from a secondary care setting.

Conclusions: Individuals diagnosed with DLB have markedly shorter survival times compared to AD and present initially to secondary care settings with a wide range of symptoms and complaints, some of which are not immediately suggestive of a DLB diagnosis. Further examinations of large, unbiased cohorts such as this are needed to further elucidate the complex presentation and clinical course of DLB.

P.33 *Linking electronic dementia care records to national inpatient data in Dementia with Lewy bodies: Frequency, duration and cost implications of hospitalization and recording of delirium episodes*

Author: Christoph Mueller

Additional Authors: Christoph Mueller, King's College London, London, United Kingdom

James M. FitzGerald, University of Cambridge, Cambridge, United Kingdom

Gayan Perera, King's College London, London, United Kingdom

Anto P. Rajkumar, King's College London, London, United Kingdom

Annabel Price, University of Cambridge, Cambridge, United Kingdom

John T. O'Brien, University of Cambridge, Cambridge, United Kingdom

Clive Ballard, University of Exeter Medical School, Exeter, United Kingdom

Robert Stewart, King's College London, London, United Kingdom

Dag Aarsland, King's College London, London, United Kingdom

Background: Increased hospitalization is a major component of dementia impact on individuals and cost but has rarely been studied in dementia with Lewy bodies (DLB). In particular episodes of delirium and related hospitalizations have been described as a prodrome of dementia with Lewy bodies. Our aims were to harness a novel linkage between dementia/mental health care records and national hospitalization data in England to (1) describe risk and duration of hospital admissions in patients with DLB and (2) to assess the incidence of delirium recording before and after a diagnosis of dementia is established in patients with DLB and compare findings to a matched cohort of patients with Alzheimer's disease (AD).

Methods: A large database of mental health and dementia care in South London, linked to hospitalization mortality data, was used to assemble a cohort of patients diagnosed with DLB. We identified 194 patients with DLB and 1:4 matched these with 776 patients diagnosed with AD on age, gender, and cognitive status.

Results: Rates of hospital admissions in the year after dementia diagnosis were significantly higher in patients with DLB compared to patients with AD (crude incidence rate ratio 1.50; 95% CI: 1.28-1.75) or the catchment population (indirectly standardised hospitalization rate 1.22; 95% CI: 1.06-1.39). Patients with DLB had on average almost four additional hospital days per person-year than patients with AD and incurred higher hospitalization-related costs (\$3,692 vs. \$3,128 per year). Multivariate Poisson regression models indicated poorer physical health early in the disease course as the main driver of this increased rate of hospitalization, whereby neuropsychiatric symptoms additionally explained the higher number of hospital days. Patients with DLB had significantly more episodes of delirium recorded in the year before dementia diagnosis than patients with AD (incidence rate 17.6 vs 3.2 per 100 person-years; $p < 0.001$). Whereas the incidence of recording of delirium episodes reduced substantially in patients with DLB after dementia diagnosis, it remained significantly higher than in patients with AD (incidence rate 6.2 vs. 2.3 per 100-person years; $p = 0.032$). Only before dementia diagnosis (5.9 vs. 1.4 per 100 person-years; $p = 0.003$) there were significant differences between incidence rates of recording of hospitalized delirium episodes, and no significant reductions in neither the DLB nor the AD group occurred after dementia diagnosis.

Conclusions: Patients with DLB are more frequently admitted to general hospital and utilize inpatient care to a substantially higher degree than patients with AD. Establishing a diagnosis of dementia reduces episodes classified as delirium in patients with DLB and might lead to fewer potentially harmful interventions as hospitalization or use of antipsychotic medication. These data highlight an opportunity to reduce hospital days and episodes classified (and treated) as delirium by identifying DLB earlier and providing more targeted care focussed on the specific triggers for hospitalization and associations of prolonged stay.

Category: Genetics & Epidemiology - Poster Presentation

P.34 *Parkinsonian symptoms in Alzheimer's disease and vascular dementia: Co-morbid features and relationship to adverse outcomes*

Author: Christoph Mueller

Additional Authors: Ahmed M. Al-Harrasi, King's College London, London, United Kingdom

Ehtesham Iqbal, King's College London, London, United Kingdom

Judista Lasek, South London and Maudsley NHS Foundation Trust, London, United Kingdom

Dag Aarsland, King's College London, London, United Kingdom

Gayan Perera, King's College London, London, United Kingdom

Robert Stewart, King's College London, London, United Kingdom

Christoph Mueller, King's College London, London, United Kingdom

Background: Parkinsonian features are reported to be prevalent in up to one third of patients with dementia and are associated with cognitive decline, institutionalisation, death and higher health care costs. Aim of this study was to examine to which extent Parkinsonian symptoms are recorded in routinely collected data, and whether motor signs present at initial dementia diagnosis predicted adverse outcomes.

Methods: A cohort of 11,106 patients with dementia in Alzheimer's disease, vascular dementia or a combination was assembled from a large dementia care database in South East London. A natural language processing algorithm was devised to establish the presence Parkinsonian motor symptoms (bradykinesia, Parkinsonian gait, rigidity, tremor) at the time of dementia diagnosis. We examined the co-morbidity profile of patients with these symptoms and used Cox regression models to analyse associations of Parkinsonian symptoms with survival and hospitalisation adjusting for twenty-four potential confounders.

Results: Presence of Parkinsonian symptoms was associated with younger age at diagnosis, neuropsychiatric symptoms, poor physical health and higher prescribing of psychotropics. However, there were differences in co-morbidity patterns for individual Parkinsonian symptoms. While number of Parkinsonian symptoms didn't predict mortality or hospitalization, rigidity remained independently associated with a 23% increased mortality risk after adjustment for confounders ($p=0.014$). A non-significant trend for a 15% higher risk of hospitalization was detected in those presenting with a Parkinsonian gait ($p=0.094$).

Conclusion: Parkinsonian symptoms in patients with Alzheimer's disease and vascular dementia are part of a complex clinical pictures and often accompanied by neuropsychiatric and functional difficulties. Nevertheless, rigidity appears to be an independent risk factor for early mortality.

P.35 *End-of-Life Experiences in Dementia with Lewy Bodies*

Author: Melissa Armstrong

Additional Authors: Slande Alliance, University of Florida College of Medicine

Pamela Corsentino, Lewy Body Dementia Association

Angela Taylor, Lewy Body Dementia Association

Background: Dementia caregivers describe knowing what to expect as an unmet need and many are unaware that dementia can be a terminal condition. Dementia with Lewy bodies (DLB) has unique features that affect the end of life. This mixed-methods study aimed to investigate the natural history, cause of death, and end-of-life experiences of individuals diagnosed with DLB and their families.

Methods: Caregivers, family and friends of individuals with DLB who died in the past 5 years were recruited to participate in a 20-question online survey about end-of-life experiences through the Lewy Body Dementia Association. Survey respondents were queried regarding interest in participating in follow-up telephone interviews. Thirty interviews were conducted using a semi-structured questionnaire to identify and describe end-of-life experiences. Survey results are presented descriptively. A qualitative descriptive approach was used to analyze interview transcripts and identify common themes.

Results: Of 658 survey respondents, 89% were women (median age 50-69 years). Respondents reported that most individuals with DLB died within 5 years of diagnosis (median 3–4 years). Respondents indicated that physicians rarely discussed what to expect at the end of life (40% total, but only 22% to a helpful degree) and that such conversations were usually initiated by the caregiver. Death was usually expected, but less than half of respondents felt prepared for what to expect. Hospice was utilized by 78%, usually at home or in skilled care, with wide variations in duration. Failure to thrive was the most common cause of death (65%), followed by pneumonia/swallowing difficulties (23%), other medical conditions (19%), and complications from falling (10%) (multiple causes allowed).

Key themes in the 30 caregiver interviews included lack of knowledge regarding what to expect, end-of-life time course (including end-of-life symptoms, declines after hospitalization and falls, and varied end-of-life trajectories), advance care planning, lack of family understanding, hospice, views regarding right-to-die, medications at the end of life, approaching end of life, the death experience, and activities that enhanced end of life. Lack of communication between health care teams and families and difficulty predicting death timing were two frequently expressed challenges near the end of life.

Conclusions: Survey results highlighted a critical need for improved prognostic counseling and education for persons and families living with DLB. Such counseling can be informed by current results but studies are needed to further explore expected prognosis for individuals diagnosed clinically with DLB and optimal use of palliative care services. Interview results emphasized the need for improved end-of-life counseling in DLB, recognition of end-of-life symptoms, earlier hospice involvement, tailoring end-of-life care to DLB-specific needs, and clinician-family communication. Suggestions for patient and family education are provided. Further research should confirm predictors of approaching end of life in DLB, identify strategies to improve physician recognition of end of life, and develop tools to aid communication and quality end of life care.

P.36 *The causes of death in Dementia with Lewy bodies – death certificate data from two countries*

Author: Arvid Rongve

Additional Authors: Christoph Mueller, IoPPN, the Department of Old Age Psychiatry, King's College London, UK.

Audun Vik-Mo, Stavanger University Hospital, Department of Old Age Psychiatry, Stavanger, Norway.
Ragnhild Oesterhus, Stavanger University Hospital, Centre for Age-Related Medicine, Stavanger, Norway.

Dag Aarsland, Stavanger University Hospital, Department of Old Age Psychiatry and Centre for Age-Related Medicine, Stavanger and IoPPN, the Department of Old Age Psychiatry, King's College London, UK.

Introduction

Persons diagnosed with dementia have reduced life expectancy, and we recently found persons diagnosed with Dementia with Lewy bodies (DLB) to be hospitalized more often and in a meta-analysis to have shorter survival compared to persons living with Alzheimer's disease (AD) (1, 2). Little is known about causes of death in DLB. Here we want to study the causes of death in DLB compared to in AD in two cohorts in UK and Norway.

Methods

We used data from the Dementia Study of Western Norway (DemVest) and the South London and Maudsley NHS Foundation Trust (SLaM) Clinical Record Interactive Search (CRIS) application. The DemVest-study included persons with all type dementia from mild stages of the disease with annual follow ups until death. The causes of death were provided from the Norwegian Cause of Death Registry. The CRIS database contains patients with a clinical diagnosis of DLB and AD and is linked to the Office of National Statistics (ONS) death certificate database.

Results

In the Norwegian cohort, death certificate diagnoses from 46 patients with DLB and from 50 with AD were available. Bronchopneumonia was most frequently registered as the cause of death in both DLB (17%) and in AD (14%) in Norway. Preliminary data from 158 patients who died with DLB in South London showed that dementia (37%), Parkinson's disease (18%), pneumonia (5%) and stroke (4%) were the most frequently recorded causes of death. Data for AD in the UK cohort and the less frequent causes of death and the use of different types of medication like neuroleptics will be presented at the conference.

Conclusions

Preliminary data show that lower respiratory tract infections might be equally common as cause of death in AD and DLB. In the UK they frequently recorded both Dementia and Parkinsonism as the cause of death in patients with DLB. In Norway AD was recorded as underlying cause of death in 9 % of AD cases and in 8 % of AD cases unspecified dementia was given as underlying cause. In Norway, only 8% of persons who died with DLB were given the correct underlying diagnosis on the death certificate. 9% were diagnosed with unspecified dementia and 8 % with Parkinson's disease. The causes of death written on the death certificate differ for persons diagnosed with DLB between Norway and the UK, and a correct DLB diagnosis recorded on the death certificate is rare in Norway.

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Poster Presentations

Section: Imaging

Category: Imaging - Poster Presentation

P.37 White matter hyperintensities and disability in dementia-Does the association in Lewy body Dementia differ from Alzheimer's Disease?

Author: Saira Saeed Mirza

Additional Authors: Saira Saeed Mirza^{1,2}, Usman Saeed^{3,4}, Joel Ramirez^{2,4,5}, Donald Stuss^{6,7}, Sandra E. Black^{1,2,3,4,5}, and Mario Masellis^{1,2,3,4}

Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada
Hurvitz Brain Sciences Research Program, Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada
Institute of Medical Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada
LC Campbell Cognitive Neurology Research Unit, Sunnybrook Research Institute, University of Toronto, Toronto, ON, Canada
Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada
Dept. of Rehabilitation Science, Faculty of Medicine, University of Toronto, Toronto, ON, Canada
Department of Psychology, Faculty of Arts and Science; Department of Medicine (Neurology), Faculty of Medicine; Centre for Studies of Aging, University of Toronto, Toronto, ON, Canada

Background: Disability in Activities of Daily Living (ADL) features all dementia diagnoses, such as Alzheimer's Disease (AD) and Lewy body dementia (LBD)—two most common neurodegenerative dementias. White matter hyperintensities (WMHs) are prevalent in both diagnoses and also associate with disability, but this association has mostly been studied in AD, and remains unexplored in LBD. **Methods:** From the Sunnybrook Dementia Study, we included 281 (AD=228, LBD=53) dementia patients to examine the cross-sectional associations of WMH with disability in ADL, and 163 (AD=135, LBD=28) to examine longitudinal associations of WMH and ADL, in which ADL were reassessed after ~1.5 years. After testing interactions between WMH and clinical dementia diagnosis, we examined these associations in AD and LBD groups. All patients underwent standardized volumetric MRI, ADL and neuropsychiatric assessment. Total WMH volumes were quantified by semiautomatic segmentation using Lesion Explorer. Basic and instrumental ADL (BADL and IADL) were assessed using Disability Assessment for Dementia scale. We used multiple linear regression models adjusted for age, sex, cardiovascular risk factors, and Mini-Mental State Examination and Neuropsychiatric Inventory score, to test associations of WMH with BADL and IADL. We also tested which components, i.e. planning, initiation, or effective performance of ADLs drive the associations.

Results: Cross-sectionally, WMH volume was associated with disability in BADL, but not IADL; significant interaction was observed between WMH and diagnosis for BADL (p -value=0.003). We did not observe any associations in the full sample longitudinally.

Compared to AD, LBD patients were younger ($P<0.001$), had better MMSE and lower WMH volume ($P<0.001$), but higher neuropsychiatric symptoms ($P<0.001$), and more disability ($P<0.001$) at baseline.

In AD, WMH did not associate with or predict disability on BADL or IADL. In LBD, higher WMH volume was associated with a significant decline in both BADL (decline per SD (β): -13.88, 95% CI: -26.48, -1.29) and IADL (decline (β): -15.13, 95% CI: -27.0, -3.25) over time. In LBD, association of WMH with BADL was largely driven by disability in effective-performance of tasks, whereas that for IADL was driven by planning disability.

Conclusions: Despite the lower burden of WMH in LBD, WMH more strongly predicted ADL in LBD than in AD. WMH possibly interact with LBD pathology differently than with AD pathology consequently influencing functionality.

Category: Imaging - Poster Presentation

P.38 *Structural and functional connectivity changes in dementia with Lewy bodies compared to Alzheimer's disease and normal aging: implications for cognitive fluctuations*

Author: Elena Chabran

Additional Authors: Vincent Noblet, PhD, HdR,1 vincent.noblet@unistra.fr

Mary Mondino, MSc,1 mondino@unistra.fr

Catherine Demuynck, MD,2 Catherine.demuynck@chru-strasbourg.fr

Nathalie Philippi, MD, PhD, 1,2 nathalie.philippi@chru-strasbourg.fr

Pierre Anthony, MD3 pierre.anthony@ch-colmar.fr

Catherine Martin-Hunyadi, MD,2 Catherine.martin-hunyadi@chru-strasbourg.fr

Benjamin Cretin, MD, 1,2 Benjamin.cretin@chru-strasbourg.fr

Frédéric Blanc, MD, PhD, HdR,1,2 f.blanc@unistra.fr

1. University of Strasbourg and CNRS, ICube Laboratory UMR 7357 and FMTS (Fédération de Médecine Translationnelle de Strasbourg), Team IMIS, Strasbourg, France

2. University Hospitals of Strasbourg, CM2R (Research and Resources Memory Centre), Geriatric Day Hospital and Neuropsychology Unit, Geriatrics department, Strasbourg, France

3. General Hospital Centre, CM2R, Geriatric Day Hospital, Geriatrics department, Colmar, France

Background: Fluctuations are one of the core clinical features characterizing dementia with Lewy bodies (DLB). They represent a determinant factor for its diagnosis and have a significant impact on the quality of life of patients and their caregivers. However, the neural correlates of this complex symptom remain poorly understood. This study aims to investigate the structural and functional changes in DLB patients compared to Alzheimer's disease patients and healthy elderly subjects, and to interrogate their potential link with fluctuations.

Methods: Participants in the study were divided in three groups on the basis of the Dubois and McKeith criteria: DLB patients (n=79), AD patients (n=58) and control subjects (n=22). All participants underwent a detailed clinical and neuropsychological examination, including the Mayo Clinic Fluctuations Scale, and structural and resting-state functional MRI scans. Structural changes were analyzed using whole-brain voxel-based morphometry (VBM), and resting-state functional connectivity was investigated using a seed-based analysis, with regions of interest (ROIs) corresponding to the main nodes of the salience network (SN), frontoparietal network (FPN), dorsal attention network (DAN) and default mode network (DMN). In both modalities, we performed group comparisons and a multiple regression analysis to study the association between VBM or functional measures and DLB patients' fluctuation scores.

Results: We found bilateral grey matter loss in the superior and middle temporal gyri, the inferior frontal gyri and the insulae in DLB patients compared to controls, but no significant correlation was observed between these structural changes and the presence fluctuations. Only two clusters showing a trend of correlation (and located in the thalami and midbrain) were added as complementary ROIs for the subsequent functional connectivity analysis.

The functional analysis revealed significant decrease in functional connectivity within the SN and within the FPN, along with an hyperconnectivity between these two networks and the DMN, in the DLB group compared to healthy subjects. When comparing the DLB and AD groups, DLB patients showed a greater decrease in connectivity within the SN, and between the SN and the DMN. Finally, in the DLB group, cognitive fluctuations were correlated to a lower connectivity between the right thalamus and a number of regions within the DMN and the FPN, and to a greater connectivity between the SN and the DAN and left thalamus (see Figure 1).

Conclusions: These results tend to confirm that cognitive fluctuations in DLB are more likely to arise from functional connectivity disturbances than from structural changes. They also underline significantly disturbed interactions between the SN, the FPN and the DMN, three networks known for forming a switching system between different attentional states, and which could thus play an important role in the occurrence of fluctuations. Finally, and in line with previous structural and functional work, this study suggests an potential involvement of the thalamus in the etiology of this symptom.

Category: Imaging - Poster Presentation

P.39 Postmortem correlates of amyloid PET and dopamine transporter PET in the Lewy body diseases

Author: Stephen Gomperts

Additional Authors: Rong Ye, Massachusetts General Hospital

Nathan Clement, M.D., Massachusetts General Hospital

Julia Shirvan, Ph.D., Massachusetts General Hospital

Samantha Katz, Massachusetts General Hospital

Aaron Schultz, Ph.D., Massachusetts General Hospital

Keith A. Johnson, M.D., Massachusetts General Hospital

Teresa Gomez-Isla, M.D., Ph.D., Massachusetts General Hospital

Matthew P. Frosch, M.D., Ph.D., Massachusetts General Hospital

John H. Growdon, M.D., Massachusetts General Hospital

Background: Pathologic changes in the Lewy body diseases - Parkinson disease (PD), PD dementia (PDD) and dementia with Lewy Bodies (DLB) – extend beyond the core feature of α -synuclein aggregation in Lewy bodies within neurons. Neuromodulatory neuron populations are lost, including dopamine neurons of the substantia nigra pars compacta. In addition, neuropathologic changes characteristic of Alzheimer's disease, including A β -amyloid plaques and neurofibrillary tangles, are commonly observed at autopsy in both PDD and DLB. We sought to validate amyloid and dopamine transporter (DAT) imaging biomarkers of Lewy body diseases against postmortem neuropathologic findings in a cohort of cognitively impaired parkinsonian patients.

Methods: 4 cognitively normal PD, 4 PD with cognitive impairments, and 10 DLB subjects who underwent amyloid imaging with [11C]PiB and DAT imaging with [11C]altropine came to autopsy and underwent neuropathologic evaluation. [11C]PiB and [11C]altropine PET data were expressed as the standardized uptake value ratio with cerebellar reference. All 18 subjects underwent annual neurological examinations. All cognitively normal PD subjects developed cognitive impairment prior to death. Neuropathologic examinations assessed and scored Braak Lewy bodies, Thal amyloid distribution, CERAD neuritic amyloid plaques, Braak neurofibrillary tangles, and cerebral amyloid angiopathy, as well as total amyloid plaque burden in superior frontal, superior parietal, occipital and inferior temporal cortical regions. Analyses accounted for the interval between imaging and autopsy.

Results: All 18 patients met neuropathologic criteria for Lewy body disease; the DAT concentration was low in each case. All patients with elevated [11C]PiB retention measured in a neocortical aggregate had A β amyloid deposits at autopsy. [11C]PiB retention significantly correlated with neuritic plaque burden and with total plaque burden. [11C]PiB retention also significantly correlated with the severity of both Braak stages of neurofibrillary tangle and Lewy body scores. Neuritic plaque burden was significantly associated with neurofibrillary tangle pathology.

Conclusion: Antemortem [11C]altropine PET is a sensitive measure of substantia nigra degeneration. [11C]PiB scans accurately reflect cortical amyloid deposits seen at autopsy. In the Lewy body diseases, the magnitude of [11C]PiB retention predicts the severity of neurofibrillary tangle and Lewy body pathologies.

Category: Imaging - Poster Presentation

P.40 *Serotonergic 123I-FP-CIT Binding is Associated with Depression and not Neuropathology*

Author: Alice Oliver-Evans

Additional Authors: Dr Sean Colloby, Newcastle University

Prof. Alan Thomas, Newcastle University

Dr Daniel Erskine, Newcastle University

Prof. Johannes Attems, Newcastle University

Objectives: The objective of the study was to investigate the influence of dorsal and median raphe pathology on 123I-N- ω -fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl)nortropane (123I-FP-CIT) serotonin transporter (SERT) binding in a cohort of post-mortem confirmed Alzheimer's disease (AD), dementia with Lewy bodies (DLB), Parkinson's disease with dementia (PDD), mixed AD/DLBs and healthy-aged controls.

Methods: Subjects underwent ante-mortem serotonergic 123I-FP-CIT single photon emission computed tomography (SPECT), neuropsychiatric testing including, Mini-Mental State Examination and Geriatric Depression Scale (GDS) and post-mortem assessments (mean interval 6.6 years). SERT binding was estimated using region of interest procedures, with quantitative neuropathological analysis of alpha-synuclein, tau and amyloid-beta.

Results: SERT binding ratios were significantly lower in PDD than control patients ($p < 0.01$). No statistical differences in pathology, alpha-synuclein, tau or amyloid-beta, were found between PDD and DLB patients. GDS assessed at time of 123I-FP-CIT correlated with the SERT binding ratio ($p < 0.001$), with scores from PDD patients significantly higher than controls ($p < 0.01$).

Conclusions: The results suggest that the differences observed in 123I-FP-CIT SERT binding in PDD compared to controls ante-mortem, are related to the changes that underlie geriatric depression and not to the underlying pathology. Preliminary data from immunofluorescence suggests that serotonergic neurons are more vulnerable to Lewy body pathology than other neuronal subtypes in the raphe, suggesting a possible reason for the lowered SERT binding ratios observed. We are currently evaluating the expression of tryptophan hydroxylase in the raphe nuclei to determine its relationship to the 123I-FP-CIT data and clinical markers of depression.

Category: Imaging - Poster Presentation

P.41 Pathologic associations of FDG PET in Lewy body disease

Author: Jonathan Graff-Radford

Additional Authors: Jonathan Graff-Radford MD1, Qin Chen, M.D. Ph.D1, Melissa E. Murray PhD2, Scott A. Przybelski BS1, Rodolfo Savica MD1, David T Jones MD1, Val J. Lowe MD1, Bradley F. Boeve MD1, Tanis J. Ferman PhD2, Timothy G. Lesnick MS1, David S. Knopman MD1, Clifford R. Jack, Jr. MD1, Dennis W. Dickson MD2, Ronald C. Petersen MD, PhD1, Kejal Kantarci MD,MS1

Affiliations:

Mayo Clinic Rochester1

Mayo Clinic Florida 2

Background: Among individuals with Lewy body disease (LBD), pathologic correlates of clinical course include the presence and extent of coexisting Alzheimer's pathology and the presence of transitional or diffuse LBD. The objective of this study was to determine whether 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) signatures of LBD would be associated with these pathologies.

Methods: 36 participants with pathologically-confirmed LBD who underwent antemortem FDG-PET were included in this study. We evaluated whether FDG-PET features of DLB, including the cingulate island sign (CIS) and occipital hypometabolism, varied by Lewy body stage (amygdala only, transitional, diffuse) and Braak neurofibrillary tangle stage. We performed a recursive partitioning tree algorithm to classify our participants into distinctive sub-groups.

Results: The median imaging age was 73 and 75% were male. The median age at death was 75.5. 26 participants had diffuse LBD, 8 participants had transitional LBD, and 2 had amygdala only LBD. There was no difference in CIS or occipital hypometabolism by LBD type (transitional, diffuse). In contrast, those with a lower Braak stage (I-III) had a higher CIS compared to those with a higher Braak stage (IV-VI). For the CIS, there were 3 distinct groups based on the partitioning analysis (Braak I-II), (Braak III-IV) and Braak (V-VI). The partitioning found two groups for occipital hypometabolism (Braak I-III and Braak IV-VI). Boxplots by of CIS and occipital hypometabolism by Braak tangle stage are presented in the figure by low (Braak I-II), intermediate (Braak III-IV) and high Braak (V-VI) tangle stage.

Discussion: Among pathologically confirmed LBD patients, FDG-PET features varied by Braak neurofibrillary tangle stage, but not LBD subtype. Predicting the extent of AD pathology antemortem may allow for improved prognostication of the clinical course of patients with LBD.

P.42 Age-corrected quantitative 123I-FP-CIT results in older patients may be misleading since striatal uptake does not continue to decrease significantly in old age

Author: Gemma Roberts

Additional Authors: Jim Lloyd¹, George Petrides¹, Paul Donaghy², Joseph Kane², Rory Durcan², Sarah Lawley², Kim Howe¹, John-Paul Taylor², John O'Brien³, Alan Thomas²

1. Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

2. Newcastle University, UK

3. Cambridge University, UK

Background

I-123-2 β -Carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl)nortropane (FP-CIT) imaging is an established biomarker used in the diagnosis of Lewy body disease (LBD). Images are often reported with the aid of semi-quantitative striatal binding ratios (SBRs), comparing uptake to a normal database via Z scores. Karrer et al. confirmed that striatal uptake is age-dependent in healthy adults in their 2017 meta-analysis (Neurobiol Aging. 2017 Sep;57:36-46). However, the studies included tended to cover wide age ranges between 20 and 80 years, rather than focusing on older adults. Typically a linear relationship is reported, with the same rate of decline at all ages, although some authors have suggested that SBRs do not decline as rapidly in old age.

Commercial software packages usually adjust the Z score to attempt to compensate for age-related decline using a linear or bi-linear model. Our experience with older adults has been that scans with abnormal visual appearances often have age-corrected Z scores within the normal range.

Ensuring the age-correction model is appropriate for older adults is important, given that the majority of patients referred for FP-CIT scans are over 60 years of age and may be much older. We sought to examine the relationship in older age using scans from 123 adults over 60 years of age recruited as research subjects.

Methods

Twenty-nine healthy older adults and twenty-three older adults with MCI due to Alzheimer's disease (MCI-AD) were included (60 - 92 years (mean 76; SD 7.9)) as controls (subjects confirmed free of Lewy body disease). SBRs and Z scores were calculated using BRASS (Hermes Medical) and DaTQUANT (GE Healthcare). Images were reconstructed in accordance with the manufacturers' recommendations. SBRs were plotted against age and linear mixed effects models applied. We tested the effect of removing age-correction in BRASS using an independent dataset of 71 older adults with dementia or mild cognitive impairment due to either LBD or Alzheimer's disease.

Results

The slopes of the linear fits between SBR and age for controls aged over 60 were very small and showed no statistically significant difference from zero when processed with either BRASS (p=0.30) or DaTQUANT (p=0.35). The measured slopes (rate of change of SBR per year) were lower than those reported in the literature, which are derived from scans of adults of all ages. Switching age correction off in BRASS reduced Z scores by approximately 1 standard deviation at 80 years of age. Three of the 20 MCI Lewy body cases and three of the 18 MCI-AD cases had Z scores above -2 with age correction on and below -2 with it switched off.

Conclusion

We found no evidence of a statistically significant age-related decline in SBR in adults over 60 years of age without Lewy body disease. Commercial software packages that continue to apply a fixed rate of age correction into old age may be overcorrecting for age in older adults and failing to detect neurodegeneration in some cases. This could contribute to false negative reporting and misdiagnosis, particularly in early cases of Lewy body disease with borderline results.

P.43 *Diagnostic implications of multiple biomarkers in MCI-LB.*

Author: Paul Donaghy

Additional Authors: Donaghy PC1, Durcan R1, Roberts G1, Colloby SJ1, Petrides G2, Lloyd J2, Lawley S1, Ciafone J1, Hamilton CA1, O'Brien JT3, Taylor JP1, Thomas AJ1.

1: Institute of Neuroscience, Newcastle University, UK

2: Nuclear Medicine Department, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

3: Department of Psychiatry, University of Cambridge, UK

Background

FP-CIT (123I-N-fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl)) dopaminergic and MIBG (meta-iodobenzylguanidine) cardiac imaging are both validated diagnostic biomarkers for dementia with Lewy bodies (DLB). There has been little research in the diagnostic accuracy of these biomarkers in the prodromal stages of DLB. The aim of this study was to investigate the diagnostic accuracy of MIBG and FP-CIT imaging to identify mild cognitive impairment with Lewy bodies (MCI-LB), and whether these two biomarkers are useful in combination.

Methods

69 patients aged over 60 years with MCI (n=22 probable MCI-LB, n=18 possible MCI-LB and n=29 Alzheimer's disease MCI (MCI-AD)) underwent detailed clinical assessment, FP-CIT SPECT and planar cardiac MIBG scintigraphy.

Diagnosis was made by a three-rater panel, blind to FP-CIT and MIBG results. MCI was diagnosed using NIA-AA criteria. Possible MCI-LB was diagnosed if one core clinical feature was present as defined by the 2017 DLB diagnostic criteria. Probable MCI-LB was diagnosed if two or more core clinical features were present.

FP-CIT scans were blindly rated as normal or abnormal by a consensus panel. MIBG scans were classified as abnormal if the delayed heart:mediastinum ratio was greater than two standard deviations below a locally recruited control group.

Results

FP-CIT: 59% of probable MCI-LB, 50% of possible MCI-LB and 17% of MCI-AD had an abnormal FP-CIT SPECT scan (likelihood ratio (probable/possible MCI-LB v. MCI-AD)=3.2; p<0.01).

MIBG: 59% of probable MCI-LB, 56% of possible MCI-LB and 14% of MCI-AD had an abnormal cardiac MIBG scan (likelihood ratio=4.0; p<0.001).

Combined results: 50% of probable MCI-LB, 39% of possible MCI-LB and 0% of MCI-AD had two abnormal scans (p<0.001). 68% probable MCI-LB, 67% of possible MCI-LB and 33% of MCI-AD had at least one abnormal scan (likelihood ratio=2.0; p=0.01).

In subjects with a probable or possible MCI-LB, biomarker results were correlated (82% of subjects with an abnormal FP-CIT scan had an abnormal MIBG scan; 78% of subjects with an abnormal MIBG scan had an abnormal FP-CIT SPECT scan; p=0.001).

In participants with a normal FP-CIT scan, 22% of probable MCI-LB, 33% of possible MCI-LB and 18% of MCI-AD had an abnormal MIBG scan (likelihood ratio=1.5; p=0.47).

In participants with a normal MIBG scan, 22% of probable MCI-LB, 25% of possible MCI-LB and 22% of MCI-AD had an abnormal FP-CIT SPECT (likelihood ratio=1.1; p=0.89).

Conclusions

This study demonstrates that MIBG and FP-CIT imaging are highly specific and relatively sensitive biomarkers for MCI-LB. The sensitivity of both biomarkers is lower than that reported in DLB. This is to be expected as both biomarkers reflect neurodegeneration, which will inevitably be less advanced in this early stage of the disease.

This study has important implications for the use of biomarkers in clinical practice and research studies. Patients with a normal FP-CIT or MIBG result should not have a second scan using the alternate modality as the likelihood ratio for this scan would be ≤ 1.5 . In research studies where very high specificity is required (e.g. interventional studies), a threshold of two abnormal scans could be considered to confirm diagnosis, though this will reduce overall sensitivity.

P.44 *Clinical and imaging findings associated with microbleeds in dementia with Lewy bodies*

Author: Paul Donaghy

Additional Authors: Paul C Donaghy¹, Michael Firbank¹, Dipayan Mitra², George Petrides³, Jim Lloyd³, Nicola Barnett¹, Kirsty Olsen¹, Alan J Thomas¹, John T O'Brien⁴

1: Institute of Neuroscience, Newcastle University, UK

2: Neuroradiology Department, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

3: Nuclear Medicine Department, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

4: Department of Psychiatry, University of Cambridge, UK

Background

Microbleeds are small chronic foci of blood products in brain tissue. They are associated with the development of dementia in older people and are common in Alzheimer's disease (AD). Their prevalence and clinical importance in dementia with Lewy bodies (DLB) is unclear.

Microbleeds can be classed according to location as lobar (in cortical or subcortical areas), deep (in basal ganglia, thalamus, internal capsule, external capsule, corpus callosum or deep/periventricular white matter) or infratentorial (in brainstem or cerebellum). Lobar microbleeds have been associated with cortical amyloid deposition in healthy older people and AD.

The aim of this study was to compare the rates of microbleeds in DLB with those in AD and healthy older people, and investigate the relationship of microbleeds with clinical and imaging findings in DLB.

Methods

DLB (n=32), AD (n=17) and control (n=19) participants underwent clinical assessment at baseline and 1 year including the Addenbrooke's Cognitive Examination Revised (ACE-R), Trails A and B, the Revised Unified Parkinson's Disease Rating Scale (UPDRS), and Bristol and Instrumental Activities of Daily Living Scales. 3T MRI (including T2* susceptibility weighted imaging) and Florbetapir PET were carried out at baseline. Microbleeds were rated visually and a standardised uptake value ratio (SUVR) was calculated from Florbetapir PET scans.

Results

41% of DLB subjects had microbleeds compared with 53% of those with AD and 16% of controls.

Compared to DLB without microbleeds, those with microbleeds were older and had higher systolic BP but did not have greater levels of vascular disease or amyloid deposition. Those with microbleeds had better attention, visuospatial function and functional ability, lower UPDRS scores, and less progression in parkinsonism over one year.

Conclusions

We found that microbleeds in DLB were associated with higher blood pressure but not with other measures of cardiovascular disease. They were not associated with amyloid deposition. This contrasts to findings in healthy older people and Alzheimer's disease and suggests that microbleeds in DLB are not related to concomitant Alzheimer's disease pathology. Additionally, microbleeds in DLB were associated with less severe deficits in attention, visuospatial function and less progression of parkinsonism and therefore microbleeds were associated with features suggestive of less severe Lewy body disease in DLB.

Category: Imaging - Poster Presentation

P.45 Imaging tau, neuroinflammation and A β in dementia with Lewy bodies: a deep-phenotyping case-report

Author: Elijah Mak

Additional Authors: Authors:

Elijah Mak 1* (PhD), Ajenthan Surendranathan *1 (MBBS), Nicolas Nicastro 1 (MD), Franklin Aigbirhio F2 (PhD), James Rowe2,3,4 (PhD), John O'Brien1+ (DM)

Affiliations:

1 Department of Psychiatry, University of Cambridge, UK, 2 Wolfson Brain Imaging Centre, University of Cambridge, UK., 3 Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK, 4 Medical Research Council Cognition and Brain Sciences Unit, Cambridge, UK. * Joint Co-First Authors, + Co-Senior Authors

Background

Dementia with Lewy bodies (DLB) is the second leading cause of degenerative dementia in older people after Alzheimer's disease (AD). In addition to the presence of Lewy bodies, amyloid plaques (A β) and tau neurofibrillary tangles often co-occur, and evidence of increased inflammation is accumulating in DLB. Clarifying the interactions across these processes in DLB is critical for the optimization of therapeutic approaches, but until recently could only be evaluated at post-mortem.

Methods

We present a deep-phenotyping study of the first DLB case known to undergo multi-modal MRI and PET imaging for tau ([18F]-AV1451), amyloid ([11C]-PiB) and neuroinflammation ([11C]-PK11195). The structural T1-MRI image was processed with Freesurfer v6 to obtain cortical regions of interest (ROIs) based on the Desikan-Killiany atlas. All PET examinations were performed on the GE Discovery 960 with the [11C]-PiB, [11C]-PK11195, and [18F]-AV1451 tracers. All PET data were corrected for head motion and then partial volume effects using the Geometric transfer matrix in PetSurfer. PET tracer binding for each cortical ROI was converted into z-scores relative to the cortex. This z-transformation of ROI data enabled us to evaluate the spatial concordance of imaging features with inter-regional Spearman correlations.

Results

The patient presented with parkinsonism, fluctuating cognition and REM sleep behaviour disorder, together with progressive cognitive impairment over several years (Fig 1, Top Row). Structural MRI revealed moderate hippocampal atrophy and minimal white matter lesions only, while [11C]-PiB binding showed an AD-like pattern characterized by diffuse neocortical binding, with the highest uptake in bilateral precuneus and frontal cortices (Fig 1, Bottom Row). In contrast, [18F]-AV1451 binding showed a pattern that is atypical of AD, with the highest retention in occipital regions (Fig 2). Intriguingly, inter-regional correlations also noted a striking co-localization between [11C]-PK11195 and [18F]-AV1451 uptake, particularly in the occipital cortex ($r=0.6$, $p<0.001$; Fig 2). Inter-regional covariance analysis indicated significant colocalizations of [18F]-AV1451 with [11C]-PiB binding ($r = 0.3$, $p < 0.05$) and [11C]-PK11195 ($r = 0.7$, $p < 0.001$), but no correlation between [11C]-PK11195 and [11C]-PiB uptake (Fig 2).

Conclusion

In the first observation of its kind in a DLB patient, we observed prominent colocalization of tau with neuroinflammatory processes, particularly in the occipital cortex. This finding suggests that both tau and neuroinflammation may underpin the classical occipital vulnerability in DLB. Contrary to the temporo-parietal predominance of tau binding in AD, [18F]-AV1451 retention was disproportionately highest in the primary visual cortex. This combination of multi-tracer PET imaging has revealed novel inter-relationships of amyloid, neuroinflammation and tau aggregation in DLB, paving the way for longitudinal studies that may delineate the direction and nature of how they relate to the core features of DLB.

Category: Imaging - Poster Presentation

P.46 *Dysfunctional brain dynamics in Lewy body dementia*

Author: Julia Schumacher

Additional Authors: Julia Schumacher¹, Luis R. Peraza^{1,2}, Michael Firbank¹, Alan J. Thomas¹, Marcus Kaiser^{2,3}, Peter Gallagher³, John T. O'Brien⁴, Andrew M. Blamire⁵, John-Paul Taylor¹

¹Institute of Neuroscience, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, United Kingdom

²Interdisciplinary Computing and Complex Biosystems (ICOS) research group, School of Computing, Newcastle University, Newcastle upon Tyne, NE4 5GT, United Kingdom

³Institute of Neuroscience, Newcastle University, The Henry Wellcome Building, Newcastle upon Tyne, NE2 4HH, United Kingdom

⁴Department of Psychiatry, University Cambridge School of Medicine, Cambridge, CB2 0SP, United Kingdom

⁵Institute of Cellular Medicine & Newcastle Magnetic Resonance Centre, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, United Kingdom

Background:

Lewy body dementia (LBD), which comprises dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), is characterized by transient clinical symptoms such as cognitive fluctuations which may be caused by alterations of intrinsic brain dynamics. The aim of this work was therefore to investigate how dysfunctional brain connectivity and dynamics relate to the cognitive LBD phenotype, especially with respect to attentional impairment and cognitive fluctuations.

Methods:

Reaction time data from an attention task were analyzed to investigate behavioral aspects of cognitive fluctuations in LBD in comparison to patients with Alzheimer's disease (AD) and age-matched healthy controls. Subsequently, resting-state fMRI data were analyzed using static and dynamic functional connectivity and dynamic network analyses. Faster brain dynamics on a subsecond timescale were assessed using EEG microstate analysis. To explore what processes in the brain drive whole-brain microstate dynamics in LBD, we also studied associations between microstate dynamics and temporal aspects of large-scale cortical-basal ganglia-thalamic interactions given the putative role of these subcortical areas in modulating widespread cortical function and their known vulnerability to Lewy body pathology.

Results:

AD and LBD patients exhibited slower and more variable reaction times than controls, with greater impairment in LBD than AD. Resting state functional connectivity was decreased in DLB patients compared to controls, mainly in motor, temporal, and frontal networks with relative sparing of the default mode network. Differences in static functional connectivity between AD and DLB were subtle. Considering time-varying connectivity, AD and DLB patients spent more time in sparse connectivity configurations than controls and switched less often into more highly connected states. The variability of global network efficiency was reduced in patients with DLB compared to controls. Microstate analysis revealed a marked and generalized increase in microstate duration in LBD patients compared to controls, which was not seen in AD and was related to a loss of dynamic connectivity between basal ganglia/thalamic and large-scale cortical networks. Microstate slowing was positively correlated with fluctuation severity in the DLB group indicating an association between a more severe reduction in microstate dynamics and more severe cognitive fluctuations. Furthermore, there was a positive correlation between microstate slowing and reaction time slowing and variability across all participants.

Conclusion:

The dynamic connectivity and microstate results indicate a loss of brain dynamics in LBD which might lead to a breakdown of the intricate dynamic properties of the brain, thereby causing loss of flexibility that is crucial for healthy brain function. When contrasted with the largely intact microstate dynamics in AD, the alterations in dynamic properties in LBD might indicate a brain state which is less responsive to environmental demands and might give rise to the cognitive LBD phenotype characterized by attentional impairment and cognitive fluctuations. Furthermore, we demonstrate that dynamic interactions within the cortical-basal ganglia-thalamic loop might play a role in the modulation of EEG dynamics in LBD.

P.47 Cortical brain network alterations across dementia groups: an EEG study

Author: Ramtin Mehraram

Additional Authors: Ramtin Mehraram 1,2, Marcus Kaiser 3, Ruth Cromarty 1, Alison Killen 1, Michael Firbank 1, Sean Colloby 1,2, Ian McKeith 1, Alan Thomas 1, John-Paul Taylor 1, and Luis R Peraza 1

1 Institute of Neuroscience, Newcastle University, UK;

2 NIHR Newcastle Biomedical Research Centre, UK;

3 School of Computing, Newcastle University, UK.

Background

Previous studies using electroencephalography (EEG) have found significant alterations in the brain network due to neurodegeneration associated with dementia with Lewy bodies (DLB) [1, 2] when compared with Alzheimer's disease (AD), but not compared with Parkinson's disease dementia (PDD). These alterations have been suggested to be associated with the role of attentional networks in the progression of the pathology. As the origin of the information recorded at the sensor level is a matter of debate, we investigated whether the brain network alterations are also present in the source domain.

Methods

Resting state EEG signals (128 channels, 1024 Hz) were recorded from 14 HC, 10 PDD, 17 DLB, and 23 AD participants. Signals were filtered (bandpass: 0.5-80 Hz; notch: 50 Hz), noisy epochs and bad channels were removed by visual inspection and artefactual components obtained by ICA were rejected. Magnetic resonance imaging (MRI) recordings were individually obtained with magnetization prepared rapid gradient echo (MPRAGE) sequence and a voxel size of 1.0×1.0×1.0 mm. Source estimation was performed with sLORETA technique [3] as implemented in the Brainstorm [4] toolbox (Matlab), with 148 cortical regions of interest (Destrieux atlas [5]). Connectivity strength was measured with weighted phase lag index (WPLI) [6], and proportional thresholding was applied to the connectivity matrices preserving from 3%-35% of the strongest WPLI values. Global connectivity strength was obtained by averaging the WPLI values across edges, and global network measures were computed for each thresholding level using the Brain Connectivity Toolbox (BCT) [7], and averaged across network densities.

Results

Differences in connectivity strength at the source level within the α -band (8-13.75 Hz) network reproduced the findings in the sensor domain, as the average WPLI in all dementia groups was weaker than HCs ($p < 0.05$, Holm-Bonferroni correction). However, the DLB group showed a lower WPLI compared with AD within the θ -band (4-7.75 Hz) network, and the connectivity strength was significantly reduced in PDD compared with HC and DLB within the β -band (14-20.75 Hz) network. The clustering coefficient decreased in DLB compared with HC in the α -band. No differences between groups were found in other network properties.

Conclusions

We confirmed that the EEG α -band network is consistently affected in all dementia types at the source level in terms of connectivity strength, and that this network is less segregated in DLB. However, contrary to the sensor domain, the θ -band network was significantly weakened in AD compared with DLB, and for the β -band network only the PDD group was affected. Overall, these novel findings suggest that resting-state EEG frequency patterns are suitable for differentiating dementia subtypes. Further investigation will assess the biological causes of these alterations and the subcortical areas involved in the progression of the disease, which are known to be firstly affected by the pathology [8].

Category: Imaging - Poster Presentation

P.48 Hippocampal Volumes in Prodromal Dementia with Lewy Bodies

Author: Rory Durcan

Additional Authors: R Durcan¹, M Firbank¹, PC Donaghy¹, S Lawley¹, JP Taylor¹, JT O'Brien^{1,2}, AJ Thomas¹

Institute of Neuroscience, Newcastle University, United Kingdom

Department of Psychiatry, University of Cambridge, United Kingdom

Introduction:

Relative preservation of medial temporal lobe structures on magnetic resonance imaging (MRI), particularly the hippocampus is recognised as a supportive biomarker consistent with DLB rather than Alzheimer's disease (AD). A previous retrospective study by Kantarci et al showed that preserved hippocampal volumes in mild cognitive impairment (MCI) were associated with increased risk of developing probable DLB at 2 years follow-up.

The aim of this preliminary analysis was to examine hippocampal volume differences in a prospective MCI cohort, subdivided into MCI with Lewy bodies (MCI-LB) and compared with mild cognitive impairment due to AD (MCI-AD).

Methods:

We conducted an interim analysis on the first 85 participants recruited to one of three groups; healthy controls, MCI-LB and MCI-AD, all ≥ 60 years. Alongside detailed clinical, neuropsychological assessments, all participants underwent 3T magnetic resonance imaging, 2β -carbomethoxy- 3β -(4-iodophenyl)-N-(3-fluoropropyl)-nortropane single photon emission tomography (123I-FP-CIT) and iodine-123 metaiodobenzylguanidine (123I-MIBG) myocardial scintigraphy. A fully automated hippocampal segmentation method of the MRI data was conducted to obtain hippocampal volumes.

Subjects were allocated to one of three clinical diagnoses on the basis of core symptoms and indicative biomarkers, not including MRI, as in our previous studies. The clinical diagnoses were; MCI-LB, (MCI plus two or more of the four clinical core DLB symptoms or one of these and an abnormal 123I-FP-CIT or abnormal 123I-MIBG scan) and MCI-AD (MCI with none of these four core symptoms, a normal 123I-FP-CIT and normal 123I-MIBG scan).

Results:

Groups consisted of 31 aged-matched healthy controls (mean age, 73.7 yrs; mean Mini-Mental state Examination [MMSE] score, 28.4), 20 MCI-AD (mean age, 75.6 yrs; mean MMSE score, 27.0), and 34 MCI-LB (mean age, 74.5 yrs; mean MMSE score, 26.5).

Both MCI-LB and MCI-AD had significantly lower hippocampal volumes compared to controls (Mean(SD) in mm³: Controls 5637 (1058); MCI-LB 4831 (1084); $t(63) = -3.03$, $p < 0.01$, $d = 0.75$); MCI-AD 4996 (1120), $t(49) = -2.06$, $P = 0.04$, $d = 0.59$). There was no significant hippocampal volume difference between MCI-AD and MCI-LB ($t(52) = -0.53$, $p = 0.60$, $d = 0.15$).

Discussion:

In this preliminary analysis, hippocampal volume reduction was present in both MCI-LB and MCI-AD participants in comparison to controls, but hippocampal volume loss did not distinguish between MCI-LB and MCI-AD patients.

Category: Imaging - Poster Presentation

P.49 Repeat nigrostriatal dopaminergic imaging in a prospective study of prodromal dementia with Lewy bodies

Author: Rory Durcan

Additional Authors: R Durcan¹, G Roberts^{1,2}, JJ Lloyd^{1,2}, GS Petrides², PC Donaghy¹, S Lawley¹, JP Taylor¹, JT O'Brien^{1,3}, AJ Thomas¹

Institute of Neuroscience, Newcastle University, United Kingdom

Nuclear Medicine department, Royal Victoria Infirmary, Newcastle upon Tyne NHS Hospitals Foundation Trust, United Kingdom

Department of Psychiatry, University of Cambridge, United Kingdom

Introduction:

Scintigraphy with FP-CIT [¹²³I-N-fluoropropyl-2 β -carbomethoxy-3 β -(4-iodophenyl)] is a biomarker for nigrostriatal dopaminergic loss that can distinguish dementia with Lewy bodies (DLB) from Alzheimer's Disease (AD). Recent evidence indicates that nigrostriatal dopaminergic deficits are present at the pre-dementia stage in a substantial proportion of patients with mild cognitive impairment with Lewy bodies (MCI-LB). Furthermore, repeated dopamine transporter imaging in prodromal synucleinopathy states, such as idiopathic rapid-eye-movement (REM) behaviour disorder, has shown the ability to detect progressive nigrostriatal dysfunction over time.

The aim of this preliminary analysis was to examine if serial dopamine transporter imaging could detect changes in striatal tracer uptake between MCI-LB, mild cognitive impairment due to AD (MCI-AD) and healthy controls.

Methods:

We conducted an interim analysis of participants who had repeat dopamine transporter imaging, all ≥ 60 years old. All underwent detailed clinical, neurological and neuropsychological assessments alongside imaging.

Subjects were allocated to one of three clinical diagnoses: MCI-LB (MCI plus one or more of the four core symptoms of DLB), MCI-AD (MCI with none of these core four symptoms) and healthy controls.

Subjects underwent baseline FP-CIT dopaminergic imaging and a repeat FP-CIT imaging between 12-18 months in 55 patients and between 18-38 months in 13 patients. A further, 21 participants underwent a third FP-CIT scan between 11-21 months after the second FP-CIT scan.

Semi-quantitative calculations of striatal binding ratios (SBR) were performed using DaTQUANT software. The percentage change in SBR in each striatal region was calculated as the difference between the last FP-CIT scan and baseline scan, divided by the baseline scan and the result multiplied by 100. The average annual percentage rate of change in SBR was calculated by subsequently using linear interpolation.

Results:

Groups consisted of 22 aged-matched healthy controls (mean age, 73.7 yrs; mean Mini-Mental state Examination [MMSE] score, 28.4), 19 MCI-AD (mean age, 73.5 yrs; mean MMSE score, 26.7), and 27 MCI-LB (mean age, 75.4 yrs; mean MMSE score, 26.8).

In MCI-LB, there was an annual percentage reduction in SBR in all striatal regions, mean (SD); right caudate -3.3% (11.3), left caudate -3.9% (11.7), right putamen -5.6% (11.7), left putamen -5.2% (9.3),

right striatum -5.1% (9.0), left striatum -4.8% (7.7). Comparison between MCI-LB and MCI-AD participants showed significant annual percentage difference in SBR in the right caudate ($p=0.01$), right striatum ($p=0.03$) and a trend towards differences in left caudate ($p=0.08$). Compared with controls, MCI-LB had significant annual percentage difference in SBR in both left ($p=0.03$) and right striatum ($p=0.04$).

Conclusion:

In this preliminary analysis, MCI-LB participants showed a decline in annual SBR consistent with progressive nigrostriatal striatal involvement across all striatal regions. This decline was greater than in controls and, in some areas, in MCI- AD.

Category: Imaging - Poster Presentation

P.50 *Magnetoencephalography, multimodal MRI and amyloid PET in Lewy body disorder: The MILOS study*

Author: Li Su

Additional Authors: Li Su^{1,2}, Yujing Huang¹, James Rowe³, Guy Williams⁴, Richard Henson^{1,5}, John O'Brien¹

1. Department of Psychiatry, University of Cambridge, UK
2. Sino-Britain Centre for Cognition and Ageing Research, Southwest University, China
3. Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
4. Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, UK
5. MRC Cognition and Brain Sciences Unit, University of Cambridge, Cambridge, UK

Introduction

Lewy Body dementia (LBD) includes two related conditions: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). LBD shares many symptoms with the more widely known conditions such as Alzheimer's disease (AD) thus misdiagnosis is common. However, LBD is currently under-studied and requires different management, so better understanding of its neurobiological basis is needed in order for developing new diagnosis and treatments. To detect the damage to brain structure and function associated with LBD, we are combining multiple neuroimaging techniques in the ongoing MILOS study.

Methods

We are recruiting and testing 24 patients with PDD, 24 patients with DLB and 24 healthy controls. We are using simultaneous magnetoencephalography (MEG) and electroencephalography (EEG) to detect abnormal electromagnetic activity in the brain. MEG and EEG are extremely temporally sensitive, measuring tiny changes in magnetic and electric (respectively) fields outside the scalp millisecond by millisecond. Magnetic resonance imaging (MRI) is used to measure changes in brain structure, magnetization transfer (for water-macromolecule interactions) and proton spectroscopy (occipital GABA). Patients with LBD are also invited for PIB Positron Emission Tomography (PET) scans for beta-amyloid, a hallmark for AD pathology. Cognitive tests will be carried out on all participants in order to compare the memory, attention, visuospatial and other functions between those with and those without LBD. Blood samples will be obtained for analysis of genetic and other blood-borne markers.

Preliminary results

Although the study is ongoing, our initial analysis of the first quarter of the subjects suggests an increased amyloid burden in basal ganglia, cingulate and occipital regions in LBD. In the MEG and EEG data, we found an altered spatial distribution in source estimates and a shifted spectral frequency distribution in LBD.

Expected outcomes

This unique multi-modal study is using combined MEG, EEG, MRI and PET. Our findings are intended to provide new insights into the dynamic brain changes associated with LBD, and relate such functional measures with underlying degeneration and pathology, so that new diagnostic methods and treatments can be developed.

Category: Imaging - Poster Presentation

P.51 *FP-CIT and time to DLB diagnosis in clinical care; results from the DIAMOND-Lewy WP1 study*

Author: Joseph Kane
Additional Authors: Dr Joseph Kane^{1,2}
Dr Ajenthan Surendranathan³
Mrs Sally AH Barker¹
Mrs Allison Bentley³
Dr John-Paul Taylor¹
Prof Alan J Thomas¹
Prof Louise M Allan⁴
Dr Richard J McNally⁵
Dr Louise Hayes⁵
Prof Ian G McKeith¹
Prof David J Burn¹
Prof John T O'Brien^{1,3}

1 Institute of Neuroscience, Newcastle University, United Kingdom (UK)
2 Centre for Public Health, Queen's University, UK
3 Department of Psychiatry, University of Cambridge, UK
4 College of Medicine and Health, University of Exeter, UK
5 Institute of Health and Society, Newcastle University, UK

Background

Dopaminergic (FP-CIT) brain SPECT imaging has good accuracy in differentiating dementia with Lewy bodies (DLB) from Alzheimer's disease. Currently many DLB cases are missed in clinical practice, and use of biomarkers like FP-CIT imaging may assist with diagnosis. However, access to the biomarker can vary among clinical services and long waiting times may dissuade clinicians from using this investigation. It is also possible that use of biomarkers, because of the time taken to obtain scans and results, may prolong the diagnostic process. We therefore aimed to determine the rate of diagnostic revision in patients with DLB in those who did or did not undergo FP-CIT imaging, and the impact of this investigation on time to diagnosis.

Methods

DLB cases identified during a screening process of nine memory clinics and dementia services, located across two distinct geographical areas, over an 18-month period, were approached for detailed retrospective case note review. The dates and outcomes of every clinical appointment and investigation were recorded. In particular, use of FP-CIT imaging was noted and dates of any diagnoses made, including that of the final DLB diagnosis, recorded. Mann Whitney U test was used to compare non-parametric continuous data, and χ^2 used to compare categorical data.

Results

Seventy-four patients with DLB were recruited, 36 of whom (49%) were assigned another dementia subtype diagnosis during their contact with clinical care. Thirty subjects had an FP-CIT scan as part of their clinical care (41%). 37% (11/30) of DLB subjects who underwent FP-CIT during their contact with services were previously assigned an alternative dementia subtype, compared with 59% of DLB participants who did not undergo the scan (χ^2 (1) =2.9, $p=0.09$).

The period of time from initial assessment to initial dementia diagnosis was longer in DLB patients who had FP-CIT scans (median 103 days, 56-292) than those that didn't (median 5 days, 0-129) ($U=265$, $p<0.01$). However, patients who had FP-CIT were not observed to experience a longer time from initial assessment to DLB diagnosis (median 154 days, 84-761) than other patients (median 117 days, 27-487) ($U=439$, $p=0.17$).

Discussion

Patients with DLB are often initially assigned an alternative dementia subtype. Those referred for FP-CIT scans may be less likely to undergo diagnostic revision than those who were not, although this still occurred in one in three patients who had FP-CIT imaging. Referral for FP-CIT imaging did not delay time to DLB diagnosis. Our results provide support that the use of biomarkers in clinical practice, in this case FP-CIT imaging, does not prolong the diagnostic process and results more often in a diagnosis that does not require later revision.

Category: Imaging - Poster Presentation

P.52 *Cortical Thinning in dementia with Lewy bodies, Parkinson's disease dementia and Alzheimer's disease.*

Author: Rosie Watson

Additional Authors: Authors: Rosie Watson¹, Sean J. Colloby², Andrew M. Blamire³, John T. O'Brien^{2,4} and John-Paul Taylor²

¹The Florey Institute of Neuroscience and Mental Health and the Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Australia.

²Institute of Neuroscience. Newcastle University, Campus for Health and Vitality, Newcastle upon Tyne, UK.

³Institute of Cellular Medicine & Newcastle Magnetic Resonance Centre, Newcastle University, Newcastle upon Tyne, UK.

⁴Department of Psychiatry, University of Cambridge, Cambridge., UK.

Background: Alzheimer's disease (AD) and Lewy body dementias are common forms of neurodegenerative dementia in older age. Lewy body dementias include dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), with up to 80% of people with Parkinson's disease (PD) developing dementia 15-20 years after the initial diagnosis. There is significant overlap in the clinical features and underlying neuropathological change across the Alzheimer's disease, Parkinson's disease spectrum. We aimed to investigate the pattern of cortical thinning on MRI in Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia.

Method: Two hundred and forty-five participants (76 AD, 65 DLB, 29 PDD and 76 cognitively normal (CN)) over the age of 65 years, underwent 3 Tesla T1-weighted MRI, clinical and cognitive assessments. FreeSurfer 5.1 was used to obtain cortical thickness estimates and contrast patterns of cortical thinning across groups.

Results: All participants with dementia had mild to moderate cognitive impairment and were matched across groups for dementia severity and global cognition. There was a similar pattern of regional cortical thinning in AD and DLB, but with more cortical thinning in the entorhinal and parahippocampal structures in AD. By contrast, there was no significant difference in regional cortical thickness in PDD compared with CN or DLB. Global measurement of cortical thickness found CN > PDD > DLB > AD ($F_{3, 241} \leq 123.2$, $p < 0.001$). The average difference compared to CN was PDD -1.8%, DLB -5.5% and AD -6.4%.

Conclusions: In a well-characterised cohort of people with dementia, the pattern of cortical thinning in DLB was similar to AD, but, there was more cortical thinning in the entorhinal cortices and left parahippocampal gyrus in AD, supporting the inclusion of preserved medial temporal lobe structures as a supportive biomarker in the recently revised clinical diagnostic criteria. However, there was less global cortical thinning in PDD, with no significant regional difference between PDD and CN. These findings highlight the overlap across the AD/PD dementia spectrum and the potential for differing mechanisms underlying neurodegeneration in DLB and PDD.

Category: Imaging - Poster Presentation

P.53 Topography of Cholinergic Vulnerability in Dementia with Lewy Bodies Involves Key Visual Attention, Spatial Navigation, Saliency, and Alertness Network Hubs

Author: Prabesh Kanel

Additional Authors: Prabesh Kanel, PhD^{1,4}, Martijn L.T.M. Müller, PhD^{1,4}, Robert A. Koeppe, PhD^{1,4}, Kirk A. Frey, MD, PhD^{1,2}, & Nicolaas I. Bohnen, MD, PhD^{1,2,3,4}

¹Radiology, University of Michigan, Ann Arbor, MI, United States, 48104; ²Neurology, University of Michigan, Ann Arbor, MI, United States, 48104; ³Neurology Service and GRECC, Veterans Administration Ann Arbor Healthcare System, Ann Arbor, MI, United States, 48104; ⁴Morris K. Udall Center of Excellence for Parkinson's Disease Research, University of Michigan, Ann Arbor, MI, United States.

INTRODUCTION: In vivo brain PET imaging studies of dementia with Lewy bodies (DLB) uniformly show nigrostriatal dopaminergic loss with variations in degeneration pattern of cholinergic neurons. Vesicular acetylcholine transporter (VACHT) 18F-fluoroethoxybenzovesamicol (18F-FEOBV) radioligand brain PET, unlike previous acetylcholinesterase analogue radiotracers, allows for non-invasive whole brain quantification of cholinergic terminal changes. The goal of this exploratory study was to investigate whole brain cholinergic vulnerability in DLB patients compared to age- and gender-matched control subjects (NC) using SPM voxel-based analysis of 18F-FEOBV brain PET.

MATERIAL & METHODS: Five DLB patients; 3 females; average age 77.8 ± 4.2 years, duration of disease 4.5 ± 2.1 years, and Mini-Mental State Exam score of 18.6 ± 4.8 and 21 NCs; 13 females; average age 73.5 ± 8.5 , and Mini-Mental State Exam score of 27.4 ± 2.3 underwent delayed acquisition brain PET imaging from 3-3.5 hours (scanned every 5 minutes for a total of 6 frames) following intravenous injection of 8 mCi of 18F-FEOBV. Distribution volume ratios (DVR) were calculated using supratentorial white matter as a reference region. SPM12 voxel-based t-test group comparisons were performed. VBM results were thresholded at voxel level $p < 0.001$ and corrected for whole-brain comparisons using cluster level false discovery rate ($p < 0.05$).

RESULTS: The results show four large clusters that contained multiple anatomical regions with peak level at left Brodmann (BA) area 41 (MNI[-56 -22 6] , $p < 0.001$ & cluster size = 3251), right BA6 (MNI[56 0 40], $p < 0.001$ & cluster size = 3105), left-BA32 (MNI[-6 16 36], $p < 0.001$ & cluster size = 1820) and left BA6 (MNI[-48 -6 52] ($p < 0.002$ & cluster size = 1462). Regional detailed analysis shows most prominent cholinergic denervation in DLB patients in bilateral opercula and anterior-to-mid cingulate cortices, bilateral insula, right more than left lateral geniculate nuclei, pulvinar, right proximal optic radiation, bilateral anterior and superior thalami, and right posterior hippocampal fimbria and fornix.

DISCUSSION: This study extends on previous MR studies that show degeneration of cholinergic neuron projections in DLB. With the present PET study, we have evidence that suggests that topography of cholinergic vulnerability in DLB involves regions that have been recognized as key hubs responsible for visual attention (visual thalamus), saliency (insula), spatial navigation (fimbria/fornix), and alertness (cingulo-opercular) networks. Cholinergic denervation of these regions may play an important role in specific clinical features, like cognitive fluctuations, visuo-perceptual and visual hallucinations, visuospatial changes and falls in DLB. Future studies are needed to expand on and confirm these findings and examine the relative contribution of other DLB-related pathology such as amyloidopathy and tauopathy to these clinical features.

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Category: Imaging - Poster Presentation

P.54 DLB detection with cardiac MIBG in a FP-CIT negative cohort

Author: Joseph KANE

Additional Authors: Dr Joseph PM Kane^{1,2}

Ms Gemma Roberts^{1,3}

Dr George Petrides³

Dr James J Lloyd^{1,3}

Prof John T O'Brien^{1,4}

Prof Alan J Thomas¹

¹ Institute of Neuroscience, Newcastle University, United Kingdom (UK)

² Centre for Public Health, Queen's University, UK

³ Nuclear medicine Department, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

⁴ Department of Psychiatry, University of Cambridge, UK

Background

¹²³I-2β -carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (FP-CIT) SPECT has demonstrated good accuracy in differentiating Dementia with Lewy bodies (DLB) from Alzheimer's disease (AD). However, a proportion of DLB cases may never demonstrate striatal Lewy body pathology sufficient to produce an abnormal FP-CIT scan, and may therefore fail to be detected in clinical practice. Cardiac ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy has also demonstrated good accuracy in differentiating DLB from AD, and may assist in clinical detection, but has not been specifically investigated in clinical samples of DLB patients with negative FP-CIT scans.

Methods

We screened Medical Physics databases and Psychiatry of Old Age clinics in North East England for patients who had had a normal FP-CIT (as reported by clinical services) but nonetheless fulfilled consensus criteria for possible or probable DLB. A panel of independent diagnosticians, blinded to investigation results, confirmed diagnosis. Each underwent clinical assessment and cardiac MIBG. FP-CIT scans were reprocessed and given a visual rating by panel of experienced researchers. The scans were assessed as part of a wider cohort of both DLB and AD patients, with raters blinded to diagnosis. Late heart/mediastinum ratios <1.7 defined MIBG as abnormal.

Results

From those identified, four patients with probable DLB and two with possible DLB consented to participation in the study. Mean values for Mini-mental Score Examination, Bristol Activities of Daily Living Scale and Unified Parkinson's Disease Rating Scale (motor subscale) were 23.3 (SD ±3.1), 12.3 (SD ±5.0) and 7.8 (SD ±7.7) respectively. In two cases (one probable DLB, the other possible DLB), the blinded study panel reported an abnormal FP-CIT scan result, in disagreement with the rating provided by clinical services; one of these cases also had an abnormal MIBG result. One probable DLB case had an abnormal MIBG but normal FP-CIT, while two probable DLB cases and one possible DLB case had both normal FP-CIT and MIBG.

Discussion

Differences between FP-CIT findings reported in routine clinical care, and those reported by our blinded panel of experienced researchers, may indicate that careful re-evaluation of normal FP-CIT scans, including semi-quantification, should occur prior to the use of cardiac MIBG. Although our sample size is small, our data indicates that both FP-CIT reanalysis and cardiac MIBG as a second-line investigation could improve the confidence in DLB diagnosis in those with apparently false negative results, and potentially improve DLB detection. However, the results also raise the possibility that some false negative cases may be due to preservation of nigrostriatal dopaminergic function even in the presence of Lewy body disease. Correlation of both FP-CIT and MIBG

findings with neuropathological findings will be important in further understanding disease progression and the clinical utility of both investigations.

Category: Imaging - Poster Presentation

P.55 Comparison of 123I-FP-CIT SPECT three quantification methods: a clinicopathologic analysis in 23 patients.

Author: Daniela Maltais
Additional Authors: Daniela Maltais¹
Lennon Jordan¹
Hoon-Ki Min ¹
Toji Miyagawa^{2,4}
Scott Przybelski¹
Dennis Dickson^{3,4}
Melissa Murray^{3,4}
Kejal Kantarci ^{1,4}
Bradley Boeve^{2,4}
Val Lowe^{1,4}

Institutions: 1) Department of Diagnostic Radiology, 2) Department of Neurology, 3) Neuropathology Laboratory, and 4) Alzheimer's Disease Research Center, Mayo Clinic, Rochester, MN, and Jacksonville, FL, United States

Objective: To conduct a retrospective study examining the relationship between 123I-FP-CIT SPECT and neuropathological findings comparing three 123I-FP-CIT SPECT quantitative methods in patients with neurodegenerative syndromes.

Methods: The 123I-FP-CIT SPECT and neuropathologic findings among patients with neurodegenerative syndromes from the Mayo Alzheimer's Disease Research Center (ADRC) and the Mayo Clinic Study of Aging were examined. Neuropathologic findings based on the presence or absence of Lewy body disease (LBD) were compared against results from three 123I-FP-CIT SPECT quantitative methods: MIMneuro (MIM Software Inc.), DaTQUANT (GE Healthcare), and manual region of interest (ROI) creation on an Advantage Workstation (GE Healthcare). Striatum to background ratio (SBR) was calculated on our manual method and was used for comparison with SBRs generated by MIM and DaTQUANT. The left and right SBRs for caudate, putamen and striatum were evaluated with the manual method. For DaTQUANT and MIM the left, right, total and average SBRs and z-scores for striatum, caudate, putamen, anterior putamen, and posterior putamen were calculated.

Results: The cohort includes 23 patients (19 (83%) male, age 75.4 +/- 10.2 SD at death). The antemortem clinical diagnoses were Alzheimer's disease dementia (N=6), dementia with Lewy bodies (N=12), mixed ADem/DLB (N=1), Parkinson's disease with mild cognitive impairment (N=2), corticobasal syndrome (N=1) and idiopathic REM sleep behavior disorder (N=1). Seventeen (74%) had LBD pathology. All three 123I-FP-CIT SPECT quantitative methods have AUROC values above 0.931 and up to 0.979 (p<0.001), showing good discrimination between LBD and non-LBD patients in each region assessed. There was no significant difference between which region was more sensitive, showing good discrimination between both caudate and putamen. The MIM and DaTQUANT program z-scores were more sensitive than the SBR values.

Conclusions: All three 123I-FP-CIT SPECT quantitative methods show good discrimination between LBD and non-LBD patients in each region assessed, both through the use of SBRs and z-scores, with z-scores being more sensitive.

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Keywords: Lewy body disease, dementia; 123I-FP-CIT SPECT; neuropathology; neuroimaging

Category: Imaging - Poster Presentation

P.56 Analysis of Ioflupane-SPECT Findings Using DaTQUANT in Patients with Idiopathic REM Sleep Behavior Disorder

Author: Daniela Maltais
Additional Authors: Daniela Maltais²,
Toji Miyagawa¹
Hoon-Ki Min²
Scott Przybelski⁴,
Lennon Jordan,²
Timothy Lesnik⁴
Erick St. Louis^{1,5}
Michael Silber ^{1,5}
Jonathan Graff-Radford¹
David Jones¹
Rodolfo Savica¹
Daniel Drubach¹
David Knopman¹
Ronald Peterson¹
Julie Fields³
Mary Machulda³
Leah Forsberg¹
Laura Allen¹
Zuzana Nedelska²
Bradley Boeve^{1,5},
Kejal Kantarci²
Val Lowe²

Institutions: 1) Department of Neurology, 2) Department of Diagnostic Radiology, 3) Department of Psychiatry and Psychology, 4) Department of and Health Sciences Research, and 5) Center for Sleep Medicine Mayo Clinic, Rochester, MN

Background: Reduced striatonigral uptake on ioflupane SPECT reflects dopamine deficiency, and this finding can be seen in patients with Lewy body disease (LBD) pathology. The patients with idiopathic REM sleep behavior disorder (iRBD) tend to have underlying LBD pathology, and a high percentage ultimately develop clinically-diagnosed dementia with Lewy bodies (DLB) or Parkinson's disease. We analyze ioflupane SPECT findings in patients with iRBD compared to Alzheimer's disease dementia (ADem; uptake tends to be normal) and DLB (uptake tends to be abnormal, using z-scores from DaTQUANT software (GE Healthcare)).

Design/Methods: The mean DaTQUANT z-score of the caudate and putamen for iRBD, ADem and DLB who had undergone ioflupane SPECT at the Mayo Alzheimer's Disease Research Center were analyzed and compared.

Results: Data on 22 iRBD patients (mean age 62.8 ± 7.6 years, 14 male) were analyzed and compared to 16 ADem and 40 DLB patients. The mean z-scores for each group of interest was iRBD - putamen: -0.19 ± 1.35 and caudate -0.09 ± 1.39 ; ADem - putamen: 0.47 ± 1.80 and caudate 0.89 ± 2.02 , DLB - putamen: -1.99 ± 1.28 and caudate -2.40 ± 1.41 . iRBD had z-scores which did not differ from ADem (putamen $P=0.21$, caudate $p=0.08$), but which were higher than DLB scores (putamen $P<0.001$, caudate $P<0.001$). Two (9%) iRBD patients had at least one z-score value <-1.5 , compared to 1 (6%) for ADem (this patient had mixed LBD and Alzheimer's disease pathology) and 32 (80%) for DLB.

Conclusions: The striatonigral uptake using DaTQUANT quantitation is reduced in a minority of iRBD patients. Analyses using longitudinal ioflupane SPECT and associated quantitation may provide insights on those iRBD patients who are evolving to DLB or Parkinson's disease.

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Keywords: RBD, ioflupane SPECT, neuroimaging

Category: Imaging - Poster Presentation

P.57 Mild cognitive impairment progressing to dementia with Lewy bodies: Regional atrophy rates and associations with tau and amyloid PET

Author: Zuzana Nedelska

Additional Authors: Zuzana Nedelska MD1, Bradley Boeve MD2, Tanis Ferman PhD3, Matthew Senjem MS1,4, Scott Przybelski4, Timothy Lesnick MS4, David Knopman MD2, Jonathan Graff-Radford MD2, David Jones MD2, Rodolfo Savica MD PhD2, Daniel Drubach MD2, Julie Fields PhD3, Neill Graff-Radford MD2, Val Lowe MD1, Clifford Jack Jr. MD1, Ronald Petersen MD PhD2, Kejal Kantarci MD1 from 1Department of Diagnostic Radiology, 2Department of Neurology, 3Department of Psychiatry and Psychology, 4Department of Health Sciences Research; Mayo Clinic Rochester and Jacksonville

Background: Patients with mild cognitive impairment (MCI) with visual hallucinations, REM-sleep behavior disorder, parkinsonism or fluctuations may have prodromal dementia with Lewy bodies (DLB) and Lewy body disease as an underlying cause, but they often have overlapping Alzheimer's disease-related pathology as well. Identifying the imaging findings associated with prodromal DLB is necessary for understanding the disease progression and predicting who will progress to probable DLB in the near future. We investigated the pattern and magnitude of regional brain atrophy rates in prodromal DLB. To better understand the influence of neurofibrillary tangle tau- and amyloid- β -related pathologies on atrophy rates in patients who may have prodromal DLB, we used AV-1451 and PiB PET imaging as proxy for these pathologies.

Methods: Patients with MCI (mean age=70) with one or more clinical features of DLB (n=56), who either progressed to probable DLB (n=28) or remained stable (n=28), and age- and sex-matched cognitively unimpaired adults (CU; n=112) who underwent at least two serial MRIs (average follow-up=18 months) were included. Regional gray matter atrophy rates were measured using Tensor-based morphometry with Symmetric Diffeomorphic Normalization algorithm. Regional atrophy rates were compared among DLB-progressors, MCI-stable, and CU groups using voxel-wise and atlas-based approaches. In a subset of MCI patients (n=22), we assessed correlations between regional atrophy rates and regional AV-1451 and global PiB uptake on PET performed at the time of MRIs.

Results: DLB-progressors showed greater atrophy rates in multiple subcortical and cortical regions compared to CU: caudate, thalamus, lateral temporal, parahippocampal/entorhinal, posterior cingulate, precuneus and orbital-frontal ($p<0.001$), and also lateral occipital, fusiform and middle frontal cortices ($p<0.05$). The atrophy rates in the amygdala ($p=0.072$) and hippocampus ($p=0.18$) were low. DLB-progressors, compared to MCI-stables, showed also greater atrophy rates in caudate, thalamus, lateral temporal, posterior cingulate and orbito-frontal cortices ($p<0.05$). MCI-stables, compared to CU, showed slightly greater atrophy rates in lateral temporal, parahippocampus/entorhinal, fusiform and middle frontal cortices ($p<0.05$). Higher global PiB uptake correlated with a greater atrophy rate in basal ganglia - caudate ($r=0.49$; $p=0.025$). Higher age-adjusted regional AV-1451 uptake correlated with a greater atrophy rate in the amygdala ($r=0.60$; $p=0.002$). However, we did not observe associations of global PiB or regional AV-1451 uptake with greater atrophy rates in neocortical regions in these patients.

Conclusions: MCI patients who progressed to probable DLB were characterized by greater atrophy rates in cortical and subcortical regions compared to MCI who remained stable. Associations of higher atrophy rates in the caudate with higher PiB and in amygdala with higher AV-1541 uptake suggest possible interactions among amyloid- β , tau and α -synuclein in subcortical regions. Conversely, cortical atrophy rates in MCI patients with DLB features were not associated with AV-1451 or PiB uptake in neocortical regions, suggesting that greater cortical atrophy rates in prodromal DLB are likely associated with Lewy body-related and other rather than amyloid- β and neurofibrillary tangle-tau pathology.

Category: Imaging - Poster Presentation

P.58 Analysis of Ioflupane-SPECT findings using DaTQUANT in patients with mild cognitive impairment

Author: Zuzana Nedelska

Additional Authors: Toji Miyagawa MD PhD2, Scott Przybelski3, Daniela Maltais1, Paul Min PhD1, Lennon Jordan1, Tim Lesnick MS3, Jonathan Graff-Radford MD2, David Jones MD2, Rodolfo Savica MD PhD2, Daniel Drubach MD2, David Knopman MD2, Ronald Petersen MD PhD2, Julie Fields PhD4, Mary Machulda PhD4, Leah Forsberg PhD2, Laura Allen APRN2, Bradley Boeve MD2, Kejal Kantarci MD1, Val Lowe MD1 from 1Department of Diagnostic Radiology, 2Department of Neurology, 3Department of and Health Sciences Research, 4Department of Psychiatry and Psychology

Background: Reduced striatonigral uptake on ioflupane SPECT reflects dopamine deficiency, and this finding is typical in patients with Lewy body disease (LBD) pathology. Patients with nonamnesic mild cognitive impairment (naMCI) and/or REM sleep behavior disorder (RBD) tend to have underlying LBD pathology, whereas those with amnesic MCI (aMCI) and those without RBD tend to have Alzheimer's disease or other non-LBD pathologies. In this study, we analyzed ioflupane SPECT findings in patients with aMCI vs naMCI, and then with MCI with (+RBD) vs without RBD (-RBD), using z-scores from DaTQUANT software (GE Healthcare).

Methods: The mean DaTQUANT z-score of the caudate and putamen for each patient with MCI who had undergone ioflupane SPECT were analyzed and compared.

Results: Data on 36 MCI patients (mean age 70.6 ± 7.7 years, 29 male) were analyzed, of whom 13 had naMCI and 23 had aMCI, and 26 of all MCI had RBD. The mean z-scores for each subgroup of interest were naMCI - putamen: -1.08 ± 1.83 and caudate -0.87 ± 1.40 ; aMCI - putamen: -0.36 ± 1.99 and caudate -0.23 ± 1.91 ; MCI+RBD - putamen: -1.05 ± 1.80 and caudate -0.84 ± 1.54 ; MCI-RBD - putamen: 0.49 ± 1.92 and caudate 0.52 ± 1.96 (Figure). There were no differences between naMCI and aMCI (putamen $p < 0.29$, caudate $p < 0.30$), but MCI+RBD had lower z-scores than MCI-RBD (putamen $p < 0.03$ and caudate $p < 0.03$).

Conclusions: The striatonigral uptake using DaTQUANT quantitation is lower in patients with MCI and RBD, which is most commonly associated with underlying LBD pathology. Ioflupane SPECT may be useful in identifying MCI patients with prodromal DLB.

Category: Imaging - Poster Presentation

P.59 Neuromelanin-sensitive MRI correlates of executive function and verbal memory in Parkinson's disease with freezing of gait

Author: Daniel Huddleston

Additional Authors: 2. Felicia Goldstein

Emory University School of Medicine, Department of Neurology

3. Jason Langley

University of California Riverside, Center for Advanced Neuroimaging

4. Richa Tripathi

Emory University School of Medicine, Department of Neurology

5. Morgan Lane

Emory University Rollins School of Public Health

6. Bruce Crosson

Emory University School of Medicine, Department of Neurology

Atlanta VA Medical Center, Center for Visual and Neurocognitive Rehabilitation

7. Xiaoping Hu

University of California Riverside, Department of Bioengineering

8. Stewart Factor

Emory University School of Medicine, Department of Neurology

Background:

Freezing of gait (FOG) is a disabling Parkinson's disease (PD) symptom associated with falls and poor quality of life. FOG can be classified pharmacologically as levodopa-responsive (LRP-FOG) or levodopa-resistant (LRST-FOG), and the latter is particularly disabling due to lack of adequate treatment. New insights and biomarker tools are needed to understand FOG mechanisms and assist targeted therapeutics development for its subtypes.

Multiple studies have reported an association between executive dysfunction and FOG, and in a prior study we found a specific association between executive dysfunction and LRST-FOG (Factor et al, 2014, PMID: 25446341). However, the neural substrates linking cognitive impairment and FOG remain unclear. Neuromelanin-sensitive MRI (NM-MRI) allows study of the dopaminergic and noradrenergic systems in a single 11-minute scan. Recent NM-MRI studies have established its sensitivity to PD neurodegeneration in substantia nigra pars compacta (SNc) and locus coeruleus (LC) and its very high scan-rescan reproducibility (Huddleston et al, 2017, PMID: 28240402; Langley et al, PMID: 27687624). In addition, we recently studied 29 PD patients with FOG using NM-MRI and found SNc volume significantly reduced in PD with FOG (FOG-PD) compared to controls. SNc volume also correlates positively with Montreal Cognitive Assessment in FOG-PD (Huddleston et al, 2018, p55, <https://kuleuvencongres.be/FOG2018/files/fog2018-abstract-book.pdf>). Here we present results from a subset of these patients studied with NM-MRI and detailed neurocognitive testing. To investigate the relationship between cognition, FOG subtype, and catecholamine systems, we examined correlations between SNc and LC volumes and measures of executive function and verbal memory in 19 PD patients with either LRP-FOG (8) or LRST-FOG (11).

Materials and Methods:

FOG-PD patients were recruited in the Emory Movement Disorders Clinic. FOG pharmacologic response was assessed using a structured examination in the practically defined OFF state and after levodopa challenge. Each patient was assessed with measures of executive function (Trails A and B, digit span, verbal fluency measures), and verbal memory (Hopkins Verbal Learning Test) in the ON state.

All patients were scanned with a Siemens Trio MRI system (12-channel receive-only head coil) at the Emory Center for Systems Imaging. NM-MRI data was acquired using a 2D gradient-echo sequence with reduced flip angle magnetization transfer preparation pulse (Huddleston et al, 2017, PMID: 28240402). NM-MRI processing steps to determine SNc volume and LC volume were performed using a published automated method (Langley et al, PMID: 27687624). Statistical analysis was done with SPSS-24 (IBM).

Results:

Significant correlations were identified in the LRST-FOG group between LC and SNc volumes and measures of executive function and verbal memory as shown in the Figure. No significant correlations between LC and SNc volumes and these cognitive measures were identified in the LRP-FOG group.

Discussion:

To our knowledge no prior studies have assessed LC and SNc with NM-MRI to investigate FOG and cognitive impairment in PD. Although the sample size is small, the number and strength of these correlations implicates LC and SNc neurodegeneration in the pathophysiology of executive dysfunction and verbal memory changes in LRST-FOG, but not LRP-FOG. Further study in larger groups is needed.

Category: Imaging - Poster Presentation

P.60 Clinical profiles of late-onset psychiatric patients exhibiting incidental REM sleep without atonia: comparison with those of patients with idiopathic RBD and PD/DLB

Author: Hiroshige Fujishiro

Additional Authors: 1,2Hiroshige Fujishiro MD, PhD, 1Masato Okuda MS, 1Kunihiro Iwamoto MD, PhD, 1Seiko Miyata PhD, 1Youta Torii MD, PhD, 1Shuji Iritani MD, PhD, and 1Norio Ozaki MD, PhD

1Department of Psychiatry, Nagoya University Graduate School of Medicine, 65 Tsurumai, Showa, Nagoya, Aichi 466-8550 Japan

2Departments of Psychiatry, Kawasaki Memorial Hospital, 20-1 Shiomidai, Miyamae, Kawasaki, Kanagawa 216-0013 Japan

Correspondence: Dr Hiroshige Fujishiro MD PhD

Department of Psychiatry, Kawasaki Memorial Hospital, 20-1 Shiomidai, Miyamae, Kawasaki, Kanagawa 216-0013 Japan

Introduction: Rapid eye movement (REM) sleep without atonia (RWA), which is a hallmark of REM sleep behavior disorder (RBD) on polysomnography (PSG), may represent specific characteristics of prodromal Parkinson's disease (PD) / dementia with Lewy bodies (DLB), even when dream-enactment behavior is absent. We investigated the clinical profiles associated with PD/DLB in late-onset psychiatric patients exhibiting incidental RWA.

Materials and Methods: Among patients who underwent PSG in our psychiatric ward, eight with incidental RWA, nine with idiopathic RBD, and seven with PD or DLB who had preceding RBD were included. Clinical variables, including the percentage of RWA in the total REM sleep (%RWA), were compared among the three groups.

Results: In the incidental RWA group, patients were diagnosed with major depressive disorder (MDD) (n = 6) and somatic symptom disorder (n = 2). Their initial psychiatric diagnoses were made between 50 to 66 years of age. Seven patients were receiving antidepressants when PSG was performed. The frequency of depressive disorders as a primary psychiatric diagnosis and antidepressant-usage were significantly higher in the incidental RWA group than in the other groups. There were no differences in the prevalence of supportive features of DLB among the three groups. The median %RWA was significantly lower in the incidental RWA group than in the other groups. In the incidental RWA group, isolated (twice in 2.5 years) or transient RBD episodes were suspected in three MDD patients during the observation period (mean, 19 ±16 months). Although the cardiac [123I]-metaiodobenzylguanidine uptake was significantly higher in the incidental RWA group compared with the other groups, the groups showed overlap in the specific binding ratios (SBR) on dopamine transporter imaging. When the clinical profiles were focused on dopaminergic transmission in the incidental RWA group, four patients exhibited transient drug-induced parkinsonism. The values of SBR in the examined three patients with a clinical history of drug-induced parkinsonism (mean values of SBR: 3.43, 3.89, and 4.44) were relatively lower compared to those in two without (mean value of SBR: 5.13 and 6.67). In addition to treatment with antidepressants, augmentation pharmacotherapy with aripiprazole, a partial agonist at dopamine D2 and D3, was effective in the three patients with MDD who received this treatment. All patients in the three groups exhibited cingulate island sign ratios on brain perfusion single-photon emission computed tomography within a threshold of 0.281, which is the optimal cutoff value for a diagnosis of DLB.

Conclusions: In the present study, most patients were admitted to our psychiatric ward for management of their psychiatric symptoms and they subsequently underwent PSG. In addition to this unique and small sample, taking psychotropics and the patients' relatively older ages may affect the clinical profiles. Although late-onset psychiatric patients with incidental RWA partially shared common clinical profiles with idiopathic RBD and PD/DLB in this series, further studies are needed to elucidate clinical significance of incidental RWA for diagnosis of prodromal PD/DLB.

Poster Presentations

Section: Neuropathology & Biology

Category: Neuropathology & Biology - Poster Presentation

P.61 *Neuroinflammation aggravates spreading alpha-synuclein oligomerization in Lewy body dementia mice*

Author: Kohji Fukunaga

Additional Authors: Reiko Fukunaga, Mako Fukunaga, Jing Xu, Kazuya Matsuo and Kohji Fukunaga
Tohoku University Graduate School of Pharmaceutical Sciences

[Background and Objectives] Accumulation and aggregation of alpha-synuclein in mid brain and cortex are causative for neuronal death in Lewy body with dementia (LBD). We found that the pathology is partly regulated by long-chain polyunsaturated fatty acids (LCPUFAs) such as arachidonic acid (AA) (1, 2) and brain inflammation. For example, fatty acid binding protein 3 (FABP3, H-FABP) is critical for AA-induced alpha-synuclein oligomerization (1, 2). However, the pathophysiological relevance of FABP3 and neuroinflammation remains unclear in alpha-synuclein spreading mechanism. We here documented the effect of neuroinflammation in the alpha-synuclein fibril-injected LBD mice. [Methods] To address the effects of neuroinflammation in alpha-synuclein spreading, we developed alpha-synuclein spreading model mice with or without LPS administration. The alpha-synuclein fibrils are injected into the dorso lateral of striatum and its spreading was assessed by immunohistochemistry. [Results] At two months after alpha-synuclein fibril injection, mice exhibited cognitive impairment in novel object recognition task. The phosphorylated alpha-synuclein was detected in the cerebral cortex within two months. The single administration of lipopolysaccharide (LPS) before alpha-synuclein injection aggravated the phosphorylated alpha-synuclein accumulation. The neuroinflammation-induced morphological change in astrocytes was also evident in LPS treatments. [Conclusions] The alpha-synuclein injection mice into striatum is useful for screening LBD therapeutics which inhibit spreading and aggregation of alpha-synuclein. The LBD pathology is aggravated by neuroinflammation induced by LPS. This research is partially supported by AMED (17dm0107071; <http://lewybody2016.jp/>). The authors declare no conflict of interests. (1) Shioda N et al., J Biol Chem 2014;289:18957-18965. (2) Cheng A et al., Brain Res. 2019;1807:1980-197.

Category: Neuropathology & Biology - Poster Presentation

P.62 *Retrospective evaluation of Lewy Related Pathology Staging Systems*

Author: Jon Toledo

Additional Authors: Jon B Toledo, Department of Neurology, Houston Methodist Hospital

Lauren Walker, Institute of Neurosciences, Newcastle University

John Q Trojanowski, Pathology and Laboratory Medicine, University of Pennsylvania

Johannes Attems, Institute of Neurosciences, Newcastle University

Background:

Pathological deposition of α -synuclein encompasses two different neurodegenerative conditions, multiple system atrophy and Lewy related pathology (LRP), which can clinically present as Parkinson disease, Dementia with Lewy bodies (DLB) and Alzheimer disease with LRP. Previously developed neuropathological staging criteria for DLB in 2005 have been shown not to be able to classify a large number of subjects. Since then several staging criteria have been proposed. Here, we retrospectively evaluate previously proposed and the proposed new LRP consensus neuropathological staging criteria in a large and varied sample of well characterized LRP neuropathological cases.

Methods:

We included 204 subjects followed till autopsy. All of them had all necessary areas for the proposed staging criteria, except for olfactory bulb region. Sections were stained with Syn 303. We applied the DLB 2005 third report, Braak 2003, Leverenz 2008, the Unified Staging System criteria and the new proposed criteria to these cases.

Results:

The percentage of cases not classified by each of the staging schemes were as follows: 58.3% for the DLB 2005 third report criteria, 36.3% for the Braak 2003, 6.8% for the Leverenz 2008, 0% for the Unified Staging System criteria and for the new proposed criteria. Overall, the largest percentage of unclassified cases presented clinically as AD dementia or other dementias (non-DLB). A comparison of classification between criteria was performed.

Conclusions:

The newly proposed criteria classified all the cases in this larger cohort into a single stage. Further studies to evaluate inter-rater agreement prospectively are needed.

P.63 *Introduction of an Assessment Toolkit Increases the Rate of DLB Diagnosis*

Author: Ajenthan Surendranathan

Additional Authors: L. Su - University of Cambridge and Southwest University, China;

E. Mak - University of Cambridge;

L. Passamonti - University of Cambridge;

Y.T. Hong - University of Cambridge;

P. Vázquez Rodríguez - University of Cambridge;

W.R. Bevan-Jones - University of Cambridge;

S.A.E. Brain - Royal Berkshire NHS Foundation Trust;

T.D. Fryer - University of Cambridge;

F.I. Aigbirhio - University of Cambridge;

J.B. Rowe - University of Cambridge;

J.T. O'Brien - University of Cambridge.

Background: There is increasing evidence that inflammation plays a role in the pathology of neurodegeneration, particularly in Alzheimer's disease and Parkinson's disease. There are few studies however investigating inflammation in dementia with Lewy bodies (DLB).

Here we study inflammation in DLB using MRI and PET imaging together with cytokine analysis, to investigate the relationship between clinical features and central and peripheral inflammation.

Methods: 19 patients with probable DLB and 16 similarly aged controls underwent 3 Tesla MRI and PET imaging with 11C-PK11195, a marker of microglial activation in vivo. Peripheral cytokines were also measured in all subjects, as well as in an additional 10 control subjects, using the Mesoscale Human Cytokine 36 plex panel as well as additional assays for high sensitivity c-reactive protein, tumor necrosis factor receptor 1, interleukin-34, YKL-40 (Chitinase-3-like protein 1) and colony stimulating factor.

Results: Elevated microglial activation was recorded in dementia with Lewy bodies subjects with mild disease compared to those with moderate/severe impairment (see Figure 1), with strong correlations found in patients between cognitive performance as measured by the revised Addenbrooke's Cognitive Examination and 11C-PK11195 non-displaceable binding potential, in several regions including the caudate nucleus ($R=0.83$, $P=0.00008$) and cuneus ($R=0.77$, $P=0.0005$).

Several inflammatory cytokines were found to have significantly different levels in DLB subjects compared to controls. Macrophage inflammatory protein-3 ($P=0.001$), interleukin-17A ($P=0.008$) and interleukin-2 ($P=0.046$) were all increased and interleukin-8 ($P=0.024$) was reduced.

Discussion: Our results provide evidence of central and peripheral inflammation in dementia with Lewy bodies, with microglial activation occurring early in the disease in key regions known to be associated with DLB pathology, before declining as cognition also declines. Raised peripheral cytokines associated with T-cell function additionally suggests involvement of the adaptive immune system.

P.64 *Initiation of Parkinson's Disease from Gut to Brain by Delta-secretase.*

Author: EunHee Ahn

Additional Authors: Eun Hee Ahn^{1, *}, Seong Su Kang^{1, *}, Xia Liu¹, Guiqin Chen², Zhentao Zhang², Bindu Chandrasekharan¹, Ashfaqu M. Alam¹, Andrew S. Neish¹, Xuebing Cao³ and Keqiang Ye^{1, 4, #}

¹Department of Pathology and Laboratory Medicine, Emory University School of Medicine
Atlanta, GA 30322, USA

²Department of Neurology, Renmin Hospital of Wuhan University,
Wuhan, China

³Department of Neurology, Union Hospital, Tongji Medical College, Huazhong University of Science and
Technology, Wuhan, China

⁴Translational Center for Stem Cell Research, Tongji Hospital, Tongji University School of Medicine,
Shanghai 200065, China

Title: Initiation of Parkinson's Disease from Gut to Brain by Delta-secretase.

Introduction

Lewy pathology, composed of α -Synuclein (α -Syn) inclusions, a hallmark of Parkinson's disease (PD), progressively spreads from the enteric nervous system (ENS) into the central nervous system (CNS). However, it remains unclear how this process is regulated at a molecular level. Asparagine endopeptidase (AEP) is, a lysosomal cysteine protease, specifically cleaves its substrate after asparagine. Recently, we reported that this enzyme is escalated in the brain in an age-dependent manner. It simultaneously cleaves both APP and Tau in Alzheimer's disease (AD) brains and mediates the senile plaque and NFT (neurofibrillary tangle) pathologies. Moreover, AEP cuts Tau at N368 and enhances the aggregation of Tau and augments its neurotoxicity. Most recently, we reported that AEP is activated in PD brains and cleaves human α -Syn at N103 and mediates its pathological roles in PD pathogenesis.

Material and Methods

Mice, primary cultured rat neurons; Purification of human α -Synuclein FL and α -SynN103 or GST-Tau FL and Tau N368: Proteins were filtered through a 0.22 μ m syringe filter and injected the FPLC machine (Superdex 200 column; GE Health care); Generation of 6 different PFFs (α -Synuclein, α -Synuclein N103, Tau FL, Tau N368, FL+FL and N103+N368) ; BIAcore X100 (real time binding assay); PD patients gut biopsy and immunofluorescent staining; Transmission electron microscopy (TEM); X-ray diffraction; Oral gavage of rotenone treatment; Stereotaxic injection; Mice colonic injection; Vagotomy and vagus nerve isolation; Behavioral tests (Rotarod test, Tail suspension test, Novel object recognition test and Water maze test).

Results

We show that delta-secretase (AEP) which cleaves both α -Syn at N103 and Tau at N368 mediates their fibrillation and retrograde propagation from the gut to the brain, triggering nigra dopaminergic neuronal loss associated with Lewy bodies and motor dysfunction in SNCA Tg and SNCA Tg /AEP KO mice. Also through the immunoprecipitation and immunostain experiments, we confirmed α -Syn N103 and Tau N368 robustly associate with each other and are highly elevated in PD patients' gut and brain. As well as, we observed chronic oral administration of the neurotoxin rotenone induces AEP activation and α -Syn N103/Tau N368 complex formation in the gut, eliciting constipation and dopaminergic neuronal death in an AEP-dependent manner. Preformed fibrils (PFFs) of α -Syn N103/Tau N368 are more compact, neurotoxic, and travel faster along vagus nerve than their counterparts. Colonic injection of PFFs induces PD pathologies and motor dysfunctions, associated with cognitive impairments.

Conclusion

Thus, delta-secretase plays a crucial role in initiating PD pathology progression from the ENS to the CNS. Also, these findings support that Tau pathology transmission in vivo requires either α -Syn or Tau overexpression in SNCA or Tau P301S transgenic mice. Together, our novel observations demonstrate

that AEP-cleaved Tau and α -Syn form the fibrils in the colon that travel along vagus nerve from the gut into the brain, and induce dopaminergic neuron loss in the substantia nigra (SN), initiating PD pathogenesis and various motor and non-motor dysfunctions. Clearly, delta-secretase is an innovative disease-modifying drug target for treating PD.

P.65 *The pair netrin-1/DCC regulates dopamine neuronal cell survival, death and impacts on Parkinson's disease*

Author: EunHee Ahn

Additional Authors: Mélissa Jasmin^{1*}, Eun Hee Ahn^{2*}, Merja Voutilainen^{3*}, Joanna Fombonne^{1\$}, Catherine Guix¹, Tuulikki Viljakainen³, Seong Su Kang², Li-ying Yu³, Mart Saarma³, Patrick Mehlen^{1#}, and Keqiang Ye^{2,4#}

¹Apoptosis, Cancer and Development Laboratory - Equipe labellisée 'La Ligue', LabEx DEVweCAN, Centre de Recherche en Cancérologie de Lyon, INSERM U1052-CNRS UMR5286, Université de Lyon, Université de Lyon¹, Centre Léon Bérard, 69008 Lyon, France; ²Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA 30322, USA ; ³Institute of Biotechnology, HiLIFE, University of Helsinki, FIN-00014, Helsinki, Finland; ⁴Tongji Hospital, Tongji University School of Medicine, Shanghai 200065, China

Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disease characterized by the preferential degeneration of dopamine (DA) neurons of the substantia nigra pars compacta (SNpc), leading to debilitating motor symptoms. Indeed, these neurons are involved in the control of motricity motor supplying the dorsal striatum with dopamine through long axonal projections forming the nigrostriatal pathway. Netrin-1, initially identified as an axon guidance molecule, is now emerging as a multifunctional secreted molecule implicated both during tissue patterning and adult pathologies. In the developing and adult central nervous system, netrin-1 regulates various biological processes, including axonal growth, synaptic plasticity, and inflammation. DCC, its main receptor of the Netrin-1, known to trigger cell death through its cleavage by caspases unless bound by netrin-1, is highly present in mature dopamine neurons of the substantia nigra that typically degenerate in Parkinson's disease. Moreover, polymorphisms of DCC gene are associated with the disease. Typically, when unbound to their ligands, dependence receptors undergo proteolysis, which in turn activates cell death mainly by apoptosis, whereas binding to their ligands induces a "positive" signalling ensuring cell survival but also the activation of the ligand's canonical pathway (proliferation, migration, differentiation for instance). However the role of this multifunctional cue in adult brain remains unknown.

Material and Methods

Post-mortem brain samples were dissected from frozen brains of PD patients and aged-match non-demented controls from the Emory Alzheimer's Disease Research Center; DCC D1290N mutant mice; Inducible netrin-1 transgenic mice CAG:Cre;Rosa26-LSL-Netrin-1; Immunoblotting; Netrin-1+/LacZ generation and salmon gal staining; TUNEL assay; Oral gavage of rotenone treatment; Stereotaxic injection; 6-OHDA lesioned animals (rat); Tamoxifen injection in netrin-1 inducible mice; Amphetamine-induced ipsilateral rotations in 6-OHDA lesioned rodents; Perfusion and tissue processing for immunofluorescence and immunochemistry; Immunofluorescence staining; Immunohistochemistry; Gamma counting and autoradiographic analyses; Ventral midbrain primary culture; Autoradiographic analysis of the distribution of 125I-proteins.

Results

We thus investigated the role of the pair netrin-1/DCC in normal dopamine neurons and its potential implication in Parkinson's disease. Here we show, in various Parkinson's disease models and samples from Parkinson's disease patient brains, a reduction of netrin-1 levels associated with an increase of DCC cleavage and caspase activity. Moreover, specific silencing of netrin-1 in the substantia nigra induces DCC cleavage and leads to a loss of dopamine neurons and renders motor deficits in mice. Reciprocally, intrastriatal injection of netrin-1 or genetic inactivation of DCC-induced cell death via the use of mice model, where DCC is point mutated in the caspase cleavage site, prevents dopamine neuron degeneration and improves motor behaviour in rodent models of Parkinson's disease.

Conclusion

These results highlight the role of the pair netrin-1/DCC in the dopamine neuron fate and the therapeutic potential of targeting netrin-1 signalling in Parkinson's disease.

Category: Neuropathology & Biology - Poster Presentation

P.66 Can early tau depositions in mixed Alzheimer's disease and Lewy body disease give insights into disease progression?

Author: Lauren Walker

Additional Authors: Elizabeth Thomson - Institute of Neuroscience - Newcastle University

Monalisa Thamed - Institute of Neuroscience - Newcastle University

Kirsty E McAleese - Institute of Neuroscience - Newcastle University

Mary Johnson - Institute of Neuroscience - Newcastle University

Alan J Thomas - Institute of Neuroscience - Newcastle University

Johannes Attems - Institute of Neuroscience - Newcastle University

Background

Cases that neuropathologically fulfil the criteria for both Alzheimer's disease (AD) and Lewy body disease (LBD) are classified as mixed dementia (mixed AD/LBD). Interestingly, some of these cases present clinically with AD, and others with LBD. Previous work indicates cases with an AD clinical phenotype exhibit a higher hyperphosphorylated tau burden [1]. This may suggest that tau pathology has been developing for a longer period of time and is more established in these cases. Conversely, in cases with a LBD clinical phenotype hyperphosphorylated tau may have been deposited at a later time point in LBD progression and still in the early stages of development. The evolutionary development of tau can be detected by different tau antibodies, therefore the 'age' of each tau tangle in human post-mortem brain tissue can be identified. MC1 marks a conformational change that takes place in the early stages of tau tangle development, CP13 marks an intermediate stage, and AT8 marks mature neurofibrillary tangles. The aim of this project was to determine if mixed AD/LBD cases that presented clinically with LBD have a higher burden of tau in the early stage of development.

Methods

We quantitatively assessed post-mortem tissue sections from the hippocampus of temporal lobe of cases that have fulfilled neuropathological criteria for mixed AD/DLB (n=21; mean age, 78 SE±2.1; male 12, female 9) with tau marker MC1 to identify early tau conformations. We also assessed markers of more established tau pathology including AT8 and CP13.

Results

Mixed AD/LBD cases with a LBD clinical phenotype had a greater MC1 burden in the hippocampus and temporal lobe ($p<0.05$) compared to those with an AD clinical phenotype. There was no difference between clinical groups in relation to CP13, however AT8 burden was increased in the clinically AD group compared to the LBD group ($p<0.05$).

Conclusion

These results suggest in neuropathologically mixed AD/LBD cases, those with a clinical phenotype of LBD may have developed dementia initially caused by LBD, with concomitant AD related pathology developing later in the disease course. This highlights the importance of biomarkers for co-morbid pathologies and if identified, secondary pathologies should be considered in future treatment strategies. [1] Walker, L., et al. Acta Neuropathol, 2015. 129(5): p. 729-48.

P.67 *Sub-cortical visual system pathology and hallucinations in dementia with Lewy bodies*

Author: Daniel Erskine

Additional Authors: Dr John-Paul Taylor, Institute of Neuroscience, Newcastle University, UK

Dr Nichola Lax, Wellcome Centre for Mitochondrial Research, Newcastle University, UK

Professor Alan Thomas, Institute of Neuroscience, Newcastle University, UK

Dr Ahmad Khundakar, School of Science, Engineering and Design, Teesside University, UK

Professor Ian McKeith, Institute of Neuroscience, Newcastle University, UK

Professor Johannes Attems, Institute of Neuroscience, Newcastle University, UK

Professor Sir Doug Turnbull, Wellcome Centre for Mitochondrial Research, Newcastle University, UK

Dr Chris Morris, Institute of Neuroscience, Newcastle University, UK

Background

Visual hallucinations are a core symptom of dementia with Lewy bodies (DLB) yet their underlying aetiology remains unknown. With the aim of better understanding visual hallucinations in DLB, we have conducted a comprehensive post-mortem study of the sub-cortical visual nuclei to identify whether neuropathological changes may contribute to visual hallucinations.

Methods

Post-mortem brain tissue from the lateral geniculate nucleus (LGN), primary visual cortex (V1), pulvinar and superior colliculus (SC) was obtained from hallucinating DLB cases, non-hallucinating Alzheimer's disease (AD) cases and aged controls. Quantitative neuropathological methods were employed to determine the severity of neuropathological lesions and stereology was used to quantify neuronal numbers. In addition, RNA sequencing was performed in the pulvinar and V1, and, for the first time in DLB research, imaging mass cytometry (CyTOF) was employed to quantify changes to the mitochondrial respiratory chain in individual neurons.

Results

The LGN and V1 were remarkably preserved though the SC and pulvinar demonstrated focal cell loss and Lewy pathology in DLB cases. AD cases had cell loss and neuropathology in all evaluated regions. RNA sequencing revealed synaptic changes to both the pulvinar, which manifested neuropathological changes, and V1, which appeared neuropathologically preserved. Changes to V1 appeared consistent with compensation for reduced input. CyTOF of the LGN is on-going.

Conclusions

These results suggest that, in contrast to non-hallucinating AD cases, neurodegenerative pathology in the visual system in DLB was more focal, typically affecting regions involved in attention. Furthermore, we observed transcriptomic changes to regions without obvious neuropathology and speculate these may be compensation for altered input from connected brain regions subject to neurodegeneration. These findings indicate the interplay between neuropathologically compromised regions and compensatory changes in apparently preserved regions may be driving visual hallucinations in DLB.

P.68 *Evaluation of the nuclear localisation of alpha-synuclein and tau in Lewy body diseases*

Author: David Koss

Additional Authors: Authors: David J. Koss¹, Daniel Erskine¹, Johannes Attems¹, and Tiago Outeiro^{1,2}

¹Ageing research Laboratories, institute of Neuroscience, Newcastle University.

²Department of Experimental Neurodegeneration, University Medical Center Goettingen, Goettingen, Germany.

Background

Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are defined by the cytoplasmic accumulation of alpha-synuclein (a-Syn) within neurons. Although predominately pre-synaptic, a-Syn was also originally observed within the nucleus. In-vitro, nuclear localisation is frequently observed and is associated with toxicity, yet in human brain tissue similar observations have been inconsistent and remain controversial. As a consequence of the contradictory reports in-situ, the implications of such nuclear a-Syn localisation in-vivo remains unknown. Despite several post-mortem studies observing an enrichment of a-Syn within the neuronal nuclei of PD and DLB cases, the issue is confounded by reports that many but not all a-Syn antibodies demonstrate non-specific cross reactivity with unidentified protein(s) within a-Syn knockout tissue. Thus, it is clear that a close examination of methods and antibodies employed is required to optimise detection and quantify the occurrence of nuclear a-Syn in-situ. Akin to the contention surrounding nuclear aSyn, the nuclear occurrence of tau as a result of Alzheimer's disease (AD) pathology has also received significant attention. Recent evidence suggests a disease dependent abnormal association of tau with nuclear pore complexes, resulting in the deregulation of nuclear trafficking. Whether such dysfunction is elicited in Lewy body diseases via equivalent/additive interactions with a-Syn and/or tau is unclear and requires investigation.

Methods

a-Syn (MJFR1, KM501, LB509 and pS129) and tau (Tau-5, AT-8, CP13 and PHF1) antibodies will be screened for western blot detection in nuclear fractionates, isolated via sucrose gradient centrifugation from human cortical lysates. Specificity of immunoreactivity will be verified in a-Syn KO mice tissue. High resolution subcellular location of a-Syn / tau (intranuclear cf. nuclear envelope association) will be established via immuno-fluorescent confocal microscopy, co-localisation of a-Syn/tau will be established with appropriate references markers (intra-nuclear marker: Histone H3 and nuclear envelope marker: Lamin B1). Nuclear associated a-Syn and tau in DLB and PD groups will be quantified biochemically using validated antibodies and measured against non-diseases controls as well as AD cases. Correlations with differential cortical vulnerability will be examined, comparing regions of high pathology (temporal, Brodmann area 22) and low pathology (occipital, Brodmann area 17).

Outcomes

Given the clear potential for artificial detection of nuclear a-Syn, a robust protocol for the accurate evaluation of the physiologically and/or pathologically nuclear a-Syn is required. Equally, considering the disruption of nuclear processes induced by pathological tau and the potential for synergy between tau and a-Syn, an evaluation of the nuclear occurrence of these two proteins across disease groups is required. This study will seek to further inform on the underlying pathology of neurodegenerative diseases, assist in the validation of numerous in-vitro models focused on nuclear a-Syn and may highlight potential cellular functions as targets for future therapeutic interventions.

Category: Neuropathology & Biology - Poster Presentation

P.69 Scopolamine Causes Hyper-Stimulus-Processing in the Medial Prefrontal Cortex during an Interval Timing Task

Author: Qiang Zhang

Additional Authors: Dennis Jung, University of Rochester

Benjamin DeCorte, University of Iowa, Hospitals and Clinics

Travis Larson, University of Iowa, Hospitals and Clinics

YoungCho Kim, University of Iowa, Hospitals and Clinics

Joel Geerling, University of Iowa, Hospitals and Clinics

Nandakumar Narayanan, University of Iowa, Hospitals and Clinics

Background:

Cholinergic dysfunction is a major feature of Alzheimer's disease, Parkinson's disease and Lewy body dementia. Here, we examine how cholinergic dysfunction impacts the frontal cortex in rodent models during performance of an interval timing task that can be disrupted in patients with Parkinson's disease and Alzheimer's disease. Interval timing requires attention to time and working memory for temporal rules, and involves the medial prefrontal cortex (MFC) in both humans and rodents. The MFC receives prominent cholinergic input; however, the effect of cholinergic inhibition on the MFC network activities during interval timing has not been studied.

Methods:

Eight wild-type mice were trained in a 12-second interval timing task before 16-channel microelectrode arrays were implanted into the MFC. During the interval timing task, mice were trained to respond 12 seconds after a discriminative stimulus. Responses prior to 12 seconds were not rewarded. Neuronal ensemble recordings were performed during the interval timing task 30 min after intraperitoneal injections of scopolamine (1mg/kg) or normal saline (vehicle).

Results:

225 neurons were recorded, and isolated through spike sorting. Neurons that change firing rates during the 12-second interval timing task are associated with temporal control and defined as "ramping" neurons. Scopolamine caused interval timing deficits in wild-type mice, but the "ramping" activities were not significantly changed. However, scopolamine caused prominent increase in stimulus-modulation in the MFC. These data indicate that cholinergic blockade did not change temporal processing in the MFC; rather, it changed stimulus-processing in the MFC.

Conclusions:

Muscarinic cholinergic inhibition through scopolamine enhances stimulus modulated neuronal activities and impairs interval timing in wild-type mice. However, the "ramping" activities were not significantly affected. These results are consistent with the consensus that acetylcholine plays major roles in attention, working memory and stimulus processing, while the dopaminergic system is crucial for the neuronal "ramping" activities and internal pacemaker. These data may have relevance for our understanding of cholinergic functions in human diseases such as Lewy body dementia, Parkinson's disease and Alzheimer's disease.

unctions in human diseases such as Lewy body dementia, Parkinson's disease and Alzheimer's disease.

Category: Neuropathology & Biology - Poster Presentation

P.70 A clinical and pathological report of widely confirmed Lewy bodies in the cerebral cortex including the occipital lobe without pathological changes in the hippocampal CA2/3 region

Author: Masafuchi Ryo

Additional Authors: 1. Name : Kazuko Hasegawa

Institution : Department of Neurology, National Hospital Organization, Sagamihara National Hospital

2. Name : Ikuo Saitoh

Institution : Department of Pathology, National Hospital Organization, Sagamihara National Hospital

3. Name : Saburoh Yagishita

Institution : Clinical Research Center, National Hospital Organization, Sagamihara National Hospital

【PURPOSE】 To report the clinical course and neuropathological features of a case with Lewy Body Disease (LBD) that reveals widely confirmed Lewy bodies (LB) in the cerebral cortex including the occipital lobe without pathological changes in the hippocampal CA2/3 region, one of the characteristic neuropathological findings of Dementia with Lewy bodies (DLB).

【CASE】 A man who died at the age of 59. He was born in Akita prefecture in the northern part of Japan. He had no parkinsonian and/or dementia siblings. X - 10 years, he suffered from a rest tremor of his left hand and fingers from about the age at 50. Following that a rest tremor also appeared on his right hand and fingers. He then visited the neurosurgical and neurological departments of a nearby hospital. He also visited a psychiatry clinic. Within a few year bradykinesia appeared. X - 8 years, he visited University Hospital because of his akinesia. He was shown to have 1. akinesia, 2. rigidity, 3. postural instability. Following the diagnosis of Parkinson's disease (PD), L-dopa treatment was started, and the effect was confirmed. A 123I MIBG myocardial scintigraphy H/M showed early 1.92 late 1.2.9 WO 35.2%. Among the symptoms he experienced were hallucinations, especially visual hallucinations, and he was moved to a dementia clinic in the neighborhood. X - 2 years, due to deterioration in his motor function and severe dyskinesia, he was admitted our hospital. His motor performance and mental status improved, so he was discharged to his home via a nursing home. X - 1 year, following a lapse into dyspnea with sputum clogging, he was taken into hospital by ambulance. A head MRI showed moderate atrophy in the frontal lobe. The DAT scan showed SBR right 1.00 left 1.22. January X years, death was confirmed, but the cause was unknown. Past History X - 21 years Bilateral retinal detachment, X - 11 years right inguinal hernia

【NEUROPATHOLOGICAL FINDINGS】 Brain weight 1150 g. Macroscopic findings Frontal lobes showed moderate atrophy. The cross sections of the brainstem specimen showed substantial depigmentation in the substantia nigra and the locus coeruleus. Microscopic findings Severe neuronal cell loss and gliosis was observed in the substantia nigra and locus coeruleus, together with the presence of LBs. LBs and α -synuclein positive structures were also observed in the cerebral cortex and occipital cortex. Scattered senile plaques were observed in several cortexes but there were few neurofibrillary tangles. Tau positive structures were observed in the entorhinal cortex. Despite the fact that pathological changes in CA2/3 are one of the characteristic features of DLB, in this case there were no findings of pathological changes in CA2/3.

【CONCLUSION】 We report a very rare and important case from the neuropathological point of view in DLB. This is presented here with special reference the distribution of Lewy pathology in DLB and PDD.

P.71 Cholinergic degeneration and adult hippocampal neurogenesis in a potential mouse model of dementia with Lewy bodies

Author: Paul Francis

Additional Authors: Chanati Jantrachotechatchawan¹, Emily Clarke¹, David R Whitfield¹, David R Howlett¹, Clive G Ballard^{1,2}, Paul T Francis¹

¹Wolfson Centre for Age-Related Diseases, King's College London, UK

²University of Exeter Medical School, University of Exeter, UK

Background

Dementia with Lewy bodies (DLB) is marked by deficits in basal forebrain cholinergic systems and adult hippocampal neurogenesis. Heterozygotic mutations in GBA1 gene, which encodes lysosomal enzyme glucocerebrosidase, are the most prevalent risk factor for DLB. Homozygotic mutations cause Gaucher's disease. Mice homozygous for D427V GBA1 mutation have reduced glucocerebrosidase activity and accumulation of glucosylsphingosine. The heterozygous D427V/WT mice, despite a less severe reduction in glucocerebrosidase activity, show evidence of changes in cognition. The D427V/WT mice has translational potential as DLB model but has not been extensively studied.

Methods

Paraffin-embedded sagittal brain sections from 9 WT/WT and 9 D427V/WT GBA1 mice at 12 months old were stained for synaptophysin, vesicular acetylcholine transporter (VACHT), choline acetyltransferase (ChAT), proliferative marker PCNA, HuBD, and doublecortin using fluorescence immunohistochemistry. Images were visualised with confocal microscopy. Immunohistochemical signals were quantified using ImageJ software while cell number was counted from Zen software. Western blotting SDS-PAGE was performed on TRIzol-brain extracts from 5 WT/WT and 5 D427V/WT mice. Significances of difference in any markers between two groups were evaluated by Mann-Whitney U-test (MWU).

Results

The density of innervating cholinergic axons to the dentate gyrus as represented by percentage area of ChAT staining was significantly higher ($p < 0.05$) in D427V/WT than WT/WT. However, the staining area of cholinergic vesicle marker VACHT in the dentate gyrus was significantly lower ($p < 0.001$) in D427V heterozygous mice compared to wild type. Synaptophysin staining intensity was also decreased in the D427V/WT compared with WT/WT ($p < 0.05$). Staining of VACHT was also significantly lower in the motor cortex of D427V/WT ($p < 0.01$) while ChAT or synaptophysin were unchanged. Western blot analysis of hippocampal and cortical samples only showed significant reduction in the level ratio of VACHT/ChAT in the hippocampus of D427V/WT ($p < 0.05$). In the vertical/horizontal diagonal band, the number of cholinergic neurons was unchanged between the two groups but ChAT staining area was upregulated in D427V/WT ($p < 0.05$). Data regarding hippocampal neurogenesis indicated a significantly higher total number of doublecortin-positive cells ($p < 0.01$) and specifically of doublecortin-positive cells with PCNA ($p < 0.05$) in D427V/WT than WT/WT. There was no difference in the number of HuB/D-positive cells between the two groups.

Conclusions

Mice heterozygous for a mutation associated with DLB in humans appear to have a deficit in a key element of cholinergic neurotransmission. As a novel finding, it will be important to confirm this change in other GBA1 mutant mice strains and to explore cholinergic transmission in these mice and mechanistic links between GBA1, the cholinergic system and neurogenesis.

Category: Neuropathology & Biology - Poster Presentation

P.72 Nilotinib's effect on CSF soluble TREM2 (sTREM2) in Parkinson's Disease patient's with mild cognitive impairment (MCI)

Author: Yasar Torres-Yaghi

Additional Authors: Fernando Pagan, MD- Medstar Georgetown University Hospital

Michaeline Hebron, M.S.- Georgetown University

Barbara Wilmarth- Georgetown University

Yasar Torres-Yaghi, MD- Medstar Georgetown University Hospital

Elizabeth Mundel- Medstar Georgetown University Hospital

Nadia Yusuf MD- Medstar Georgetown University Hospital

Charbel E-H Moussa, M.D., Ph.D.- Georgetown University

Background: Nilotinib is a broad-based tyrosine kinase inhibitor with highest affinity to inhibit Abelson (c-Abl) and Discoidin Domain Receptors (DDR1/2). Preclinical evidence indicate that Nilotinib reduces the level of brain alpha-synuclein and attenuates inflammation in models of Parkinson's disease (PD). We previously showed that Nilotinib penetrates the blood-brain-barrier (BBB) and potentially improves clinical outcomes in individuals with PD and Dementia with Lewy Bodies (DLB).

Method: We performed a physiologically-based population pharmacokinetics/pharmacodynamics (popPK/PD) study to determine Nilotinib effects in a cohort of 75 PD participants. Participants were randomized (1:1:1:1:1) into 5 groups (n=15) and received open label random single dose (RSD) 150:200:300:400mg Nilotinib versus placebo. Plasma and cerebrospinal fluid (CSF) were collected at 1, 2, 3 and 4 hours after Nilotinib administration.

Results: The results show that Nilotinib enters the brain in a dose-independent manner and 200mg Nilotinib increases the level of 3,4- Dihydroxyphenylacetic acid (DOPAC) and Homovanillic Acid (HVA), suggesting alteration of dopamine metabolism. Nilotinib appears to significantly reduce CSF oligomeric:total alpha-synuclein ratio and plasma total alpha-synuclein. Furthermore, Nilotinib significantly increases the CSF level of triggering receptors on myeloid cells (TREM)-2, suggesting an anti-inflammatory effect.

Conclusion: Taken together, 200 mg Nilotinib appears to be an optimal single dose that concurrently reduces inflammation and engages surrogate disease biomarkers including dopamine metabolism and alpha-synuclein.

Category: Neuropathology & Biology - Poster Presentation

P.73 C/EBP β /delta-secretase Signaling Mediates Parkinson's Disease Pathogenesis via Regulating α -SNCA and MAO-B Transcription and Proteolytic Cleavage

Author: Zhou Rui Wu

Additional Authors: Zhou Rui Wu, Shanghai Tongji Hospital and Emory University;

Kecheng Lei, Shanghai Tongji Hospital and Emory University;

Xia Liu, Emory University;

Lingjin Jing, Shanghai Tongji Hospital;

Liming Cheng, Shanghai Tongji Hospital;

Keqiang Ye, Emory University .

Background: Parkinson's disease (PD), a progressive multifactorial neurological disease, is characterized by loss of dopaminergic neurons and the presence of intracellular Lewy body inclusion with aggregated α -Synuclein (α Syn) as the major component. MAOB, a crucial monoamine oxidase for dopamine metabolism, triggers oxidative stress in dopaminergic neurons and α Syn aggregation. As a neuroinflammation-related transcription factor, C/EBP β potentially control the expression of α Syn and MAOB during PD onset.

Methods: Luciferase assay, electrophoretic mobility shift assay, and ChIP-PCR experiment are carried out to find the binding motif of C/EBP β on both SNCA and MAOB promoters. Overexpression and knockdown C/EBP β on SH-SY5Y cells and primary neurons are applied to validate these mechanisms in vitro. Moreover, shRNA-C/EBP β virus was injected into the substantia nigra (SN) of human wild-type SNCA transgenic (hSNCA) mice followed by rotenone treatment for 2 months.

Results: C/EBP β acted as an age-dependent transcription factor for both SNCA and MAOB. C/EBP β bound to upstream of the transcription start site of MAOB and SNCA. In SH-SY5Y cells and primary neurons, C/EBP β time-dependently mediated oxidative stress-induced expression of α Syn and MAOB. In contrast, knockdown of C/EBP β repressed the mRNA levels of SNCA and MAOB. Furthermore, depletion of C/EBP β decreased both SNCA and MAOB promoter activities in the neurons stimulated with various oxidative stresses. qPCR and Western blot of C/EBP β validated the knockdown efficiency of C/EBP β in primary neurons. Meanwhile, the inflammation cytokines, including IL-6, IL-1 β , and TNF α , were significantly suppressed when C/EBP β was knocked down by its specific shRNA. As a well-known regulatory target of C/EBP β , the expression of AEP was also repressed in the neurons. Overexpression of C/EBP β in hSNCA mice facilitated PD pathologies and elicits motor disorders, associated with augmentation of delta-secretase, α Syn, and MAOB. In contrast, depletion of C/EBP β from hSNCA mice abolished rotenone-elicited PD pathologies and motor impairments via suppressing the expression of these key factors.

Conclusion: C/EBP β /delta-secretase signaling mediates PD pathogenesis via regulating SNCA and MAOB expression and cleavage.

Category: Neuropathology & Biology - Poster Presentation

P.74 *Glial Abnormalities in Dementia with Lewy Bodies*

Author: Christopher Morris

Additional Authors: Philippa A Malko^{1,2}, Lina Patterson^{1,2,3,4}, Alice Kaganovich⁵, Jinhui Ding⁵, Elisa Majouni⁵, Matthew Jennings^{1,2}, Mark R Cookson⁵, Amy K Reeve⁶,

¹School of Biomedical Sciences, ²Medical Toxicology Centre, and ⁶Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK.

³Ageing Research Laboratories, and ⁴Alzheimer's Society Doctoral Training Centre, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK.

⁵Cell Biology and Gene Expression Section, Laboratory of Neurogenetics, National Institutes on Aging, National Institutes of Health, 35 Convent Drive, Bethesda, Maryland 20814, USA.

Introduction: A prominent feature of neurodegenerative disorders is the presence of microglial and astrocytic responses to pathology and this is particularly the case in Alzheimer's disease (AD). While this glial response in neurodegeneration is thought to be mainly deleterious, astrocytes and microglia play a major role in supporting neuronal function and survival, providing trophic support and engaging in organelle exchange. Previous studies have shown the presence of synaptic changes in AD, and glia are known to modulate synaptic activity with astrocytes supporting synaptic health and microglia promoting synaptic pruning. This might suggest that glial activity and synaptic function are linked. In Dementia with Lewy bodies (DLB) glial changes are less well characterised and we therefore sought to determine how glia may influence pathological changes and in particular the association with synapses.

Methods and Results: RNAseq based analysis of post mortem frontal and temporal cortex demonstrated multiple glial transcripts to be upregulated in DLB compared to age matched control tissue. Despite transcript changes, quantitative neuropathology showed no change in GFAP positive or CD44 positive astrocytes in DLB, although a significant increase in areal fraction covered by GFAP was seen in AD. Increased GFAP expression was also seen in AD using western blotting, but not in DLB. A non-significant increase in areal fraction of microglia (HLA-DR positive, or CD74 positive) was seen for both AD and DLB, however total numbers of hypertrophic microglia were seen to be increased in both AD and DLB temporal cortex. Confocal microscopy with volumetric 3D rendering was used to visualise the interaction of synapses with astrocytes. Total synaptic numbers were reduced in DLB and AD temporal lobe. A significant reduction of astrocytic interaction with synapses was seen in DLB, but not in AD, and these synapses were significantly more likely to lack mitochondria in DLB but not AD.

Conclusion: These data suggest that there is an imbalance in microglial and astrocytic activity in DLB with increased microglial activity and reduced astrocyte function. This imbalance may lead to synaptic dysfunction and potentially synaptic loss and the progressive cognitive decline observed in DLB.

P.75 *Extensive Interneurone Changes in Dementia with Lewy Bodies*

Author: Christopher Morris

Additional Authors: Lina Patterson^{1,2}, Alice Kaganovich³, Daniel Erskine¹, Jinhui Ding³, Elisa Majouni³, Madhurima Dey⁴, Isobel Hiskett⁴, Kayleigh Hughes⁴, Joanna Myslinska⁴, Peter Hanson⁵, Ahmed Khundakar¹, Amy Reeve⁶, John Paul Taylor^{2,7}, Ian McKeith⁷, Johannes Attems^{1,2}, Alan Thomas^{2,7}, Mark Cookson³

¹Ageing Research Laboratories, ²Alzheimer's Society Doctoral Training Centre, and ⁷Biomedical Research Building, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK.

⁴School of Biomedical Sciences, ⁵Medical Toxicology Centre, and ⁶Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, NE2 4HH, UK.

³Cell Biology and Gene Expression Section, Laboratory of Neurogenetics, National Institutes on Aging, National Institutes of Health, 35 Convent Drive, Bethesda, Maryland 20814, USA.

Introduction: One aspect of the biology of Dementia with Lewy bodies (DLB) is the presence of lower levels of pathology compared to other neurocognitive disorders such as Alzheimer's disease. This is despite the presence of similar levels of cognitive impairment. While α -synuclein pathology can be widespread, in certain regions such as the primary visual cortex, Lewy bodies and Lewy neurites can be absent although biochemical changes can still be present¹. This may suggest that CNS biochemical changes in DLB patients may be a major factor in causing the prominent clinical symptoms such as hallucinations and anxiety. Identifying these biochemical changes in the brain, particularly in relation to clinical symptoms may provide indications on how to treat neuropsychiatric symptoms in DLB.

Methods and Results: Using RNA-seq analysis of post mortem brain tissue we compared DLB samples with elderly normal individuals and identified widespread differences in gene expression in DLB. These transcriptome data demonstrated similar alterations in gene expression in frontal, temporal, and occipital cortical regions. RNA changes were focussed on synaptic alterations that were most prominent in GABAergic neurones. Using further post mortem brain samples, western blotting techniques showed marked loss of proteins associated with GABAergic synapses although no loss of GABAergic neurones, along with smaller reductions in glutamatergic synapses. These changes were most marked in temporal lobe but also found in frontal and occipital cortex. Confocal microscopy showed the presence of α -synuclein within GABAergic synapses suggesting α -synuclein accumulation leads to alteration of GABAergic synapses.

Conclusion: Our findings indicate widespread synaptic changes in DLB, particularly associated with GABA suggesting abnormal interneurone function. Strategies targeting GABA synapses and neurones and aimed at restoring synapses may therefore provide therapeutic opportunities in DLB.

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Category: Neuropathology & Biology - Poster Presentation

P.76 *Monoaminergic changes within subgenual cingulate cortex in depression in Dementia with Lewy bodies*

Author: Lina Patterson

Additional Authors: Lina Patterson¹, Rolando Berlinguer-Palminio², Johannes Attems^{1,3}, Alan J Thomas^{1,4}, Christopher M Morris⁵

¹Alzheimer's Society Doctoral Training Centre, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK.

²Bio-Imaging Unit, Medical School, Newcastle University, Newcastle upon Tyne, UK.

³Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, UK.

⁴Gateshead Health NHS Foundation Trust, Queen Elizabeth Hospital, Gateshead, Tyne and Wear, UK.

⁵NIHR Biomedical Research Centre Newcastle, Biomedical Research Building, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK.

Background

Major depression is found in around half of individuals with dementia with Lewy bodies (DLB) and is associated with faster rate of cognitive decline. The subgenual anterior cingulate cortex (sgACC) has been shown to be integral in mood regulation, with considerable evidence of its involvement in major depressive disorder (MDD), with deep brain stimulation of the sgACC showing positive clinical outcome as a treatment for long standing refractory MDD. Monoaminergic deficits in depression are well established and are also observed in DLB, therefore we assessed changes in monoaminergic neurotransmission within sgACC in DLB in relation to depression.

Methods

Post-mortem sgACC tissue from individuals with and without depression was used to assess monoaminergic changes using proteomic methods. Stimulated emission depletion (STED) confocal microscopy has been used to further assess serotonergic, dopaminergic and noradrenergic synaptic changes.

Results

Dopaminergic deficits were observed in sgACC in DLB cases compared to control donors, with a greater reduction in dopaminergic neurotransmission in DLB cases with depression. No changes in serotonergic neurotransmission were observed.

Conclusion

Our work demonstrates the major role of dopaminergic neurotransmission in the aetiology of depression in DLB. Selective targeting of dopaminergic systems may be a therapeutic option for treatment of depression in DLB.

Category: Neuropathology & Biology - Poster Presentation

P.77 Abnormalities of the subgenual cingulate cortex and depression in Dementia with Lewy bodies: GABAergic and glutamatergic synaptic imbalance is associated with alpha-synuclein

Author: Lina Patterson

Additional Authors: Lina Patterson¹, Johannes Attems^{1,2}, Alan J Thomas^{1,3}, Christopher M Morris⁴

¹Alzheimer's Society Doctoral Training Centre, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK.

²Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, UK.

³Gateshead Health NHS Foundation Trust, Queen Elizabeth Hospital, Gateshead, Tyne and Wear, UK.

⁴NIHR Biomedical Research Centre Newcastle, Biomedical Research Building, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, UK.

Background

Depression is a common feature in dementia with Lewy bodies (DLB), observed in over half of patients, often occurring early in the clinical course of the illness and persisting over time. The subgenual anterior cingulate cortex (sgACC) is intimately involved with emotional processing and shows early and extensive pathological changes in DLB and in particular is a site of major α -synuclein deposition. Little is known however, about how changes in sgACC contribute to the aetiology of depression.

Methods

Using immunohistochemical and biochemical approaches we assessed pathological changes in the sgACC in DLB cases with and without depression. Additionally, we assessed GABAergic and glutamatergic synaptic changes in relation to α -synuclein deposition.

Results

We observed no differences in α -synuclein, tau or amyloid- β pathological burden between DLB with and without depression. While overall neuronal cell density was not significantly different between the groups, interneurone density was reduced in DLB cases with depression. A reduction in the total number and also a significant reduction in average volume of GABAergic neuron terminals was observed in DLB cases with depression, although no difference in the proportion of α -synuclein GABAergic terminals was seen in DLB cases with and without depression. Glutamatergic neuron terminal numbers were unchanged in DLB however, synaptic volume was increased overall and glutamatergic synapses containing α -synuclein were increased in DLB cases with depression.

Conclusion

Our results indicate an imbalance in GABAergic/glutamatergic transmission in DLB, with potentially greater glutamatergic drive in those individuals with depression.

Category: Neuropathology & Biology - Poster Presentation

P.78 *Neurodegenerative Pathological Burden in Dementia with Lewy Bodies and the Cingulate Island Sign*

Author: Lina Patterson

Additional Authors: Lina Patterson¹, Michael J Firbank², Sean J Colloby², Johannes Attems^{2,3}, Alan J Thomas^{1,4}, Christopher M Morris⁵

¹Alzheimer's Society Doctoral Training Centre, Newcastle University, Newcastle upon Tyne, UK

²Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK

³Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, UK

⁴Gateshead Health NHS Foundation Trust, Queen Elizabeth Hospital, Gateshead, Tyne and Wear, UK

⁵NIHR Biomedical Research Centre Newcastle, Newcastle University, Newcastle upon Tyne, UK

Background

The cingulate island sign (CIS) is a supportive biomarker in discriminating DLB from AD, and refers to the relative sparing of metabolism in the posterior cingulate cortex (PCC) in relation to precuneus and cuneus (Pr/Cu). The semi-quantitative scoring of pathology using NFT Braak staging has been suggested to be a correlate of the CIS, with CIS in DLB thought to be reflective of lower Tau pathological burden, although the intrinsic pathological basis of the CIS is unknown. Therefore our aim was to investigate which neurodegenerative changes underpin the formation of the CIS.

Methods

Using quantitative neuropathology, α -synuclein, phosphorylated Tau (p-Tau) and amyloid- β (A β) burden was assessed in DLB, AD and control cases in cingulate subregions, as well as Pr/Cu and parahippocampal gyrus (PHG). All cases had undergone MRI and HMPAO SPECT imaging during life, which was used to define the presence or absence of CIS.

Results

The CIS ratios and HMPAO uptake in PCC did not show significant correlations with α -synuclein, p-Tau and A β pathology, or cell density in PCC or Pr/Cu in DLB. This may suggest that factors other than pathological burden, cell loss or atrophy play a role in reduced metabolism in specific brain regions.

Conclusion

Our results indicate that neurodegenerative pathology does not directly correlate with the CIS and preserved metabolism in the PCC in DLB. Therefore other metabolic or pathological deficits are more likely to be relevant for the development of the CIS.

Category: Neuropathology & Biology - Poster Presentation

P.79 Cardiac Sympathetic Denervation and Synucleinopathy in Alzheimer's Disease and Lewy-Type-Synucleinopathies

Author: Geidy Serrano

Additional Authors: 1Geidy E. Serrano; 1David Shprecher; 1Michael Callan; 1Brett Cutler; 1Michael Glass; 2Charles H. Adler; 1Thomas G. Beach

1 Civil Laboratory of Neuropathology, Banner Sun Health Research Institute, Sun City, AZ

2 Department of Neurology, Mayo Clinic College of Medicine, Mayo Clinic Arizona, Scottsdale, AZ

Comorbid Lewy body (LB) pathology is very common in Alzheimer disease (AD), and may confound clinical trial design, yet there is no in-vivo test to identify it. Tissue (and/or radioligand imaging) studies have shown cardiac sympathetic denervation in Parkinson disease (PD) and dementia with Lewy bodies (DLB) but have not been explored in Alzheimer subjects with Lewy bodies (AD/LB). To determine if AD/LB show sympathetic cardiac denervation, we analyzed: 19 cases with autopsy-confirmed PD, 19 AD/DLB, 20 AD/LB not meeting DLB criteria, 12 AD no LB, 30 incidental Lewy body disease (ILBD) and 22 controls without LB. Lewy-type-synucleinopathy (LTS) and Tyrosine hydroxylase (TH) and neurofilament (NF) staining of epicardial and myocardial tissue were graded on a 0-3 point Likert scale, (0=absent, 1=sparse, 2=moderate, 3=numerous). Kruskal-Wallis analysis of variance between groups indicated a significant difference ($p < 0.01$) of TH staining between the groups (medians: control 2.5; ILBD 1.5; AD/DLB 1.0; PD 1.0; AD/LB 3.0; AD-no LB 2.0). Subsequent pair-wise Mann-Whitney analysis showed that PD ($p < 0.05$) and DLB ($p < 0.01$) subjects have significantly reduced TH fiber density as compared to controls; while AD/LB showed no difference. Both PD and AD/DLB subjects also showed significant losses of NF protein-immunoreactive nerve fiber bundles as compared to controls ($p < 0.01$) and both groups showed high LTS densities ($p < 0.0001$). Cardiac LTS densities correlated significantly with brain LTS ($p < 0.001$); while cardiac TH- and NF-immunoreactive nerve fiber densities were negatively correlated with the densities of both brain and cardiac LTS, and UPDRS scores ($p < 0.05$). The clear separation of AD/DLB from controls based on cardiac TH fiber density is the first report of a statistically significant difference between these groups. Our data do not indicate a significant sympathetic cardiac denervation in AD/LB, but strengthen the rationale for using cardiac nuclear imaging with a noradrenergic radioligand, 123I-metaiodobenzylguanidine (123I-MIBG) to separate AD from AD with DLB, an important concept as most cases of AD/DLB are not recognized as such during life.

Category: Neuropathology & Biology - Poster Presentation

P.80 Hippocampal tau pathology burden in Lewy body disorders

Author: Ranjit Ittyerah

Additional Authors: Ranjit Ittyerah¹, David G. Coughlin^{2,3}, Jeffrey Phillips^{3,4}, Simon Miller³, Edward B. Lee^{5,6}, John Q. Trojanowski^{6,7}, Daniel Weintraub^{2,8,9}, Andrew Siderow², John E. Duda^{2,9}, Howard I. Hurtig², David A. Wolk⁷, Paul Yushkevich^{1,7}, Murray Grossman³, David J. Irwin^{3,4}

¹ Penn Image Computing and Science Lab, Dept. of Radiology, University of Pennsylvania Perelman School of Medicine

² Parkinson's Disease and Movement Disorders Center, Dept. of Neurology, University of Pennsylvania Perelman School of Medicine

³ Penn Digital Neuropathology Lab, Dept. of Neurology, University of Pennsylvania Perelman School of Medicine

⁴ Penn Frontotemporal Degeneration Center, Dept. of Neurology, University of Pennsylvania Perelman School of Medicine

⁵ Translational Neuropathology Lab, Dept. of Pathology, University of Pennsylvania Perelman School of Medicine

⁶ Center for Neurodegenerative Disease Research, Dept. of Pathology, University of Pennsylvania Perelman School of Medicine

⁷ Alzheimer's Disease Center, Dept. of Neurology, University of Pennsylvania Perelman School of Medicine

⁸ Department of Psychiatry, University of Pennsylvania Perelman School of Medicine

⁹ Parkinson's Disease Research, Education and Clinical Center, Michael J. Crescenz VA Medical Center, Philadelphia PA, USA 19104

Objective:

To compare regional patterns of tau and alpha-synuclein (SYN) pathology in hippocampal subfields (HIPPSf) in Lewy body disorders (LBD: Parkinson's disease dementia-PDD, Dementia with Lewy bodies-DLB).

Background:

Alzheimer's disease (AD) tau co-pathology is common in LBD and predicts poor prognosis. We previously found the neocortical distribution of tau mapped closely with SYN and diverged from the distribution of tau in AD. Here we use digital pathology in hippocampal-subfields (HIPPSf) to test whether prominent SYN pathology in CA2/3 associates with Tau in LBD, and if HIPPSf tau in LBD differs from AD.

Design/Methods:

Forty-nine autopsy-confirmed LBD subjects were categorized using neuropathological criteria as either medium/high (LBD+AD=22: Braak(B) stages B2-3) or low/negligible (LBD-AD=27: B0-B1) whole brain tau co-pathology and compared to age-matched AD (n=29). Hippocampal sections were stained for tau (AT8) and adjacent LBD sections stained with SYN (SYN303). Digital images of histology sections were analyzed using previously validated methods to manually segment HIPPSf [Entorhinal Cortex (ERC), CA2/3, CA1/Subiculum and CA4/dentate gyrus (DG)] by cytoarchitectural features and measure percent area-occupied (%AO) of tau and SYN. Linear-mixed effects models and independent t-tests tested within- and between-group comparisons.

Results:

In the total LBD cohort, the distribution of SYN%AO was highest in CA2/3 ($t=4.3, p<0.001$); LBD+AD and LBD-AD had similar SYN%AO across HIPPSf ($t=0.01, p>0.1$). Tau%AO associated with SYN%AO across HIPPSf ($\beta=1.8, p<0.01$) with greatest association in CA2/3 ($\beta=0.04, p<0.0001$). In LBD, the distribution of tau%AO was lowest in CA4/DG ($t=-3.5, p<0.001$) compared to higher levels in CA2/3, ERC and A1/Subiculum. Across HIPPSf, AD had higher Tau%AO than both LBD+AD and LBD-AD ($t>6.0, p<0.001$, both) and LBD+AD had higher tau%AO than LBD-AD ($t=4.8, p<0.0001$); however, LBD-AD had a higher ratio of Tau%AO in CA2/3 compared to CA1/Subiculum than both LBD+AD ($t=3.6, p<0.001$) and AD ($t=4.1, p<0.001$).

Conclusion:

The distribution of tau in HIPPsf in LBD correlates with SYN pathology in a relative greater distribution in CA2/3 that is distinct from AD.

P.81 *The prevalence and influence of tau pathology in Lewy body dementias: A meta-analysis*

Author: Kai Sin Chin

Additional Authors: Authors: Kai Sin Chin^{1,2}, Nawaf Yassi^{1,2}, Leonid Churilov^{1,3}, Colin Masters^{1,3} and Rosie Watson^{1,2}.

¹The Florey Institute of Neuroscience and Mental Health, Parkville, Australia

²Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Parkville, Australia.

³The University of Melbourne, Melbourne, Australia.

Background: Lewy body dementias (LBD), including dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), are the second most common form of neurodegenerative dementias in older adults. Neurofibrillary tangles (NFT) formed by tau proteins, a pathological hallmark of Alzheimer's disease, are a common co-pathology in LBD. However, the influence of tau pathology in people with LBD is not completely understood. We aimed to investigate the prevalence and influence of tau pathology on clinical outcomes in people with LBD.

Methods: A systematic literature search was conducted using three major electronic databases (Medline, Embase and PubMed). The search terms were ("dementia with Lewy bodies" OR "diffuse Lewy body disease") AND ("tau protein" OR "tauopathy" OR "neurofibrillary tangle"), entered as both MeSH term and Keyword. After screening all titles and abstracts, relevant studies which investigated the influence of tau pathology on clinical outcomes (clinical phenotypes, cognition, rate of decline and survival) in LBD were included.

Results: Fifty-two studies were identified, which included 34 neuropathologic, 15 cerebrospinal fluid (CSF) and three AV-1451 PET studies. Raw prevalence data from 15 neuropathologic studies showed that 65.5% (290/443) of DLB and 52.0% (223/429) of PDD patients had a Braak NFT stage of III or higher. In six CSF studies, pathological total tau and phosphorylated-tau levels were detected in 27.9% (194/696) and 28.0% (185/661) of DLB, and 22.5% (55/244) and 15.4% (26/169) of PDD patients, respectively. Despite the significant heterogeneity in study designs, people with DLB and high tau burden seemed to be less likely to manifest the core clinical features of DLB, resulting in lower clinical diagnostic accuracy. Higher tau burden also appeared to be associated with worse cognition. There were conflicting results on the influence of tau burden on rate of decline and survival in people with LBD. Formal results of meta-analysis will be presented at the conference.

Conclusion: Tau pathology is common in people with LBD. Understanding the role and significance of co-morbid neuropathological changes in LBD is important as it might improve clinical diagnosis, have implications on disease progression and prognosis, and help to develop effective treatment options. Longitudinal studies, utilizing in vivo, disease specific biomarkers (e.g. Tau PET or CSF) are needed.

P.82 Comparative Grey Matter and White Matter Tau Pathology in LBD and PSP using Digital Histologic Measurements

Author: David Coughlin

Additional Authors: David G. Coughlin MD 1,2,3, Lucia Gianinni BSc, Claire Petersen BSc2, Rebecca Lobrovich2 MSc, David Wolk MD1,4, Andrew Siderowf MD1,3, Daniel Weintraub MD1,6, Edward Lee MD PhD1,7, John Trojanowski MD PhD1,7, Murray Grossman MD1,4 and David Irwin MD MSTR1,2,3

1 Department of Neurology,

2 Digital Neuropathology Laboratory,

3 Lewy Body Disease Center of Excellence,

4 Frontotemporal Dementia Center

5 Alzheimer's Disease Center, at Perelman School of Medicine at the University of Pennsylvania

6 Michael J. Crescenzi VA Medical Center, Parkinson's Disease Research, Education, and Clinical Center,

7 Department of Pathology, Hospital of the University of Pennsylvania, in Philadelphia PA, USA 19104

Objective: To compare the regional distribution of cortical tau pathology between Lewy body disorders (LBD: Parkinson's disease and dementia with Lewy bodies) and progressive supranuclear palsy (PSP) using digital histologic measurements in grey and white matter.

Background: Alpha-synuclein is the primary pathology in LBD; however, half of LBD patients have sufficient Alzheimer's disease (AD) neuropathologic change at autopsy for a secondary neuropathological diagnosis of medium-to-high level AD (LBD+AD), which is associated with decreased survival and faster time to dementia. Tau in particular appears to be related to cognitive deficits. Tau is the primary pathology in PSP, but there are few studies detailing pathologic distribution of tau in PSP, and no direct comparisons with clinically similar LBD. We used digital histology to compare objective, parametric measurements of tau pathology burden in grey matter (GM) and white matter (WM) from post mortem tissue of LBD and PSP.

Design/Methods: 10 neuropathological cases of PSP with focal cognitive deficits (5: primary progressive aphasia, 5 behavioral variant frontotemporal dementia) and 20 cases of LBD+AD (medium-to-high level AD neuropathologic change) with dementia (12: dementia with Lewy bodies, 8: Parkinson's disease dementia) were selected. Tissue sections from angular gyrus (ANG), superior temporal gyrus (STG), and mid-frontal gyrus (MFG) were stained for tau (AT8). Lamina slide scanning system and Halo digital image software v1.90 calculated percentage area occupied (%AO) of tau in GM and WM from digital histology imaging slides. %AO was natural log-transformed (ln) to obtain normal distribution. T-tests compared regional GM and WM tau between LBD+AD and PSP, and across regions within LBD+AD and PSP.

Results: Neocortical average GM tau%AO was equivalent between LBD+AD and PSP (LBD+AD ln-tau%AO mean (+SD):-0.58 (+1.84) v PSP ln-tau%AO: -1.21(+1.5), p=0.4). In LBD+AD, STG had the highest GM tau burden (STG ln-tau%AO: 0.38(+2.24) vs ANG: -0.73(+1.90) and vs MFG: -1.40(+1.98), p<0.001 for both). GM tau burden in STG also was higher in LBD+AD than PSP (PSP STG ln-tau%AO: -1.82(+1.99), p=0.02). In PSP, ANG had the highest mean tau%AO in GM (ANG ln-tau%AO: -1.17(+1.89)), although not significantly greater than STG or MFG (p>0.05). In WM, average tau%AO was higher in PSP than LBD+AD (LBD+AD WM ln-tau%AO: -1.63(+1.59) vs PSP WM ln-tau%AO:-3.00(+1.12), p=0.01). LBD+AD had the highest WM tau burden in STG (-2.25(+1.38) vs ANG :-3.15(+1.38) and vs MFG: -3.59(+1.22), p<0.001 for each). WM tau burden in STG of LBD+AD was equivalent to PSP, but all other regions had higher WM tau%AO in PSP (MFG: -1.65(1.61) p<0.01, ANG:-1.86(1.41), p=0.03).

Conclusion: In this pilot study comparing tau pathology between LBD+AD and PSP using digital histology, we found selectively greater GM tau burden in LBD+AD than PSP in the STG.. However, WM tau pathology was more severe in PSP than LBD+AD, particularly in MFG and ANG. Further studies will elucidate the consequences of these distinct regional patterns of tau pathology for disease progression, survival and in vivo clinical manifestations of disease.

P.83 Identification of DLB-Specific Molecular Changes in a Neuropathology Sample

Author: Lawrence Honig

Additional Authors: Benjamin Tycko, Hackensack University Medical Center

Catherine Do, Hackensack University Medical Center

Min-Suk Kang, Columbia University Irving Medical Center

Karen S. Marder, Columbia University Irving Medical Center

Introduction: Lewy Body Disease and Alzheimer's disease (AD) are commonly co-pathologies. About 90% of brains from individuals with clinical Lewy Body Dementia (LBD) who have pathologically confirmed Lewy Body Disease have some AD pathology, including plaques, more than tangles. Conversely, ~35% of brains from persons with clinical (AD), pathologically confirmed with a high degree of Alzheimer's neuropathological change (ADNC) have some degree of Lewy Body (LB) involvement. The molecular reasons why AD changes (especially amyloid aggregates) and LB changes (synuclein aggregates) co-occur is not known. But because differing amounts and topographical distributions of AD and LB involvement may affect clinical course, prognosis, and treatment, it is important to differentiate during life. Co-occurrence of pathologies also complicates analysis of brain specimens, because comparison of LBD brains versus controls is confounded by the co-occurrence of AD pathology. Hence, our principal comparison is of brains with both DLB and AD (DLB/AD) with brains that have only AD. This is also advantageous in that these two categories are the most common categories in brain banks, with pure LBD and completely normal controls being both much less common. This comparison of DLB/AD with AD, in different brain regions, should allow teasing out of genetic, epigenetic factors, and gene expression differences specific to DLBAD.

Materials and Methods: We have utilized 193 clinically and neuropathologically well-characterized brains from the Columbia University Alzheimer's Disease Research Center Brain Bank, with well-preserved frontal and limbic (cingulate) cortex banked frozen samples. AD is defined as brains having high ADNC without discernible LB. DLB/AD is defined as brains having neocortical LB, and moderate of high ADNC. DLB(pure) is defined as brains showing cortical LB, with minimal plaques or tangles. Normal controls (NC) were selected on the basis of no significant AD pathology, no LB, and no other significant degenerative pathology. Brain specimens were homogenized, high quality DNA (by A260/A280) and RNA (RIN>8) isolated and being sequenced, and DNA sent for EPIC methylation chip analysis.

Results: A comparison of the brain samples in table below, shows that APOE4 allele is of similar frequency in DLB/AD as in AD, and higher than in DLB(pure) or NC. For GBA, variant alleles are present more commonly in DLB/AD or DLB than in AD or NC. Tau H1/H2 haplotype is similar in all four groups. We will present preliminary analysis of RNA sequence and EPIC methylation gene expression data.

DLB/AD

AD

DLB(pure)

Normal Control

NUMBER OF BRAINS

N=59

N=62

N=30

N=42

SEX(M/F)%

64%M/36%F

48%M/52%F

73%M/27%F

55%M/45%F

ETH(W/B/A/H) %

90/0/0/10

84/3/2/10

93/0/3/3

67/11/0/22

AGE (yr)

79±8(65-94)

81±11(55-100)

79.5±8(50-97)

70±17(34-97)

EDUCATION (yr) [N]

15±3(6-20)[47]

14±4(0-20)[60]

17±2(12-20)[14]

16±2(12-20)[18]

LANGUAGE(Eng/Spa/Oth) %

80/12/8

79/12/9

100/0/0

94/6/0

APOE E4pos%[N]

69%[56]

64%[47]

19%[26]

24%[25]

GBAmut pos%[N]

24%[42]

8%[26]

52%[25]

0%[21]

Tau hap(H1H1/H1H2/H2H2)%[N]

60/37/3[38]

53/40/7[15]

65/30/4[23]

0/100/0[1]

Discussion: Large scale RNA sequencing and EPIC methylation analysis may identify LB specific gene expression differences using a comparison of DLB/AD to AD brain tissues, and such differences may be of use as biomarkers and as clues to molecular pathogenesis and potential treatment avenues.

Poster Presentations

Section: Patient/Care Partner

Category: Patient/Care Partner Poster Presentation

P.84 *Crafting Culturally-Appropriate DLB Care: A Case Study*

Author: Trang Tu

Additional Authors: none

BACKGROUND

A substantial portion of those experiencing DLB in the United States are members of racial and ethnic communities whose cultural norms, beliefs, and health practices have been largely under-represented in the dementia research to date. This has led to spillover effects in the form of gaps and biases throughout the continuum of care, from assessment and diagnosis to ongoing symptom identification to disease management and treatment.

The presentation proposed is a descriptive case study that:

1. provides anecdotal evidence on the consequences of under-representation and cultural gaps in the dementia field,
2. illustrates a method of devising culturally-specific dementia care, and
3. demonstrates the implementation of such method in one case.

METHODS

The study tracks and collects data from the experiences of one Vietnamese family over the past 4.5 years, as one of the children serves as primary caregiver to her mother, who was diagnosed initially in 2014 with Alzheimer's dementia and updated in spring 2018 to DLB.

The family experienced repeated and pervasive cultural gaps across multiple provider systems, including medical, research, social services and other support entities. The family caregiver, in conducting lit review on dementias to educate herself, learned that much of the research does not well take into account different cultural norms and practices. In some cases, applying certain best practices was detrimental to her mother's well-being.

A qualitative analysis was conducted that included analysis of patient daily log notes, mapping of provider systems, observation of patient in natural settings, caregiver participant observation, synthesis of patient's medical assessments and visits, and identification of relevant cultural norms and beliefs.

The presentation will share data on how the caregiver conducted the analysis, filtered existing information from the dementia field, and adapted and combined it with her cultural knowledge to create tailored treatment and therapies for her mother.

RESULTS

The family's approach of utilizing existing knowledge and best practices and adapting within a specific cultural context has allowed the patient to optimize quality of life and have the "best of both worlds", at least in their home setting and when the caregiver can coach and guide others who interact with her. However, limitations and challenges remain when the patient interacts externally. She is caught between existing mainstream systems that are often not culturally competent, and community-based resources that may be language- or culturally-responsive, but lack expertise about dementia.

CONCLUSION

The goal of this presentation is to demonstrate that it is possible to develop and implement culturally-specific care approaches and methods. But achieving this at scale will require system-level changes that are predicated on collaboration amongst the dementia field and those with cultural knowledge. The hope is that sharing this case with both the professional field and caregiver community will yield multiple benefits. The field can improve and deepen the way in which it serves diverse communities all along the dementia continuum. And caregivers can gain peer-to-peer support through learning of one family's efforts to bridge cultural needs in dementia care. Together, this can begin to effectuate system-level change.

Category: Patient/Care Partner Poster Presentation

P.85 Living with the Physical (autonomic) symptoms of Lewy body dementia: Research to explore the experiences of people with Lewy body dementia and family carers living in the community.

Author: Allison Bentley

Additional Authors: Allison Bentley - Cambridgeshire & Peterborough NHS Foundation Trust

Professor O'Brien - University of Cambridge

Chris Carling - Cambridge & Peterborough NHS Foundation Trust

Jackie Buck - University of East Anglia

Background: Lewy body dementia (LBD) is associated with higher levels of disability than other dementia subtypes. Symptoms are broad and result in a cluster of complex physical, cognitive, neuropsychiatric, autonomic symptoms. As LBD progresses its impact on the autonomic (involuntary) nervous system is significant. This system regulates the involuntary actions of many bodily functions such as bladder and bowel function, temperature regulation and cardiac function. As these are poorly understood, and often not thought to be part of the dementia, we undertook a qualitative study exploring how physical symptoms affect people with LBD and their family carers. Patient and Public Involvement, in the form of a Carers Advisory Group, ensured those with lived experience of dementia were involved at all stages of the research process.

Aims: To understand: 1) how autonomic symptoms affect people with LBD and their family carers, 2) strategies used to manage the symptoms 3) how to improve support 4) the impact of people with lived experience being involved throughout the research process.

Methods: The Carers Advisory Group, consisting of 4 people, were actively involved with the study design, patient information, advising on recruitment, posters, refining interview questions, lay summaries and analysing interviews. Semi-structured interviews with 21 participants were conducted; 10 people with LBD and 11 spouses. 9 of the interviews were conducted jointly. Data were analysed using thematic analysis and reported using the Consolidated Criteria for Reporting Qualitative Research. The final phase involved raising awareness of the research findings.

Results: Autonomic symptoms were embarrassing and difficult to manage, with bowel, bladder, falls and swallowing issues being particularly disabling. Continence problems reduce social activities and interrupt sleep, having considerable impact on daily life. Three themes emerged: 1) adaptability and coping strategies 2) negotiating access to services, and the role of having a 'key supporter' and 3) noticing when carers may be reaching a crisis point. Collaboration between the researcher, the Carers Advisory Group and participants brought valuable and different perspectives. They advised the clinical researcher on use of language and style when interviewing people with dementia. They noted additional themes and highlighted advice and tips. This resulted in the development of a poster, leaflet and video to be disseminated to a wider audience.

Category: Patient/Care Partner Poster Presentation

P.86 Development of a group-based support and information intervention for people with DLB and their caregivers

Author: Alison Killen

Additional Authors: None

Background

Dementia with Lewy bodies (DLB) is a complex condition. Awareness within the general population is limited and diagnosis can be protracted. Consequently, people with DLB and their families often feel under supported and isolated. Caregivers experience a significantly greater burden and lower quality of life than with other dementias due to the impact of hallucinations, mood disturbances and cognitive fluctuations. Effective DLB focused provision is paramount given the limitations of pharmacological solutions. However psychological support is often minimal and research on this topic is negligible. The objective was to investigate the acceptability and feasibility of a short, group-based, psycho-social support and information intervention aimed at increasing the coping ability of people living with DLB and their caregivers.

Methods

Dyads consisting of participants with a recent DLB diagnosis and informal caregivers attended three to four sessions lasting two and a half hours, held weekly within a memory clinic. Provision was reinforced by a take-home manual. Dyad were separated into caregivers and people with DLB at times for tailored delivery. Content comprised information around cognitive, behavioural and physical changes to equip people to recognise, understand and respond to DLB-specific challenges including ways of maintaining a positive outlook. People living with DLB covered symptom management, peer engagement, exploring feelings and goal planning. Caregivers addressed issues including managing behavioural difficulties, planning ahead and meeting their own needs, including managing personal anxiety and uncertainty. Knowledge sharing between attendees was encouraged. Participants completed assessment measures and post-intervention interviews.

Results

Thirty two participants (sixteen dyads) attended over three groups. Attendance was 73% with attrition predominantly attributable to illness or caregivers' work commitments. People with DLB and caregivers were highly satisfied with the structure including session numbers and length. The separate delivery of some topics was popular with both dyad members. Session content was well received, with many participants highlighting the importance of specifically DLB focussed face to face information after difficult journeys through the diagnostic pathway. Peer contact was also highly valued with most participants knowing no-one with DLB previously. People living with DLB described benefiting from sharing experiences with others in similar situations, and becoming more informed. Three quarters of caregivers identified feeling more able to cope in eight or more of thirteen areas covered, most notably understanding visual disturbances, and changes in thinking abilities.

Conclusion

This study has established the acceptability and feasibility of a support and information package uniquely focussed on DLB, designed both for people with this condition and caregivers. The indication of benefits, particularly in caregiver coping, offers scope for larger scale formal testing to determine effectiveness. With training, this intervention is deliverable by non-DLB specialist health professionals within primary care, where memory support services are commonly located, using the session manual to ensure replicability and minimise fidelity loss. Attendance could provide participants with increased understanding and effective coping strategies thus mitigating some of the difficulties unamenable to pharmacological solutions, which generally increase as the condition progresses. This may have the impact of reducing demands on health and social care.

Category: Patient/Care Partner Poster Presentation

P.87 Non-pharmacological Approaches Care Partners can Use to Address the Behavioral Changes in Loved Ones Living with Lewy Body Dementia (LBD)

Author: Rosemary Dawson

Additional Authors: Norma Loeb - Lewy Body Dementia Resource Center (LBDRC)

Pat Synder - Lewy Body Dementia Association (LBDA) - Volunteer

Helen Buell Whitworth - LBDTools.com

James Whitworth - LBD Tools.com

See the uploaded file for relevant experience.

Background

Most people living with Lewy body dementia (LBD) experience behavioral or mood changes which vary from person to person, occurring at different times as the disease progresses. Some types are more common than others; some are benign while others are more intrusive and distressing. Behavioral changes contribute significantly to caregiver burden. Fortunately, there are ways to address these behavioral changes - with and without drugs. Clinical and research experts in LBD recommend that non-pharmacological approaches comprise the first course of action (unless the person living with LBD poses a significant danger to self or others).

LBD care partners need resources to help them acquire the knowledge and skills to apply non-drug approaches when their loved ones experience hallucinations, illusions, delusions, paranoia, misidentification, Capgras syndrome, reduplicative paramnesia, depression, apathy, anxiety, agitation, verbal and physical aggression, disinhibition, wandering, and catastrophic reactions.

Methods

The authors have been care partners for loved ones living with LBD (spouses or parents); volunteered in numerous ways to support people living with LBD and their care partners and to advocate for funding, research, and other support; founded the two LBD organizations in the US; served on the Board of Directors and committees of the LBDA; and written extensively about LBD in books, articles, blogs, care briefs, etc. including research-based information on non-drug approaches to behavioral changes in people living with LBD.

The proposed panel presentation will draw from this body of work to present non-pharmacological approaches care partners can use to address the behavioral changes in loved ones living with Lewy body dementia (LBD).

Results

The panel presentation will

- provide definitions, descriptions, and examples of common behavioral and mood changes
- summarize possible causes or triggers for behavioral changes which may help LBD families understand, prevent or minimize the symptoms; develop strategies to cope with them; and support the person with LBD and their care partners
- summarize evidence-based, non-drug strategies that care partners can incorporate into daily life that may possibly prevent or curb behavioral changes
- describe strategies that care partners can use to manage, reduce, or perhaps even eliminate many behavioral changes
- discuss the non-drug therapies that can be used alone or in combination: physical, occupational, speech, art, music, aroma, reminiscence, touch, massage, pet, nutrition, light, validation, support group, individual, and family therapies
- suggest online and print resources related to behavioral and mood changes in LBD.

Conclusions

Many people with LBD are extremely sensitive to drugs and experience severe, sometimes irreversible, adverse effects. When care partners don't know how to use non-drug approaches, their loved ones may be given antipsychotics, benzodiazepines, anticholinergics, tricyclic antidepressants and other potentially dangerous medications as the first line of treatment. Care partners who implement non-pharmacological approaches to behavioral changes in their loved ones with LBD may avoid or reduce the use of these drugs and their adverse effects.

Category: Patient/Care Partner Poster Presentation

P.88 *Communication abilities and perception of stigma in Parkinson's disease*

Author: Samantha Holden

Additional Authors: Samantha K. Holden, MD, MS - University of Colorado Anschutz Medical Campus

Kayla C. Schneider - Monarch High School

Natalie C. Wilcox - Monarch High School

Abigail E. Simpson, BS - University of Colorado Anschutz Medical Campus

Luis D. Medina, PhD - University of Houston

Benzi M. Kluger, MD, MS - University of Colorado Anschutz Medical Campus

Background: Non-motor symptoms of Parkinson's disease (PD) significantly affect everyday function and health-related quality of life, as well as contribute to stigmatization. Stigma in PD is a complex phenomenon encompassing devaluation, discrimination, and discomfort within society related to having PD. Cognitive impairment in PD can add to stigmatization, particularly if language abilities are impaired as communication is a vital part of everyday life. We hypothesized that the ability to communicate well with others, both verbally (spoken language) and non-verbally (facial expression, body language), which is a fundamental factor for societal integration, would correlate with perceived stigma experienced by people living with PD.

Methods: 110 PD participants with a range of cognitive abilities completed a cognitive functional assessment (University of California San Diego Performance-Based Skills Assessment (UPSA) [Table 1]); scales of health-related quality of life (PDQ-39), global cognition (Dementia Rating Scale (DRS)), and mood (Hospital Anxiety and Depression Scale (HADS), Apathy Evaluation Scale (AES)); neuropsychological battery; and motor examination (UPDRS Part III). Cognitive classification (PD-normal cognition (PD-NC), PD-mild cognitive impairment (PD-MCI) or PD dementia (PDD)) was determined by consensus conference. Communication abilities, including non-verbal, objectively-rated verbal, and subjectively-reported verbal communication [Table 2], were evaluated for all participants. Relationships between self-reported perception of stigma related to having PD (PDQ-39 Stigma score) and our defined domains of communication were investigated.

Results: PDQ-39 Stigma scores varied widely among participants (range 0-75/100), with no significant differences between cognitive classes [Table 3]. Univariately, PDQ-39 Stigma was significantly correlated with participant age ($r=-0.27$, $p=0.005$), HADS-Depression ($r=0.29$, $p=0.002$), HADS-anxiety ($r=0.25$, $p=0.01$), and PDQ-39 Communication ($r=0.32$, $p=0.001$). No other demographic or outcome measure variables were significantly correlated with PDQ-39 Stigma. PDQ-39 Communication correlated with UPSA Communication ($r=-0.26$, $p=0.007$) and UPDRS Speech ($r=0.38$, $p<0.001$); there were no differences between cognitive classes for these relationships. The difference between scaled scores on PDQ-39 Communication and UPSA Communication also correlated with PDQ-39 Stigma, where those who subjectively reported poor communication abilities but objectively performed well reported more perceived stigma ($r=0.40$, $p<0.001$); this relationship was strongest in the PD-MCI group ($r=0.63$, $p=0.002$). Multivariately, only participant age ($t=-2.06$, $p=0.04$) and communication mismatch ($t=3.05$, $p=0.003$) explained a significant amount of variance in PDQ-39 Stigma scores.

Conclusions: Overall, people with PD accurately rate their communication abilities; however, those who subjectively underestimate their ability to communicate are more likely to also report perceived stigma related to having PD. Younger age is also significantly associated with more perceived stigma in PD. Mood symptoms were not significantly associated with perceived stigma when controlling for age and the aforementioned communication mismatch. Objective communication abilities, whether verbal or non-verbal, are not correlated with perception of stigma in PD. Therapies focusing on increasing confidence in communication abilities, with real-time feedback such as voice recordings, could serve to decrease perceived stigma and therefore improve health-related quality of life, especially for younger people with PD.

Category: Patient/Care Partner Poster Presentation

P.89 *Music Therapy to Address Behaviors Presented by Lewy Body Dementia at Home*

Author: Rebecca Wellman

Additional Authors: No additional authors

Introduction:

With more families choosing to “age in place” with their loved ones living with Lewy Body Dementia (LBD), families are looking for approaches which can help address concerns such as sleep, cognitive decline, depression or apathy, movement disorder, and hallucinations or delusions. Music therapy is an evidenced based therapeutic approach which may be helpful in informing music use at home. This session will discuss and experience music interventions which can be led by caregivers in the home, understand different music programs, learn some technology approaches to access music which may assist with these concerns.

Methods and Materials:

The intention of this session is to help families learn how they can use music at home to ease some of the concerns associated with LBD. Families will learn about current research on the use of music to address issues prevalent in LBD, learn about different approaches which may help them navigate potentially challenging or distressing behaviors, and formulate a plan which they feel they can use immediately to increase quality of life for the individual with LBD and decrease caregiver stress or distress. These approaches may include singing, music listening, relaxation with music, music initiated conversations, music to accompany exercise or activities of daily living to increase compliance, and music to support movement. A board certified and licensed music therapist will lead discussion and hands on experiences to help families increase confidence in utilizing these skills. The session will also explore music technology which may be utilized to increase access to and portability of music. Differences between music therapy, home approaches, and other music programs will be discussed.

Results:

The intended results of this session are to help families recognize when music may be effective, feel comfortable finding music selections, and be able to utilize music in the home to address challenging or problematic behaviors associated with LBD.

Discussion:

Research shows that music and music therapy can help ease the behavioral, emotional, and motor challenges associated with LBD. Caregivers need real support and realistic interventions available in the home, not just in the therapeutic environment. Through a group environment, caregivers and individuals with LBD can practice these skills, be introduced to different approaches which may be effective for them, and go home with tools to have better and more meaningful connections and interactions.

Category: Patient/Care Partner Poster Presentation

P.90 Recognition, Diagnosis, and Management of Neurogenic Orthostatic Hypotension in Patients With Lewy Body Dementia or Related Neurodegenerative Disorders

Author: Robbin Brodbeck

Additional Authors: Authors: Robbin Brodbeck, PhD, L. Arthur Hewitt, PhD, Antonella Favit, MD, PhD

Affiliations: Lundbeck, 6 Parkway North, Deerfield, IL

Background: Neurogenic orthostatic hypotension (nOH), a condition characterized by a sustained blood pressure drop when standing up after sitting or lying down, is common in patients with neurodegenerative diseases associated with autonomic nervous system dysfunction. Individuals with nOH may experience symptoms such as dizziness, lightheadedness, feeling faint, or fainting when changing to a standing position. It is estimated that 31% of patients with Lewy body dementia may also have symptoms of nOH. Additionally, symptomatic nOH may occur in approximately 81% of patients with multiple system atrophy and 18% of patients with Parkinson disease. nOH occurs when blood pressure cannot adapt as needed in response to a positional change because of autonomic nervous system dysfunction. Although nOH may frequently occur in patients with Lewy body dementia, multiple system atrophy, or Parkinson disease, it may be under-recognized because the symptoms are often associated with their underlying neurodegenerative disorder and are not specifically attributed to nOH. The purpose of this presentation is to help patients, caregivers, and healthcare practitioners understand and recognize symptoms of nOH so all members of the care team can work together to develop an appropriate symptom management plan. **Methodology:** The characteristic features and current management practices for nOH were identified by literature review.

Results: Although the most frequent symptoms of nOH are dizziness, lightheadedness, and near or total loss of consciousness, these symptoms often vary from patient to patient. Other symptoms may include visual disturbances, head/neck pain ("coat hanger headache"), cognitive impairment, fatigue, and weakness. Patients with nOH often experience blood pressure variability throughout the day, with low blood pressure (nOH) during daily activities involving being in an upright posture (ie, standing and walking) and high blood pressure when lying down (known as supine hypertension). nOH symptoms can impair a patient's ability to function in daily tasks and decrease their quality of life. Patients with nOH also have an increased risk of falls, which can cause serious injury. The diagnosis of nOH involves recognition of symptoms, consideration of other potential causes (eg, cardiac disorders, certain medications, dehydration), blood pressure and heart rate measurements while the patient is lying down and while standing, and a neurologic examination. Clinically, nOH can be diagnosed if there is a decrease in systolic blood pressure of ≥ 20 mmHg or diastolic blood pressure ≥ 10 mmHg within 3 minutes of standing, accompanied by an inadequate heart rate increase (< 15 bpm). Initially, the symptoms of nOH may be managed without medication, using strategies such as discontinuation of antihypertensive medications, use of compression garments, increased fluid/salt intake, and physical countermeasures. If the symptoms do not improve, medication options should be considered.

Conclusions: Patients with nOH may experience a substantial burden because of the condition. Open communication between patients, caregivers, and healthcare practitioners is essential to achieve an appropriate diagnosis of and management plan for nOH.

Support: Lundbeck

Category: Patient/Care Partner Poster Presentation

P.91 *Life Beyond Diagnosis: Patient and carer ideas for future support in LBD*

Author: Anne Lister

Additional Authors: Valerie Argent

Andrew Brown

Derek Forster

All authors of this abstract are not employed by Newcastle University but are affiliated to the University as members of the Patient and Public Involvement Group for the DIAMOND Lewy programme.

Background

The DIAMOND Lewy programme of research aimed to improve the diagnosis and management of LBD. As part of the programme, we convened a patient and public involvement (PPI) group to advise the research team from patient and carer perspectives. The PPI group was keen to explore patient and carer priorities for Life Beyond Diagnosis. A member of the PPI group will present the findings.

Methods

We sent a questionnaire to patients and carers who had participated in the DIAMOND Lewy study. This included the question 'What one thing could be offered in future to improve the quality of life for patients and carers?' 47 participants were sent the questionnaire. Two members of the PPI group reviewed all responses and identified recurrent themes.

Results

We received responses from 28 people (60%). A small number of respondents suggested 'a cure', or effective treatment, but were realistic in their expectations of how soon that could be available. A common theme was a sense of being abandoned by services, with one person commenting "After diagnosis it feels like you are just left to get on with it yourself".

Respondents identified a number of practical measures to support carers in their crucial role and enhance patient well-being:

- Carer information pack on diagnosis
- Ongoing network of professional support
- Training for carers on supporting patient independence
- Emergency carer relief
- Recognition of carer expertise, including them in decision-making.

They also called for solutions which would address their sense of isolation including:

- Opportunities for regular social contact in a safe and caring setting
- Peer support through meeting and talking to others in a similar situation
- Increased professional and public awareness of LBD.

Conclusion

Support available to patients following a diagnosis of LBD is limited. Patients and carers report feeling isolated and abandoned. While a minority of participants indicated that effective treatment or a cure would be key to improving quality of life, most focused on non-medical interventions. There is, however, little evidence on which non-medical interventions are effective or how best to provide them, despite their obvious importance to patients and carers. Future research must urgently address how best to meet the needs of patients and carers as a way of improving their quality of life.

Acknowledgements

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Category: Patient/Care Partner Poster Presentation

P.92 The brain will not live without "Hands only CPR" for lay persons

Author: Marye Kellermann
Additional Authors: Marye Kellermann PhD CRNP FAANP
Clinical Assistant Professor
The Catholic University of America
School of Nursing

Title -"NECESSARY "Hands only CPR" "by Dr. Marye Kellermann -

Brain function and the implications of neurological compromise are foremost in a caregiver's mind. Their families and friends also focus primarily on the patient's "Brain issue". But what about the heart? Heart disease is the #1 killer in adults. As most heart attacks happen in the home, delayed CPR results in extremely poor survival rates.

The American Heart Association's "Hands only CPR" campaign started almost 10 years ago. AHA projects the "hands only CPR" will save thousands of lives. Yet, in neurological disease management and caregiver education by healthcare providers, focus on brain issues. This neurological "microvision" approach overlooks potential fatal effects of lack of exercise and physiological effects of chronic stress in neuro patients. For example, people living with Parkinson's disease (PD) are twice as likely as the general population to develop cardiovascular disease, and they have a 50% greater chance of dying from it

The AHA research backing for "Hands only CPR", its history, implications, steps, will be presented. Relevance to the neurological caregiver arena will be integrated. Audience participation will be offered via manikins on tables.

Category: Patient/Care Partner Poster Presentation

P.93 A Model to Assess Outcomes Associated with Dementia with Lewy Bodies

Author: Stephanie Cline

Additional Authors: Authors: Matthew Davisa, Robert Espinosaa, Scott Johnsona, Stephanie Clineb, Daniel Weintraubc,d

Affiliation: aMedicus Economics, Milton, MA, USA; bTakeda Pharmaceuticals, Deerfield, IL, USA; cPerelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; dParkinson's Disease Research, Education and Clinical Center (PADRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, PA

Introduction: Developing models of dementia with Lewy bodies (DLB) disease progression would provide information on disease burden and facilitate evaluation of symptomatic and disease-modifying treatments from a clinical and cost perspective. The objectives of this study were to 1) use a large longitudinal US dataset to create a health state transition model specific to DLB progression that incorporates a decline across multiple functional domains to define clinically-relevant DLB health states, and 2) apply this model and a counterfactual scenario in a US patient cohort to estimate the impact of a reduction in DLB disease progression.

Materials and Methods: Patient-level, longitudinal data used to estimate transition probabilities across the DLB disease continuum were obtained from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) between 2005-2016. The NACC database is funded by NIA/NIH Grant U01 AG016976. Published literature and consultation with a clinical expert were used to define four distinct health states for patients with DLB according to symptom progression in the cognitive, motor, neuropsychiatric, and sleep domains: mild DLB, severe DLB, institutionalization, and death. Based on physician responses to survey questions, each patient visit was categorized to a health state. Annual transition probabilities between health states were estimated and applied to a health state transition model to evaluate outcomes for a hypothetical closed cohort (fixed membership) of 100 patients with mild DLB starting at age 60. The number of patient-years spent in each state over a time horizon of 20 years was assessed. To estimate the impact of slowing DLB progression, the model was replicated with a 40% reduction in the relative risk of disease progression. The number of patient-years in each disease state were summed over the time horizon. Outcome measures included cases of severe DLB, number of patients institutionalized, average number of years to onset of severe DLB, average number of years spent institutionalized, and average number of years to death.

Results: Mean age among the 269 eligible patients identified from the NACC UDS was 72.5 years, and there was no appreciable difference in the patients' mean age between health states. Estimated transition probabilities indicated that after one year a patient >60 years of age with mild DLB has a 54%, 30%, 4%, and 12% chance of remaining in the mild DLB disease state, progressing to severe DLB, being institutionalized, and dying. Applying a 40% reduction in the annual risk of transitioning from mild DLB to severe DLB delayed transition to severe DLB by 1.85 years, decreased time spent institutionalized by 1.78 years, and increased life expectancy by 1.73 years, avoiding 0.24 cases of severe DLB and 0.11 cases of institutionalization over the time horizon of the model.

Discussion: This study used real-world data to create a clinically-relevant DLB disease progression model, which demonstrated that a hypothetical reduction in the rate of disease progression resulted in meaningful benefits with potentially significant public health implications. These findings suggest that therapies capable of slowing DLB disease progression could have significant implications for rates of DLB-associated dementia, institutionalization, and death.

Category: Patient/Care Partner Poster Presentation

P.94 *Neuropsychiatric symptoms have distinct associations to cognitive decline and survival in Lewy-body dementia and Alzheimer's disease*

Author: Audun Osland Vik-Mo

Additional Authors: Audun Osland Vik-Mo a,b*, Lasse Melvaer Giil a,c, Dag Aarsland b,d

a Department of Clinical Science, University of Bergen, Norway

b Centre for Age-Related Diseases (SESAM), Stavanger University Hospital, Norway

c Department of Internal Medicine, Haralds plass Deaconess Hospital, Bergen, Norway

d Department of Old Age Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, Kings College, United Kingdom

Background: Little is known regarding the effects of neuropsychiatric symptoms on cognitive decline and survival in Lewy-body dementia. To which degree NPS are indicators of permanent differences (trait-like effects) or just intermittently associated to decline while symptomatic (state-like effects) are also unknown.

Methods: Patients with mild Alzheimer's disease (AD, n = 111) and Lewy-body dementia (LBD, n = 85) were assessed annually until death (mean 5.4 years, range 1-12). Trait-like and state-like association of NPS (Neuropsychiatric Inventory, NPI) and cognition (Mini-Mental State Examination, MMSE) were analyzed using a Tobit mixed model. The trait-like association effect was described by a between-person effects, which is the mean probability of experiencing symptoms over the trajectory for each individual. The state-like effect was described through the within-person effect, which is the deviance from the mean probability at each occasion.

Results: Cognitive decline was significantly associated with delusions, hallucinations, and aggression/agitation. Hallucinations, apathy and anxiety were associated to cognition with state-like effect. The strongest association was found for hallucination, in both AD and LBD. Delusions and agitation were significantly associated in AD but not LBD patients. Severity of NPI symptoms increased the strength of the association. Survival was strongly associated with LBD ($p < 0.001$), but the association of each NPS to survival was low and only apathy (NPI score > 3) was significant ($p = 0.20$, hazard ratio = 1.56).

Conclusion: There were differences in the strength of associations between NPI symptoms, rate of cognitive decline and survival between LBD and AD groups, but comparisons are difficult due to unequal group size. Psychotic symptoms, aggression/agitation and aberrant motor behavior are trait-like and associated to more severe cognitive decline, while anxiety is state-like associated with more severe cognitive decline. NPS are more associated with cognitive decline than survival.

Category: Patient/Care Partner Poster Presentation

P.95 *Updating and Conversations with Caregivers of Early onset dementia, needs and support*

Author: Stephanie Ruckstuhl

Additional Authors: Timothy Hudson

Social Media Page Creator

LewyBodyDementia.ca

Historically, research has shown that early onset dementias have been poorly studied and caregivers have had the least support of all dementias. This lack of support and early diagnosis has had a significant impact on both the patients and the families. It is generally believed that there are many benefits to having a positive family environment supported and followed with prompt early diagnosis with continued support. When searching the internet for Research on Early Onset LBD and its impact along with the issues faced by the patient or caregiver there is very little documented. In Canada the emphasis continues to be on Alzheimer's with few family physicians or geriatricians extremely familiar with early onset (under 50.) Which leads to a long road of investigation and very few physicians agreeing on the same diagnosis. What is the impact of this disease on the family? What is the impact on quality care for the patient with a clear treatment plan like there would be for Cancer or MS or even Alzheimer's. The literature demonstrates success through implementing a team approach to dealing with the family and patient however this is never the experience in rural communities. Knowledge and emotional support for Early Onset families is currently best received through social media support groups. These groups are invaluable in that they provide support and knowledge although not necessarily always medically sound/research fact based at times. These support groups give reassurance that these symptoms and occurrences are part of the disease process and that they are not alone facing these occurrences. As a caregiver in a rural community in Canada these support networks are some days the only thing that keep me understanding the process and the events of the disease. They give me hope and understanding of what to research and look deeper into the care my spouse will need.

Why do I want to present to the family and caregivers at this international conference?

I feel that sharing my life experiences so far will lead to understanding and interest from those who are from far and know the isolation that this disease has when not from a major urban center. I feel that my story will lead to improved services and guidance for those walking the early onset path like my Spouse and our family are.

What will others learn from your project?

What others will take away from my presentation is a call to action. They will also take away the great support that social media groups play in the life of caregivers in rural communities facing this rarer less understood dementia.

Category: Patient/Care Partner Poster Presentation

P.96 Pilot Study Comparing Home Sleep Profiler to In-laboratory Polysomnogram for REM Sleep Behavior Disorder Diagnosis

Author: Gregory Lazarz

Additional Authors: David Shprecher, DO MSci; 1 2 Dan Levendowski; 3
Cyrus Guevarra; 2 Gregory Lazarz; MD,;2 Joyce Lee-Iannotti 2

1 Banner Sun Health Research Institute, Sun City, AZ

2 Department of Neurology, University of Arizona, Phoenix, AZ

3 Advanced Brain Monitoring, Carlsbad, CA

Title: Pilot Study Comparing Home Sleep Profiler to In-laboratory Polysomnogram for REM Sleep Behavior Disorder Diagnosis

Authors:

David Shprecher, DO MSci; 1 2 Dan Levendowski; 3

Cyrus Guevarra; 2 Gregory Lazarz; MD,;2 Joyce Lee-Iannotti 2

1 Banner Sun Health Research Institute, Sun City, AZ

2 Department of Neurology, University of Arizona, Phoenix, AZ

3 Advanced Brain Monitoring, Carlsbad, CA

Objective: To compare the Sleep Profiler (SP), an FDA-approved device for home evaluation of sleep disorders, to the gold standard sleep laboratory polysomnogram (PSG) in evaluation of dream enactment behavior.

Background: Diagnosis of REM sleep behavior disorder (RBD) is strongly associated with risk of synucleinopathy, particularly Lewy body dementia and Parkinson disease, but requires PSG for confirmatory diagnosis. Capturing RBD during a one-night PSG opportunity can be challenging due to night-to night variability of dream enactment behaviors and can be costly to repeat.

Methods: During an overnight PSG (with seizure and four-limb RBD protocol), we simultaneously collected Sleep Profiler data on 6 subjects recruited with recurrent dream enactment behavior but no evidence of neurodegenerative disease. Independent sleep reviewers analyzed the data from each source.

Results: Sleep efficiencies by PSG and SP were 85.3% and 84.6%, respectively, while the median sleep times were identical (358 min). The median sleep onset latency for the PSG was 16 min and 22 min for the SP with a median difference of 5 minutes. The PSG and SP REM percentages were 14.5% and 13%, with a median difference of 1.3%. The SP appeared to under-report N3 sleep and over-report N1 sleep. Of the 6 subjects, 4 had REM sleep without atonia (RSWA) and concordant dream enactment on both the PSG data and the SP data, but comparisons were not completely blinded. Of the 4 subjects with RSWA, 3 had newly diagnosed obstructive sleep apnea (mean AHI 13.3, range 9.7-16.2/hr).

Conclusions: The Sleep Profiler is worthy of larger scale validation studies to show equivalence with PSG in diagnosis of RBD. We suggest the SP be configured to include capabilities to measure airflow signals to screen for sleep apnea and monitor movement in all four limbs for better detection of RSWA. Such studies should also measure potential benefits in terms of cost and feasibility of recruitment of RBD subjects into neurodegenerative disease research trials.

Category: Patient/Care Partner Poster Presentation

P.97 *Patterns of Lewy body dementia diagnosis and treatment in Florida*

Author: Bhavana Patel

Additional Authors: Cynthia Garvan, PhD University of Florida

Robert Eisinger University of Florida

Melissa Armstrong, MD University of Florida

Objective: To characterize the demographic and treatment characteristics for the Lewy body dementia (LBD) population in Florida using a statewide Patient Centered Outcomes Research Institute (PCORI) funded clinical data research network, OneFlorida Clinical Research Consortium (CRC).

Background: LBD is the second most common degenerative dementia in the United States, however information about LBD population demographics and common treatment strategies is limited.

Cholinesterase inhibitors are generally considered standard of care in LBD, but the frequency of use is not well reported.

Methods: We included patients (≥ 40 years-old) with an ICD-9-CM 331.82 or ICD-10-CM G31.83 diagnosis code associated with at least 1 encounter (January 2012-March 2018) in the OneFlorida CRC.

Prevalence and age, gender, and racial/ethnic demographics were identified. Frequency of medications and provider specialties was assessed using prescription and provider information (RXCui and NPI number).

Results: 3659 individuals with a diagnosis code for LBD were identified. Among nearly 4 million patients in the clinical research database, the prevalence of LBD was 0.10%. Males accounted for 55.7% of included individuals. Of the LBD cohort, 40% were within the age group 70-80 years and 32% were in the 80-90 years group. For those 304 individuals for whom we have age at death information, the average age at death was 79.6 (range 47-96). LBD was most commonly diagnosed in individuals identifying as white (79.7%), African American/black (11.1%), Asian (1.2%) and other (8%). Almost 19% of the population identified as Hispanic. Approximately 43% of individuals with LBD received a cognitive enhancing medication during the examined period. Donepezil was most commonly prescribed (19.9%), followed by memantine (12.7%), rivastigmine (9.6%), and galantamine (<1%). These medications were most commonly prescribed by neurologists/psychiatrists (20.2%) followed by internal medicine physicians (8.6%). The most frequently prescribed anti-psychotics were quetiapine (17.4%), risperidone (5.4%), and olanzapine (3.2%). Frequency of pimavanserin (0.7%) and clozapine use (0.7%) was low. Most commonly used dopaminergic medications were levodopa (28.5%) followed by dopamine agonists (7.3%).

Conclusions: Fewer than half of individuals with LBD in this cohort received a cholinesterase inhibitor trial, a clear area to target improvement. African-Americans account for a lower percent of LBD cases than the proportion of African-Americans (17%) in Florida suggesting LBD may be underdiagnosed in this population. Opportunities to improve care include diagnosis amongst racial/ethnic minorities and decreased use of inappropriate antipsychotics.

Category: Patient/Care Partner Poster Presentation

P.98 *End of Life and Use of Hospice Care in Patients with Dementia with Lewy Bodies*

Author: Brianna Arman

Additional Authors: Brianna Arman, B.S. Cleveland State University.

Babak Tousi MD, Lou Ruvo Center for Brain Health, Cleveland Clinic

Background: Patients with DLB have a different rate of overall decline as compared to other dementia, especially towards end of life. Understanding service provision for patients with advanced disease is a research priority, with a need to improve our knowledge of end of life disease process and utilization of care resources in DLB.

METHOD: The retrospective study cohort comprised patients who were diagnosed with dementia with Lewy bodies between 2009 and 2019 in a suburban specialty memory care clinic and were deceased at the time of this study with documentation of their time of death in EMR (n=49).

RESULTS:

72% of patients waited about 24 months or more after their first symptoms to receive the diagnosis of DLB. The approximate length of time between the patients' initial diagnosis and date of death was 2 years. The average time between the onset of symptoms and date of death was 5.75 years.

Approximately 63% of the reviewed patients did utilize hospice care near end of life. In the patients who utilize hospice care, the average duration of the service utilization was less than or equal to 10 days. 55% of patients lost more than 5% of weight the last 6 months of life prior to death with 22% of more than 10% weight loss in that period.

The cause of death was unknown in 20% of the patients but the top 3 most common causes of death among the reported ones were as following: Pneumonia (30%), heart failure (23%), renal failure (13%). The most common health changes reported in EMR within 6 months prior to death were: Falls, agitation, UTI and pneumonia.

CONCLUSION:

Study results highlight the need for better education of patient and their families. Use of hospice for DLB patients was higher than previously reported but the duration of utilization remains very low. Most of the patients utilized the hospice services for less than 2 weeks; hence there is a need to increase knowledge of care provider to offer these service to the patients when certain health changes (red flags) occur in the advanced stage of the disease.

Category: Patient/Care Partner Poster Presentation

P.99 The Imagine Series: A knowledge exchange model merging global research evidence with patient and carer insight to help shape the future of research and innovation- a case study of Lewy Body Dementia

Author: Lynne Corner
Additional Authors: Lynne Corner,
Director, VOICE
Director of Engagement, NIHR Innovation Observatory
Alex Mitchell
Engagement Officer, NIHR Innovation Observatory
Sonia Garcia Gonzalez-Moral
Evidence Synthesis Specialist, NIHR Innovation Observatory
Dawn Craig
Deputy Director, NIHR Innovation Observatory

Please note: this abstract submission is to be considered for a poster presentation only. Dr Lynne Corner has already accepted an invitation to present on this topic, but we would greatly appreciate the opportunity to also host a poster on The Imagine Series to complement Dr Corner's presentation.

Background:

The NIHR Innovation Observatory (NIHRIO) is the UK horizon scanning centre funded by the national institute for health research. It identifies, monitors, and collates evidence around new health technologies. . The Imagine Series is an innovative knowledge exchange and patient and public involvement programme devised and coordinated by VOICE, a national citizen involvement network, delivered in collaboration with NIHRIO and the National Innovation Centre for Ageing to ensure that patient and carer priorities are taken into account.

Objectives:

The Imagine Series aims to harness the insights and experience of patients and carers with health conditions, including experience of living with DLB. By identifying key insights, needs, challenges and priorities, we highlight gaps in research and explore how current research evidence reflects met or unmet needs. As well as understanding what is in the pipeline, it is equally important to identify gaps and stimulate new areas of research activity and innovation. The Imagine Series enables patients and carers to access, debate and discuss research evidence and influence future research agendas to benefit the way in which their condition is understood and treated.

The aims: share the latest research evidence; identify future innovations; ascertain alignment of patient and carer priorities for research; and inform future funding priorities and research agendas.

Methods:

A combination method involving systematic literature searches, mapping of evidence against current care pathways and horizon scanning of upcoming innovation was used to inform the patient and carer workshops. This knowledge exchange model provides patients and carers with an overview of the research landscape, and through informed discussion, gap analysis and priority setting exercises key challenges, unmet needs and priorities are identified.

Results:

A report summarising research evidence, patient and carer insights and future recommendations has been produced. Patients and carers prioritised continence, sleep disturbance, lack of interest/ motivation, hallucinations, mood changes and carer burden as areas where they would like to see more research undertaken.

Conclusion:

Patients and carers have immense insight, but often lack access to the latest research evidence and information about the innovation landscape. The Imagine Series facilitates an evidence informed dialogue with patients and carers about their insights, identified needs and priorities and helps to ensure future research is focused on patient and carer needs. Patients and carers are involved in the series through a range of workshops and digital engagement approaches. The VOICE digital platform enables us to obtain insights on an international scale, whilst making it accessible for people to contribute their

insights, regardless of location and socio-economic circumstances. We work in partnership with national charities and support groups and have a strategic focus on inclusion and diversity.

Poster Presentations

Section: Therapeutics

Category: Therapeutics - Poster Presentation

P.100 *Discovery of Disease-modifying Drug Inhibiting Alpha-synuclein Aggregation in Lewy Body with Dementia*

Author: Kohji Fukunaga

Additional Authors: Kohji Fukunaga, An Cheng and Yasuharu Shinoda

Tohoku University Graduate School of Pharmaceutical Sciences

In Lewy body with dementia (DLB), α -synuclein (α Syn) accumulation and inclusion triggers mid-brain and cortical neuronal death and synapse dysfunction in vivo. We previously reported that fatty acid-binding protein 3 (FABP3) is highly expressed in substantia nigra dopaminergic and cortical GABAergic neurons and accelerates α Syn oligomerization when cells are exposed to oxidative stress. Here, we demonstrate that α Syn oligomerization was markedly enhanced by co-overexpressing FABP3 in neuro-2A cells when cells were treated with arachidonic acid (AA). We developed FABP3 ligands, which bind to the fatty acid binding domain of FABP3, using an 8-Anilinonaphthalene-1-sulfonic acid (ANS) assay with a recombinant FABP3 protein. The prototype for the FABP4 ligand, BMS309403, has no affinity for FABP3. We developed more FABP3-specific ligands derived from the chemical structure of BMS309403. Like AA, ligands 1, 7, and 8 had a relatively high affinity for FABP3 in the ANS assay. Then, we evaluated the inhibition of α Syn oligomerization in neuro-2A cells co-overexpressing FABP3 and α Syn. Importantly, AA treatments markedly enhanced α Syn oligomerization in the co-expressing cells. Ligands 1, 7, and 8 significantly reduced AA-induced α Syn oligomerization in neuro-2A cells. Taken together, our results indicate that FABP3 ligands that target FABP3 may be used as DLB therapeutics that inhibit α Syn aggregation in vivo.

[References] (1) FABP3 protein promotes alpha-synuclein oligomerization associated with 1-methyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity. Shioda N et al., J Biol Chem 2014;289:18957-18965.

(2) Chang A, Shinoda Y, Yamamoto Y, Miyachi H, Fukunaga K. Development of FABP3 ligands that inhibit arachidonic acid-induced α -synuclein oligomerization. Brain Res. Doi:10.1016/j.brainres.2018.11.036(2-18)

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Category: Therapeutics - Poster Presentation

P.101 A phase 3 study to evaluate pimavanserin for the treatment of hallucinations and delusions associated with dementia related psychosis

Author: Feldman Peter

Additional Authors: Foff E,¹ Youakim JM,¹ Owen R,¹ Knowles M,¹ Ballard CG,² Cummings J,³ Tariot PN,⁴ Fredericks D,¹ Abler V,¹ Stankovic S¹

¹ ACADIA Pharmaceuticals Inc., Princeton, NJ, USA

² University of Exeter Medical School, Exeter, UK

³ Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

⁴ Banner Alzheimer's Institute and University of Arizona College of Medicine, Phoenix, AZ, USA

Background: There are no FDA-approved treatments for psychosis in any of the major dementias. Pimavanserin is an atypical antipsychotic that acts as an inverse agonist/antagonist at the 5-HT_{2A} receptor. The antipsychotic efficacy and safety of pimavanserin for treatment of hallucinations and delusions has been shown in patients with Parkinson disease psychosis, with or without cognitive impairment. There is also evidence of efficacy and favorable tolerability of pimavanserin in a short-term study in Alzheimer disease psychosis. Like most antipsychotic trials in dementia, previous trials of pimavanserin have used an acute treatment paradigm and evaluated, as the primary outcome measure, the change from baseline in a hallucinations and delusions score on a psychometric scale (eg, Scale for the Assessment of Positive Symptoms Hallucinations and Delusions subscales [SAPS-H+D] or Neuropsychiatric Inventory–Nursing Home version Psychosis score). Such psychometric scales are used principally in clinical trials but seldom in clinical practice. The aim of this study (HARMONY) is to employ a randomized-withdrawal study design and the clinically relevant endpoint (relapse of psychosis) to evaluate the efficacy and safety of pimavanserin for dementia-related psychosis (DRP) in a long-term (chronic) treatment paradigm. Additionally, because the clinical approach to psychosis is shared across neurodegenerative dementias, the study population includes multiple major dementias: dementia associated with Parkinson disease, dementia with Lewy bodies, Alzheimer disease, frontotemporal degeneration spectrum disorders, and vascular dementia.

Methods: HARMONY is a Phase 3, multinational, placebo-controlled relapse prevention trial.

Approximately 360 participants with dementia experiencing moderate to severe psychosis (based on SAPS-H+D and Clinical Global Impression scores) will be enrolled. Eligible patients will receive pimavanserin once daily for 12 weeks during the open-label period. After 12 weeks, participants who experienced a clinically meaningful improvement in their hallucinations and/or delusions ($\geq 30\%$ reduction on the SAPS-H+D Total Score AND a CGI-I score of 1=very much improved or 2=much improved, relative to open-label baseline) at Weeks 8 and 12 will be randomized 1:1 either to continue pimavanserin or to initiate placebo for up to 26 weeks (double-blind period). The primary outcome measure is the time from randomization to relapse of a participant's DRP during the double-blind period.

Results: Methodological and clinical advantages of this approach will be discussed. These include patient-friendly active treatment initiation, efficiency and power of the enriched design, management of natural symptom variability and placebo response, as well as clinically meaningful end-points. These and other design features contribute to increased probability of operational success and to results that are clinically meaningful and translate readily to clinical practice.

Conclusions: There are no approved therapies for the treatment of DRP. Variable and only modest efficacy along with significant safety concerns complicate the off-label use of other available antipsychotics. The goal of HARMONY is to evaluate the efficacy and safety of pimavanserin in patients with DRP. Use of a randomized-withdrawal study design and a relapse prevention paradigm allows for assessment of long-term efficacy in a clinically relevant manner.

Category: Therapeutics - Poster Presentation

P.102 A Co-formulated Drug Delivery System for High Dose Rivastigmine/Glycopyrrolate Treatment in Dementia with Lewy Bodies

Author: Steve Rich

Additional Authors: Steven A. Rich M.D., QAAM Pharmaceuticals, Canandaigua NY, USA 14424

BACKGROUND

A case series presented at the Dementia with Lewy bodies Symposium 2015 (Am J Neurodegenerative Disease 2015;4(Supplementary Issue 1): 1-178) described patients with DLB who were treated with high dose rivastigmine and glycopyrrolate given separately. Patients had improved symptom control and reduced rate of progression compared to historical control data. A subsequent study of coadministration of rivastigmine and glycopyrrolate was complicated by the need for glycopyrrolate to be administered in a fasted state, while optimum absorption kinetics of rivastigmine required administration with food. Separated administration improved tolerance and kinetics of the regimen but increased the pill burden for the patient. A new formulation was developed to address the need for concurrent administration and reduced pill burden.

We compare the rivastigmine serum concentration-time profiles in a normal control subjects obtained with concurrent administration of rivastigmine and glycopyrrolate in a fasting state, separated administration in fasting and fed state, with those obtained with the novel co-formulated drug delivery system.

METHODS

A co-formulated drug delivery system was designed for immediate release glycopyrrolate and delayed release rivastigmine. Allowing for administration 1 hour prior to eating.

Normal control subjects were administered immediate release glycopyrrolate and increasing doses of rivastigmine in a fasted state, 1 hours prior to a meal. 2 subjects were administered the medications separately, glycopyrrolate fasting and rivastigmine with food 1 hour later. Another subject was administered the new co-formulated dosage form 1 hour before a meal. Serum rivastigmine levels were obtained over time for 12 hours after dosing.

Two DLB patients on separate dosing of two components were transitioned to the co-formulated dosage form and steady state rivastigmine levels were obtained. These were compared to the steady state levels of other patient who were felt to have benefited from combined therapy with improvements in symptoms and disease course.

RESULTS

Co-administration of glycopyrrolate and rivastigmine in a fasted state resulted in a rapid absorption and maximum concentration (C_{Max}) of rivastigmine which was associated with reports of nausea.

Separate administration of glycopyrrolate (fasting) and rivastigmine (fed) attenuated and delayed the C_{max} and reduced nausea, corresponding to the experience in clinical use.

The co- formulated preparation administered in a fasting state showed absorption kinetics similar to that of the separately administered components. It was associated with easier administration, reduced adverse gastrointestinal adverse effect and steady state serum levels similar to other DLB patients responding to high-dose rivastigmine

CONCLUSIONS:

A co-compounded formulation of glycopyrrolate and rivastigmine has a pharmacokinetic profile similar to separately administered components when taken one hour before meals. It is associated with greater ease of administration, reduced adverse effects, and rivastigmine serum concentrations that have been associated with improved symptom control and delayed progression compared to historical control DLB patients.

Category: Therapeutics - Poster Presentation

P.103 Effects of zonisamide on parkinsonism in patients with dementia with Lewy bodies by severity of cognitive dysfunction and BPSD: subgroup analysis of pooled data from two trials

Author: Hidenori Maruyama

Additional Authors: Hidenori Maruyama¹, Jennifer G. Goldman², Kazuko Hasegawa³, Toshinari Odawara⁴, Kenji Kochi¹, Shunji Toya¹, Osamu Konishi¹, Kenji Kosaka⁵, Miho Murata⁶, Ian McKeith⁷

¹ Sumitomo Dainippon Pharma Co., Ltd., Tokyo, Japan

² Physical Medicine and Rehabilitation and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

³ Neurology, Sagamihara National Hospital, Kanagawa, Japan

⁴ Health Management Center, Yokohama City University, Kanagawa, Japan

⁵ Shonan Inaho Clinic, Kanagawa, Japan

⁶ Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

⁷ Institute of Neuroscience, Newcastle University, Newcastle Upon Tyne, UK

Background: Since treatment of parkinsonism in dementia with Lewy bodies (DLB) requires risk management, taking cognitive function and BPSD into account, effects of zonisamide (ZNS) was assessed by severity of cognitive dysfunction or BPSD in a pooled analysis of two trials (phase 2 and 3 trials; multicenter, randomized, double-blind, parallel-group, placebo-controlled trials).

Methods: This analysis included 498 patients, who were stratified by severity (mild, moderate or severe) of cognitive dysfunction based on the baseline score of MMSE, and also severity of BPSD based on the baseline score of NPI-10. In terms of each efficacy variable (UPDRS part III, MMSE and NPPI-10), the change from baseline at week (W) 12 of treatment with ZNS (25 or 50 mg) was calculated by severity of cognitive dysfunction or BPSD, and compared to that with placebo.

Results: In all strata of the severity of cognitive dysfunction, ZNS reduced or tended to reduce UPDRS part III score (Fig.1a). By severity of BPSD, ZNS reduced or tended to reduce UPDRS part III score in the mild and moderate strata, with similar score reductions also in the severe stratum (Fig.1b). In addition, the changes in the scores of MMSE by severity of cognitive dysfunction and NPI-10 by severity of BPSD did not differ between ZNS and placebo in any stratum of severity (Fig.1c, 1d).

Conclusions: The analysis indicated that ZNS is effective for parkinsonism irrespective of the severity of cognitive dysfunction or BPSD in DLB patients, without major safety concerns.

Category: Therapeutics - Poster Presentation

P.104 Efficacy and safety of zonisamide in patients with dementia with Lewy bodies with parkinsonism: pooled analysis of phase 2 and 3 trials

Author: Shunji Toya

Additional Authors: Jennifer G. Goldman¹, Kazuko Hasegawa², Toshinari Odawara³, Kenji Kochi⁴, Shunji Toya⁴, Hidenori Maruyama⁴, Osamu Konishi⁴, Kenji Kosaka⁵, Miho Murata⁶, Ian McKeith⁷
¹ Physical Medicine and Rehabilitation and Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

² Neurology, Sagamihara National Hospital, Kanagawa, Japan

³ Health Management Center, Yokohama City University, Kanagawa, Japan

⁴ Sumitomo Dainippon Pharma Co., Ltd., Tokyo, Japan

⁵ Shonan Inaho Clinic, Kanagawa, Japan

⁶ Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

⁷ Institute of Neuroscience, Newcastle University, Newcastle Upon Tyne, UK

Background: A pooled analysis of phase 2 and 3 trials (multicenter, randomized, double-blind, parallel-group, placebo-controlled trials) was performed to characterize the efficacy and safety of zonisamide (ZNS) in patients with dementia with Lewy bodies (DLB) with parkinsonism.

Methods: In efficacy analysis (n=498), ZNS (25 or 50 mg) was compared with placebo in terms of (1) changes from baseline in UPDRS part III total and subscale (i.e., tremor [UPDRS items 20, 21], rigidity [UPDRS item 22], bradykinesia [UPDRS items 23, 24, 25, 26, 31], and postural instability/gait disturbance [PIGD, UPDRS items 29, 30]) scores at week (W) 12; (2) the responder (defined as $\geq 10\%$ improvement in UPDRS part III total score) proportion at W4, W8, W12 and W12 (last observation carried forward [LOCF]); and (3) changes from baseline in MMSE and NPI-10 total scores at W12. In safety analysis (n=508), ZNS was compared with placebo in terms of the incidence proportions of adverse events.

Results: ZNS significantly reduced UPDRS part III total, tremor, rigidity (on ZNS 50 mg only), and bradykinesia scores (figure 1a, 1b). The responder proportions at W12 (LOCF) were 61.2%, 55.0%, and 37.6% for ZNS 25 mg, ZNS 50 mg, and placebo, respectively (figure 1c). The changes in MMSE and NPI-10 total scores at W12 did not differ between ZNS (25 or 50 mg) and placebo. The incidence proportion of adverse events did not significantly differ between ZNS and placebo, except for somnolence on ZNS 50 mg.

Conclusions: The analysis indicated that ZNS is effective for parkinsonism in DLB, particularly bradykinesia, tremor and rigidity, and is well tolerated.

Category: Therapeutics - Poster Presentation

P.105 Zonisamide improves parkinsonism in dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase 3 trial

Author: Kazuko Hasegawa

Additional Authors: Kazuko Hasegawa¹, Toshinari Odawara², Ritsuko Kajiwar³, Hisao Takeuchi³, Osamu Konishi³, Hidenori Maruyama³, Shunji Toya³, Masaaki Tagawa³, Miho Murata⁴, Kenji Kosaka⁵

¹ Neurology, Sagamihara National Hospital, Kanagawa, Japan

² Health Management Center, Yokohama City University, Kanagawa, Japan

³ Sumitomo Dainippon Pharma Co., Ltd., Tokyo, Japan

⁴ Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

⁵ Shonan Inaho Clinic, Kanagawa, Japan

Background: Parkinsonism in dementia with Lewy bodies (DLB) is responsive to levodopa, but the response is often less than in Parkinson's disease (PD) and the higher dose has a risk of worsening underlying psychiatric symptoms. In Japan, zonisamide (ZNS) is now available as anti-Parkinson drug. Previously, our randomized trials with PD showed ZNS improves parkinsonism and wearing off without affecting psychiatric symptoms. Therefore, we hypothesized ZNS would improve parkinsonism in DLB and conducted the randomized phase 2 trial (Murata et al., 2018). Here, we will show results of a randomized phase 3 trial using larger number of patients, to verify the efficacy and safety of ZNS for parkinsonism in patients with DLB.

Methods: The trial consisted of 12-week randomized double-blind confirmatory and subsequent 40-week open-label extension phases. Outpatients diagnosed with probable DLB were enrolled. The patients randomized into placebo, ZNS 25 or 50 mg/d groups and received any of drugs at fixed dose for 12 weeks in the confirmatory phase. In the extension phase, the patients received ZNS at an initial dose of 25 mg/d over 2 weeks, and then at a flexible dose of 25 or 50 mg/d depending on patients' condition. Change from baseline in UPDRS part III score at week (W) 12 was the primary endpoint. Throughout the trial, UPDRS part III, MMSE, NPI-10 as well as safety were evaluated.

Results: Of 373 patients screened, 351 were randomized. Patients' background for primary endpoint was following, mean age, 77.2 years; mean durations of dementia and motor dysfunction, 3.6 and 2.7 years; mean UPDRS part III score, 31.2. Although any groups showed the score reduction in UPDRS part III at W12 (change from baseline; -1.4 [placebo], -4.1 [ZNS 25 mg], -4.0 [ZNS 50 mg]), the reduction in both ZNS groups was statistically greater than in placebo (figure 1a). Subsequently, the UPDRS part III scores further reduced until W24-28 by ZNS treatment and then were almost constant until W52 (figure 1b). In contrast, the score reduction in MMSE at W12 was greater in ZNS 50 mg than in placebo, but in term of long-term evaluation, the scores of MMSE as well as NPI-10 were not affected by ZNS treatment (figure 1c). Of 335 patients for long-term evaluation, 230 completed the 52-week treatment. There was no remarkable adverse event throughout the trial.

Conclusions: ZNS improves parkinsonism in DLB and is well tolerated.

Category: Therapeutics - Poster Presentation

P.106 The PRESENCE Study: A Phase 2 study of LY3154207 on cognition in mild-to-moderate dementia due to Lewy Body Dementia

Author: Leanne Munsie

Additional Authors: Leanne Munsie, Eli Lilly and Company

Kjell Svensson, Eli Lilly and Company

Kevin Biglan, Eli Lilly and Company

Background: LY3154207 is an orally available, selective positive allosteric modulator (PAM) of the D1 receptor subtype (D1PAM). D1PAM increases the affinity of dopamine for the D1 receptor and is hypothesized to amplify the response to endogenous dopamine by increasing D1 tone when and where dopamine is released. As an allosteric modulator, this mechanism demonstrates low propensity for overstimulation or development of rapid tolerance unlike D1 agonists. Phase I studies of LY3154207 in healthy volunteers and in subjects with Parkinson's disease showed it was safe and well-tolerated, and also demonstrated evidence for central target engagement.

LBD, including both Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), is a progressive neurologic disorder associated with degeneration of nigro-striatal dopaminergic and cortical cholinergic neurons. D1PAM is a hypothesized mechanism to treat cognitive deficits associated with LBD by enhancing cortical D1 neurotransmission and acetylcholine release. In addition, D1PAM may show benefit on other domains affected by LBD including motor function, daytime sleepiness, and mood/apathy.

Objective: To evaluate the efficacy of LY3154207 on cognition in mild-to-moderate LBD

Methods: PRESENCE is a multicenter, randomized, double-blind, parallel-group, placebo-controlled, fixed-dosage, Phase II study comparing 3 dosages of LY3154207 to placebo administered orally once a day over 12 weeks in 340 LBD participants (probable PD or probable DLB) with mild-to-moderate dementia on change in cognition as measured from baseline to week 12 on the Cognitive Drug Research Computerized Cognition Battery (CDR-CBB). Secondary outcomes include a number of measures of cognition, function, mood, sleep, and motor symptoms, as well as safety and pharmacokinetic measures. In addition, digital devices are included in the study to assess biomarkers of sleep, motor function, and cognition.

Results: The study is sponsored by Eli Lilly and Company and is being conducted at 78 sites in US, Canada, and Puerto Rico. The study is currently enrolling. (ClinicalTrials.gov Identifier: NCT03305809)

Conclusion: The PRESENCE study provides opportunity to assess D1PAM as a novel mechanism to improve cognition associated with LBD, as well as other domains relevant to LBD such as motor impairments, daytime sleepiness and mood/apathy. The study design incorporates well-accepted and validated measures across domains, and also includes several digital devices to assess functional biomarkers in real-time. The PRESENCE study may provide evidence of the potential efficacy of LY3154207 in patients with LBD.

Category: Therapeutics - Poster Presentation

P.107 Lifting big with PRIDE: A novel, high intensity, multi-modal exercise intervention to improve clinical outcomes in individuals with Lewy Body Dementia

Author: Michael Inskip

Additional Authors: Dr Yorgi Mavros - University of Sydney, Faculty of Health Sciences, NSW, Australia
Professor Perminder Sachdev, Centre for Healthy Brain Ageing, University of New South Wales, NSW, Australia

Professor Maria A. Fiatarone Singh - University of Sydney, John Sutton Chair of Exercise and Sports Science, Faculty of Health Sciences, NSW, Australia.

Background

Lewy body dementia (LBD) is the second most prevalent neurodegenerative dementia, with a complex presentation of cognitive, affective, autonomic and motor symptoms. Pharmacological treatments target mood, memory and Parkinsonian symptoms with varied success, and frequent adverse events. Non-pharmacological therapies such as exercise have not been extensively investigated within LBD cohorts who are generally excluded from Parkinson's disease and Alzheimer's dementia studies. Exercise therapy, particularly robust, progressive resistance training (PRT) consistently improves strength, muscle mass, motor severity, executive function and function within daily activities in other aged clinical cohorts. The PRIDE study; Promoting Independence in Lewy Body Dementia through Exercise, conducted in Sydney, Australia is the first controlled trial to specifically investigate robust PRT in a LBD cohort.

Methods

The PRIDE study is a non-randomised crossover trial of a multi-modal exercise intervention including high intensity PRT, challenging dual-task balance exercise, and functional task practice in a cohort of individuals with either Dementia with Lewy Bodies (DLB) or Parkinson's Disease Dementia (PDD). Following an 8-wk usual care control period, participants underwent intensive 1-hour training sessions with an Accredited Exercise Physiologist 3 days/week for 8 weeks, for a total of 24 sessions. Each session was performed one-on-one in the University of Sydney, Lidcombe Clinic using Keiser pneumatic resistance machines, cable-pulleys, and other balance/dual tasking apparatus. Outcomes included physiological and disease-staging assessments of LBD, affect, physical performance tests, strength, sleep quality and habitual activity and sedentary behavior via accelerometry. Outcomes were assessed at baseline, following usual care control (8 weeks), and post-exercise (16 weeks).

Results

In total, 10 participants (n=5 PDD, age 74.7 ± 5.6 years, n=8 male) took part in baseline cross-sectional assessment, 9 participants subsequently commenced the intervention but 2 withdrew due to health complications. Participants were prescribed on average 5.9 ± 3.3 medications, including dopamine in 6 participants. Participants who completed the intervention had a higher Mini-mental State Exam (21.9 ± 10.5 vs. 6.3 ± 7.1) and Parkinson's disease Cognitive Rating Scale (51.7 ± 30.7 vs. 12.7 ± 9.0) score than those did not complete all assessment periods.

Mean session attendance was 22.4/24 sessions (93%). At baseline, participants weighed $70.45 \text{ kg} \pm 10.9 \text{ kg}$, and lost a mean of $4.1\% \pm 7.9\%$ baseline weight during usual care period but regained $2.8\% \pm 3.5\%$ post intervention. Leg press strength declined during the usual care period ($-11.0\% \pm 11.7\%$) and increased substantially following the intervention period ($41.0\% \pm 28.5\%$). There were 6 adverse events reported during the study (n=1 related to exercise, not causing withdrawal.)

Discussion

The PRIDE study is the first controlled trial of high intensity, progressive exercise to be conducted specifically within a LBD cohort. The intervention shows potential as an adjunctive therapy to improve strength, physical function, and prevent weight loss/sarcopenia in individuals with LBD. Future randomized controlled are needed to evaluate the efficacy and feasibility of such multi-modal, robust exercise in a larger cohort to better ascertain the clinical meaningfulness of improvements in strength and body weight, including impacts on quality of life and functional independence.

Category: Therapeutics - Poster Presentation

P.108 Alzheimer's Disease-Related Dementias (ADRD) Summit 2019: LBD Research Recommendations for the National Plan

Author: Jordan Gladman

Additional Authors: Jordan T. Gladman PhD; National Institute of Neurological Disorders and Stroke

Sophia Jeon PhD; National Institute of Neurological Disorders and Stroke

Debra Babcock, MD, PhD; National Institute of Neurological Disorders and Stroke

Roderick A. Corriveau PhD; National Institute of Neurological Disorders and Stroke

Introduction: Goal 1 of the National Plan to Address Alzheimer's Disease is to prevent and effectively treat Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) by 2025. To inform the national research agenda toward achieving this goal, the NINDS leads periodic Summits that set and refine relevant research priorities for multiple etiology dementias (MED), Lewy body dementias (LBD), frontotemporal degeneration (FTLD), and vascular contributions to cognitive impairment and dementia (VCID), collectively referred to as the Alzheimer's Disease-Related Dementias (ADRD).

Materials and Methods: As with the previous AD/ADRD Summits hosted by the NIH, the ADRD Summit 2019 steering committee solicited input from nationally and internationally recognized dementia science experts, as well as from public and private stakeholders, to update and further develop prioritized recommendations to guide ADRD research for the next 5 to 10 years. The research recommendations will be delivered to the National Advisory Neurological Disorders and Stroke Council for additional input and approval before being finalized and delivered to the Department of Health and Human Services (DHHS) National Alzheimer's Project Act (NAPA) Council for inclusion in the National Plan.

Results: The eight 2019 LBD research recommendation focus on both clinical and basic science and proved scientific rational and details to guide implementation. The top clinical recommendation address the need for clinical trials that target, prevent, or delay LBD. Additional clinical recommendations encourage the use of longitudinal antemortem studies, better neuroimaging and neuropathological characterization of LBD. The top basic science recommendation prioritizes biomarkers development and use across LBD with additional recommendations prioritizing research on alpha-synuclein, protein spreading, genetic and environmental risk factors.

These research recommendations are meant to be a national guide for all research originations, private, nonprofit and governmental. The research recommendations reported herein help guide NIH investments in ADRD research, including for LBD, by informing future NIH AD/ADRD Bypass Budgets that NIH submits to Congress each year. The NINDS uses these recommendations as it implements funding decisions, including in the release of targeted funding opportunity announcements. These opportunities represent the top research priorities based on scientific progress and broad stakeholder input provided at the ADRD Summit.

Discussion: The investment by the NIH in LBD research has doubled since 2014, in part due to the additional funding made available by Congress to address AD/ADRD. The NINDS continues to use the ADRD summits as a foundation for the advancement of LBD relevant research, and the 2019 research recommendations represent the next step in the commitment to address the unmet scientific and medical needs in the Lewy Body Dementias.

P.109 Alzheimer's Disease Co-Pathology is a Major Substrate of Clinical Heterogeneity in Lewy Body Disorders.

Author: David Irwin

Additional Authors: David Coughlin, Daniel Weintraub, Howard I Hurtig, Rizwan Akhtar, David Wolk, Edward B Lee, Andrew Siderowf, Murray Grossman MD and John Q. Trojanowski MD PhD.
University of Pennsylvania Perelman School of Medicine

Introduction: The clinical distinction between Dementia with Lewy Bodies (DLB) and Parkinson's disease dementia (PDD), based on the "one-year rule", is currently a matter of debate, as the majority of PD patients develop dementia during the course of disease and clinical features of PDD and DLB are often similar. Moreover, these two clinical syndromes are both characterized by postmortem findings of alpha-synuclein (aSYN) Lewy pathology, representing a varied clinical spectrum of Lewy body disorders (LBD). However, there is no neuropathological substrate that can reliably distinguish these clinical syndromes at autopsy, suggesting the clinical distinction of PDD and DLB may not have clear biological relevance. Indeed, clinical features of LBD are heterogeneous, and the biological basis is poorly understood. Finally, PD, PDD and DLB share prodromal features (e.g. REM sleep-behavior disorder), monogenic sources of hereditary disease (e.g. SNCA mutations/duplications/triplications) and genetic risk factors (e.g. GBA mutation carriers).

We propose to improve the clinical classification of LBD, based on detailed neuropathological and emerging biomarker studies by our group and others, to include stratification of PD, PDD and DLB patients based on the presence or absence of Alzheimer's disease (AD) co-pathology.

Methods: Position statement based on neuropathological/biomarker studies in LBD.

Results: AD co-pathology is common in LBD, as ~50% of all LBD (30-40% of PDD and ~70% of DLB) have sufficient amyloid-plaque and tau-tangle pathology (i.e. medium-high level AD neuropathological change) for a second neuropathological diagnosis of AD. LBD patients with significant AD co-pathology have greater neocortical aSYN pathology, shorter overall survival and shorter time-interval between onset of motor symptoms and development of dementia. Moreover, these poor prognostic associations of plaque and tangle pathology in LBD appear to be independent of age and may represent a synergistic interaction with aSYN. Indeed, the severity of neocortical tau pathology is a strong correlate of dementia in LBD and maps closely with the cerebral distribution of aSYN in LBD in a manner distinct from "pure" AD without aSYN co-pathology. Finally, rare autopsy-confirmed clinical data suggest specific cognitive and motor features linked to AD co-pathology in LBD. These postmortem findings are mirrored by emerging prospective antemortem cerebrospinal fluid and molecular imaging studies that find similar frequencies of AD co-pathology across LBD with poor prognostic implications in PD/PDD and DLB. Thus, the presence of AD co-pathology is a significant source of clinical heterogeneity in LBD that may be a more biologically-relevant distinction than traditional LBD clinical syndromes.

Conclusions: While there is debate over the clinical distinction of PD/PDD and DLB, a more salient issue may be the antemortem detection and differentiation of LBD patients with AD co-pathology from those with "pure" aSYN pathology. LBD patients with AD co-pathology have a worse prognosis that may influence clinical trial outcomes for both symptomatic therapies and emerging disease-modifying therapies.

Thus, we propose clinical trials and research studies in LBD consider stratification of LBD patients based on AD biomarker profiles. Moreover, we suggest harmonized assessments across PD/PDD and DLB with autopsy-confirmation to further refine the biological basis for clinical heterogeneity in L