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Review Article

The role of nuclear medicine in neurodegenerative diseases: a narrative review

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Abstract: Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Lewy body dementia, are associated with the accumulation of brain proteins, leading to neuroinflammation, disruption of cellular clearance mechanisms, and neuronal death. Nuclear medicine, utilizing technologies like PET and SPECT, plays a crucial role in diagnosing and managing these disorders. Recent advancements in nuclear medicine have enhanced the understanding of disease pathophysiology and facilitated the development of tailored therapeutics. This study aims to address gaps in understanding nuclear medicine's potential to improve early diagnosis, monitor disease progression, and evaluate therapeutic effectiveness. In this review, we analyzed 28 papers and summarized their findings. PET radioligands have revolutionized the in vivo measurement of pathological targets in neurological diseases, offering new insights into the pathophysiology of neurodegenerative conditions. Amyloid PET has emerged as a reliable diagnostic imaging tool, accurately identifying cerebral amyloid-beta accumulation and enabling early differential diagnosis in clinical settings. Furthermore, radiopharmaceuticals such as [18F]Flortaucipir, [18F]FDOPA, and TSPO ligands provide significant advancements in the diagnosis and treatment of neurodegenerative disorders.

Keywords: Neurodegenerative disease, nuclear medicine, PET, SPECT, review

Introduction

Neurodegenerative diseases (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), and Lewy body dementia (LBD), are frequently associated with protein accumulation in the brain. These disorders are characterized by neuroinflammation, disruption of molecular clearance mechanisms, and neuronal death [1]. Certain NDs involve intracellular or extracellular macro-aggregates within cerebral structures, such as amyloid-beta (Aβ) in AD, tau (τ) protein in AD and dementia, α-synuclein in PD and LBD, and prion-associated aggregates in Creutzfeldt-Jakob disease [2].

Risk factors for NDs include aging, genetic predisposition, cerebrovascular injury, and lifestyle choices, all of which may contribute to the clinical onset of these conditions. However, the primary etiology in some individuals remains unclear, and the potential role of infectious organisms is currently under investigation [3].

Nuclear medicine plays a critical role in the diagnosis and management of neurodegenerative disorders. Advanced imaging technologies such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are utilized to observe and quantify nuclear and cellular activities within the brain [4]. For instance, amyloid PET imaging is used to detect amyloid plaques in Alzheimer's disease, while dopamine PET imaging assesses the loss of dopaminergic neurons in Parkinson's disease [5]. Nuclear medicine-related tests are particularly warranted in neurodegenerative diseases when clinical symptoms require a more precise or differential diagnosis, early detection, or monitoring of therapeutic response. These tests are invaluable in cases where conventional clinical evaluations, such as neuroimaging or laboratory studies, are inconclusive or when the early diagnosis can significantly influence management and prognosis. For instance, Amyloid PET imaging is recommended for patients with atypical presentations of dementia or younger onset, as it reliably

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identifies cerebral amyloid-beta deposition, facilitating early and accurate diagnosis of Alzheimer's disease [6, 7]. Similarly, [18F] FDOPA PET plays a pivotal role in distinguishing idiopathic Parkinson's disease from other parkinsonian syndromes by evaluating dopaminergic neuronal function. Additionally, TSPO ligands and other advanced radiopharmaceuticals are increasingly utilized to assess neuroinflammation and disease progression in conditions like multiple sclerosis or Lewy body dementia [8]. The decision to utilize nuclear medicine techniques is based on clinical judgment, supported by international guidelines and the potential for these tests to provide critical information to guide personalized treatment strategies [8, 9].

Recent advancements in nuclear medicine have enhanced the comprehension of disease pathophysiology and enabled the formulation of tailored therapeutics. Amyloid and tau PET imaging have emerged as essential instruments for detecting Alzheimer's disease and informing therapy strategies [5]. Nuclear imaging methods have proven crucial in finding new therapeutic targets and assessing therapy responses. Nuclear medicine, due to its capacity to deliver precise imaging and insights into disease causes at the nuclear level, has considerable potential.

This study aims to address gaps in understanding nuclear medicine's potential to improve early diagnosis, monitor disease progression, and evaluate therapeutic effectiveness. Despite advancements in PET and SPECT imaging for neurodegenerative disorders, extensive research assessing their efficacy across various clinical contexts remains limited. Additionally, this study seeks to review novel biomarkers and imaging agents that can differentiate between diseases and their stages. Addressing these gaps may lead to enhanced diagnostic accuracy, personalized treatment strategies, and improved patient outcomes, thereby contributing to the development of new imaging methodologies and therapeutic approaches.

Methods

Literature search

We used PubMed, Embase, Google scholar, Web of science and the Cochrane Library databases to perform a thorough search of the literature. Only articles written in English published between 2010 and 2024 were included in the search. "((Nuclear Medicine) AND (Nuclear Imaging OR Radiotracer* OR Positron Emission Tomography OR PET OR Single Photon Emission Computed Tomography OR SPECT OR β-amyloid Tracer* OR Tau Protein Imaging OR Dopamine* Transporter Imaging OR Fluorodeoxyglucose PET OR FDG-PET OR Neuroinflammation Imaging OR Synaptic Density Imaging OR Hybrid PET OR Hybrid MRI OR Total-body PET OR Advanced Image Acquisition OR Radiomic* OR Artificial Intelligence in Imaging) AND (Neurodegenerat* Disease* OR Alzheimer's Disease OR Parkinson's Disease OR Huntington's Disease OR Amyotrophic Lateral Sclerosis OR ALS OR Multiple Sclerosis OR MS OR Frontotemporal Dementia) AND (Protein Aggregation OR Neuroinflammat* OR Neurotransmitter System* OR Neurovascular Interaction* OR Bioenergetics and Metabolism))" was the search line utilized. In order to find more research, we also manually looked over the relevant articles' reference lists.

Inclusion and exclusion criteria

Two reviewers separately assessed the titles and abstracts of the chosen publications to make sure they were pertinent. If an article satisfied the inclusion requirements, its full text was retrieved for additional evaluation. The following criteria were used to determine if an article qualified for inclusion: (1) Articles published between 2000 and 2024 to ensure relevance to contemporary advancements in nuclear medicine. (2) Original research articles presenting primary data related to nuclear medicine applications in neurodegenerative diseases. (3) Articles published in peer-reviewed journals and written in English to ensure quality and accessibility. (4) Studies involving human subjects, focusing on the use of PET, SPECT, or other nuclear medicine techniques in diagnosing, monitoring, or treating neurodegenerative diseases such as Alzheimer's, Parkinson's, or Lewy body dementia. (5) Papers providing insights into the development or application of radiopharmaceuticals in the context of neurodegeneration. Exclusion criteria: (1) Articles that are reviews, letters to the editor, editorials, commentaries, or case reports, as they do not provide original research data.

(2) Studies conducted exclusively on animal models or in vitro without clear translational relevance to human neurodegenerative diseases. (3) Articles not focusing on neurodegenerative diseases or nuclear medicine as the primary research domain. (4) Publications in languages other than English due to translation and accessibility constraints. (5) Studies lacking adequate methodological rigor, as determined by the reviewers during the initial screening process.

Further assessments

Data extraction from the papers that were provided was done using a standard data collection form. Information that was removed included the author, publication year, methodology, number of participants, intervention or exposure, outcome measures, and findings. The quality of the included studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials and the ROBINS-I tool for non-randomized studies. The indicators extracted for evaluation in this study included the use of imaging modalities such as PET and SPECT, which were analyzed for their diagnostic utility and feasibility in detecting pathological changes like amyloid plaques, tau tangles, dopaminergic dysfunction, and neuroinflammation. Radiopharmaceuticals, including [18F] Flortaucipir, [18F]FDOPA, and TSPO ligands, were reviewed to assess their specificity and sensitivity in targeting key pathological processes. The study also examined disease-specific applications, focusing on Alzheimer's disease, Parkinson's disease, and Lewy body dementia to evaluate diagnostic accuracy, differential diagnosis capabilities, and potential for monitoring disease progression. Clinical outcomes related to therapeutic monitoring and response to interventions were considered, highlighting the role of nuclear imaging in tracking changes over time and informing treatment strategies. Additionally, the analysis included temporal and regional changes in the brain, providing insights into spatial and temporal patterns of neurodegeneration and advancing the understanding of disease pathophysiology. A narrative technique was used to to analyze the data, resulting in concise findings presented alongside relevant supporting evidence.

Results

Assessed studies

A total of twenty-eight articles were found to meet our inclusion criteria (**Figure 1**). The majority of the studies were conducted in the Europe (n=18), followed by Asia (n=5), United states (n=4), and Australia (n=1).

Final literature

The studies had a diverse range of study trends and the results of the studies were mixed. Our synthesis of the literature tried to provide a comprehensive theory about the use of nuclear medicine and its related modalities and radiotracers in diagnosing neurodegenerative diseases, especially Alzheimer's disease (AD), Parkinson's disease (PD), and Lewy body dementia (LBD).

Discussion

The goal of the current review was to give a thorough overview of the role of nuclear medicine in neurodegenerative diseases. We found 28 papers in total that satisfied our inclusion criteria, with a wide range of study trends.

Neuroimaging modalities, such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET), and dopamine transporter (DAT) imaging, have been recognized as biomarkers in the diagnostic criteria for neurodegenerative disorders [10]. Nuclear imaging is a field that combines nuclear biology with in vivo imaging to study cellular functions and processes in living organisms [11]. It primarily includes PET and SPECT imaging, although other imaging modalities such as MRI, CT, ultrasound, and optical imaging may also be used [12]. The contrast agents employed in these techniques are often used at higher concentrations than those in PET and SPECT [13]. Nuclear imaging integrates multiple research disciplines, advancing diagnostics, pharmacological development, and personalized nuclear medicine.

The advancement of PET radioligands has enabled the in vivo measurement of several targets in neurological diseases, such as synaptic vesicle glycoprotein 2A, translocator protein,

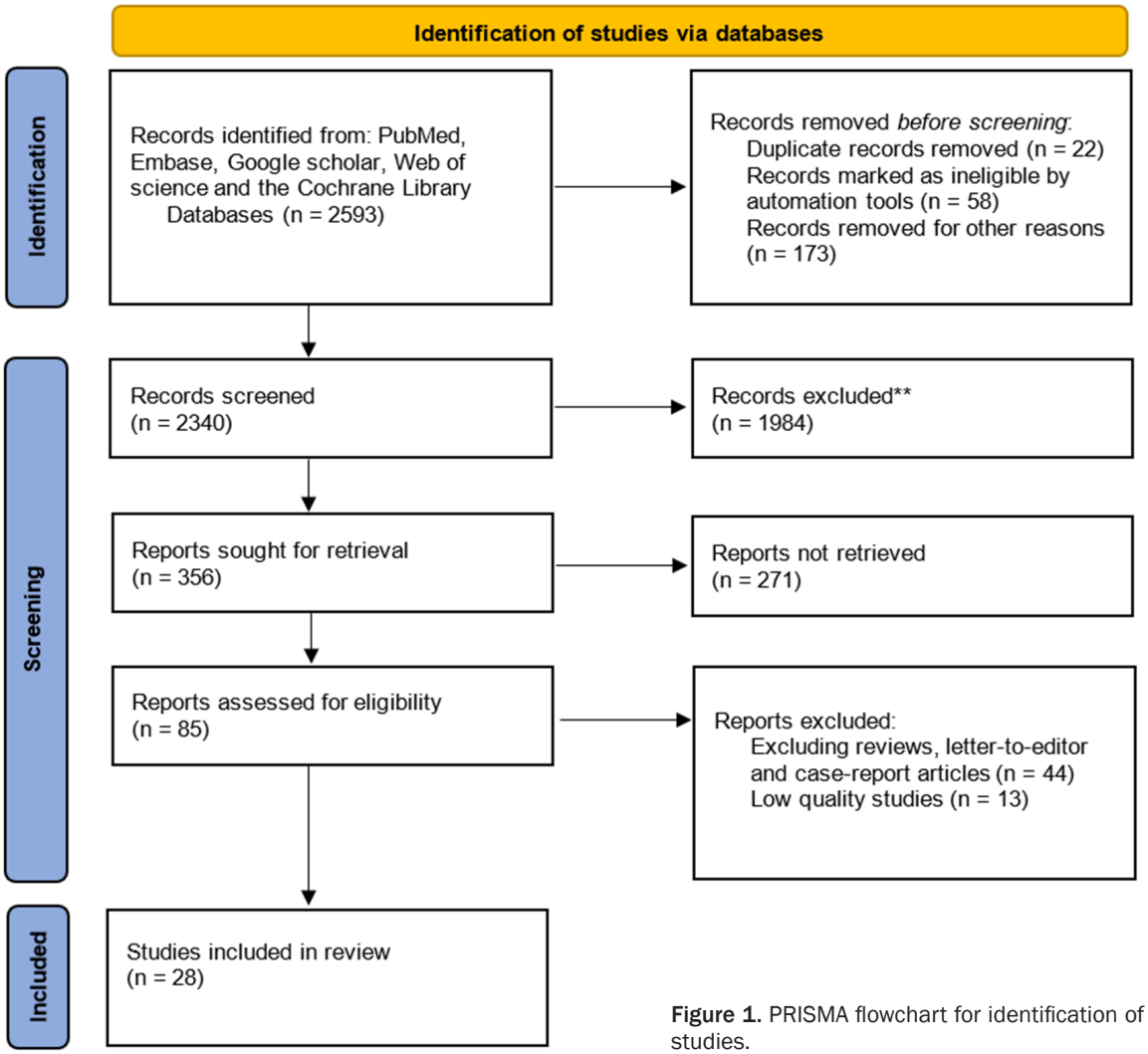

Figure 1. PRISMA flowchart for identification of studies.

dopamine, alpha7-nicotinic acetylcholine receptors, and amyloid-beta plaques. These radioligands have shown promising results in both preclinical and clinical studies. PET imaging of cholinergic neurotransmission has provided new insights into the pathophysiology of neurodegenerative diseases, including the loss of cholinergic neurons, impairment of cholinergic transmission, and the relationship between cholinergic dysfunction and cognitive and motor symptoms [14].

PET radioligands targeting nAChRs and mAChRs may serve as valuable biomarkers for neurodegenerative disorders. The correlation between cognitive performance and a4b2 nAChR availability in Alzheimer's disease suggests that these receptors may contribute to cognitive decline [15]. Alterations in a4b2 nAChRs in the thalamus, caudate nucleus, and cortical regions in Alzheimer's disease, Parkinson's disease, and Lewy body dementia indicate that these receptors may play a role in the pathogenesis of these conditions [10]. Muscarinic acetylcholine receptors (mAChRs) and acetylcholinesterase (AChE) are also key contributors to neurodegenerative diseases. PET imaging of mAChRs and AChE activity can aid in diagnosis and help monitor disease progression [14].

Amyloid PET is a dependable diagnostic imaging modality that accurately identifies cerebral Ab accumulation, elucidates the existence of associated amyloid copathology in other conditions, and facilitates early differential diagnosis in clinical environments. Chapleau et al. [16] demonstrated that amyloid PET correlated with modifications in fundamental aspects of

patient care 90 days post-scan in 60.2% of individuals with mild cognitive impairment and 63.5% of those with dementia. The diagnosis was altered following PET in around 35% of patients (25% transitioned from AD to non-AD, and 10% transitioned from non-AD to AD). The 12-month hospitalization rates post-PET were 23.98% among IDEAS participants, in contrast to 25.12% in a matched sample of Medicare seniors who had not received amyloid PET. A negative amyloid PET result effectively excludes Alzheimer's disease at any age; however, the positive predictive value of amyloid PET diminishes with advancing age, as older individuals are more likely to have incidental amyloid findings, with alternative conditions potentially accounting for the symptoms [16].

The combination of PET and MR imaging presents a distinctive opportunity to cross-validate novel and established imaging techniques, yielding high-quality image data in dynamic patients with constant counting rates and statistics, hence possibly enhancing the detection of neurodegenerative diseases [17]. The integration of PET and MR imaging yields high-quality image data in ambulatory patients, and the concurrent acquisition of PET and MR data facilitates the cross-validation of novel and established imaging techniques. The integration of amyloid PET and structural MR imaging may enhance the likelihood of identifying Alzheimer's disease in preclinical and minimally cognitively impaired phases [18]. The prognostic significance of an amyloid-positive result in these participants for subsequent cognitive deterioration has been examined. The results suggest that amyloid imaging might be advantageous for identifying Alzheimer disease pathology, possibly even prior to 18F-FDG PET. Concerning follow-up and therapeutic monitoring, PET/MR imaging may provide a more informed measurement of disease progression and therapeutic effects across several dimensions [19]. The optimistic outlook suggests that the diagnostic evaluation of dementia and other neurodegenerative diseases might significantly benefit from combined PET/MR imaging, positioning it as the preferred approach for these indications.

PET imaging utilizing several radiopharmaceuticals, including [18F]Flortaucipir, [18F]FDOPA, and TSPO ligands, offers significant insights into the diagnosis and treatment of neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and frontotemporal dementia [20]. PET/MRI imaging enhances the diagnosis of Alzheimer's disease, frontotemporal dementia, and Lewy body dementia by integrating structural and functional methodologies. CBF obtained from ASL has demonstrated comparability with [18F]FDG PET in the differential diagnosis of Alzheimer's disease, frontotemporal dementia, and Lewy body dementia [18]. Amyloid imaging utilizing [18F]Flortaucipir enhances diagnostic precision and alters clinical treatment in individuals with cognitive impairment. The buildup of tau protein correlates with cognitive impairment and can be evidenced by tau protein tracers like [18F]Flortaucipir [5]. [18F]FDOPA is valuable for diagnosing and monitoring Parkinson's disease, and it helps distinguish Parkinson's disease from other movement disorders [21].

SPECT and PET imaging agents substantially influence clinical diagnosis and patient treatment [22], and chemists will persist in their crucial roles in discovering particular targets and manufacturing target-specific probes. Radiolabeled imaging agents possess the capacity to transform the diagnosis and monitoring of neurodegenerative diseases [23], necessitating more study to investigate their potential for early detection and therapy of these conditions [24]. Creating a diagnostic molecule necessitates substantial resources, and fundamental research is essential for the early validation of novel therapeutic candidates [25].

The advancement of radiolabeled imaging agents, including [123I]FP-b-CIT and [99mTc], has been significant. The use of TRODAT-1 and 11C-DTBZ for diagnosing Parkinson's disease, along with [11C]PIB, [18F]flutemetamol, and [18F]florbetapir for diagnosing Alzheimer's disease, has proven valuable [26]. These compounds exhibit strong binding affinity and selectivity for their specific targets and have been employed in clinical studies to visualize dopamine transporters and beta-amyloid plaques in the brain.

Table 1 presents a detailed summary of several radiotracers employed in the diagnosis and monitoring of neurodegenerative disorders. It enumerates radiotracers such as [18F]FDG, [11C]PIB, [18F]Flutemetamol, and [18F]

Table 1. Radiotracers used in neurodegenerative diseases

Radiotracer	Neurodegenerative Disease	Mechanism of Action	Clinical Utility	Reference
[18F]FDG	Alzheimer's Disease	Glucose metabolism	Identifies hypometabolism	Tiepolt et al., 2019 [20]
[11C]PIB	Alzheimer's Disease	Binds to amyloid plaques	Detects amyloid deposition	Young et al., 2020 [10]
[18F]Flutemetamol	Alzheimer's Disease	Binds to amyloid plaques	Detects amyloid deposition	Young et al., 2020 [10]
[18F]Florbetapir	Alzheimer's Disease	Binds to amyloid plaques	Detects amyloid deposition	Tiepolt et al., 2019 [20]
[18F]Flortaucipir	Alzheimer's Disease	Binds to tau protein	Detects tau deposition	Tiepolt et al., 2019 [20]
[11C]CFT	Parkinson's Disease	Binds to dopamine transporter	Measures dopaminergic neuron loss	Pike, 2023 [27]
[99mTc]TRODAT-1	Parkinson's Disease	Binds to dopamine transporter	Measures dopaminergic neuron loss	Huang et al., 2001 [28]
[18F]FDOPA	Parkinson's Disease	Dopamine precursor	Assesses dopaminergic function	Pike, 2023 [27]
[18F]AV-45	Alzheimer's Disease	Binds to amyloid plaques	Detects amyloid deposition	Tiepolt et al., 2019 [20]
[11C]PBB3	Alzheimer's Disease	Binds to tau protein	Detects tau deposition	Pike, 2023 [27]
[18F]DTBZ	Parkinson's Disease	Binds to vesicular monoamine transporter type 2 (VMAT2)	Measures dopaminergic neuron loss	Pike, 2023 [27]

Florbetapir, which are crucial for diagnosing Alzheimer's disease by binding to amyloid plaques, hence facilitating the detection of amyloid deposition. In the context of Parkinson's disease, tracers such as [11C]CFT, [99mTc]TRODAT-1, and [18F]FDOPA are emphasized for their role in quantifying dopaminergic neuron degeneration and evaluating dopaminergic functionality. The incorporation of [18F]Flortaucipir and [11C]PBB3 illustrates its function in identifying tau protein accumulation, providing understanding of cognitive deficits linked to Alzheimer's disease.

This study had some limitations. First, restricting publications to English may induce selection bias, overlooking excellent research in other languages or beyond this era. While narrative reviews can summarize findings, they lack the rigor and repeatability of systematic reviews and meta-analyses, which may introduce subjectivity in data interpretation. A key limitation of this study is its design as a narrative review, which lacks the structured methodology of systematic reviews, such as adherence to PRISMA guidelines or registration with PROSPERO. This may introduce selection bias and limit the reproducibility of the findings.

Conclusions

This narrative review concludes that neuroimaging techniques such as MRI, SPECT, PET, and DAT imaging are crucial biomarkers for diagnosing neurodegenerative diseases. Nuclear imaging, which combines nuclear biology with in vivo imaging, includes both PET and SPECT. Advanced PET radioligands enable the quantification of targets in neurological diseases, such as synaptic vesicle glycoprotein 2A, translocator protein, dopamine receptors, and amyloid-beta plaques. PET imaging of cholinergic neurotransmission provides insights into the degeneration of cholinergic neurons and their correlation with cognitive and motor symptoms. Amyloid PET accurately detects cerebral amyloid deposition, influencing both patient management and diagnosis. The integration of PET and MRI imaging enhances image quality, improving the detection of Alzheimer's disease and other neurodegenerative disorders. SPECT and PET imaging agents play a significant role in clinical diagnosis and patient management, with chemists being instrumental in the discovery and production of target-specific probes.

Disclosure of conflict of interest

None.

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