

Original Article

Somatic complaints in frontotemporal dementia

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Abstract: Frontotemporal dementia (FTD) is associated with a broad spectrum of clinical characteristics. The objective of this study was to analyze the prevalence of unexplained somatic complaints in neuropathologically verified FTD. We also examined whether the somatic presentations correlated with protein pathology or regional brain pathology and if the patients with these somatic features showed more depressive traits. Ninety-seven consecutively neuropathologically verified FTLD patients were selected. All 97 patients were part of a longitudinal study of FTD and all medical records were systematically reviewed. The somatic complaints focused on were headache, musculoskeletal, gastro/urogenital and abnormal pain response. Symptoms of somatic character (either somatic complaints and/or abnormal pain response) were found in 40.2%. These patients did not differ from the total group with regard to gender, age at onset or duration. Six patients showed exaggerated reactions to sensory stimuli, whereas three patients showed reduced response to pain. Depressive traits were present in 38% and did not correlate with somatic complaints. Suicidal behavior was present in 17 patients, in 10 of these suicidal behavior was concurrent with somatic complaints. No clear correlation between somatic complaints and brain protein pathology, regional pathology or asymmetric hemispherical atrophy was found. Our results show that many FTD patients suffer from unexplained somatic complaints before and/or during dementia where no clear correlation can be found with protein pathology or regional degeneration. Somatic complaints are not covered by current diagnostic criteria for FTD, but need to be considered in diagnostics and care. The need for prospective studies with neuropathological follow up must be stressed as these phenomena remain unexplained, misinterpreted, bizarre and, in many cases, excruciating.

Keywords: Frontotemporal dementia, somatic complaints, pain, sensory disturbances, neuropathology, depressive mood, suicidal behavior

Introduction

Frontotemporal dementia (FTD) patients exhibit a wide range of neuropsychiatric symptoms and signs emerging from the gradual degeneration of predominantly the frontal and temporal lobes as well as the affection of specific neuronal networks. Major brain structures seen to show early changes in FTD partially overlap with brain areas known to be involved in pain pathways. Therefore, an affected perception of emotion and pain could theoretically be suspected and has also been described [1-6].

Knowledge that a substantial subset of FTD patients exhibit excessive somatic complaints or an abnormal reaction to sensory stimuli is far from new. More than half a century ago Robertson published detailed clinical descrip-

tions of 3 cases with Pick's disease where somatic complaints and generalised hyperalgesia were prominent clinical symptoms. According to the author, this is similar to the consequences of thalamic vascular lesions [7]. Thirty years ago Gustafson made similar observations in FTD cases and discussed the possible neuroanatomical background of these symptoms. These observations suggest that damage to the frontal lobe structures involved in the modulation and suppression of emotional reactions to sensory stimuli are a more plausible neuropathological correlate than thalamic lesions [8]. Subsequently, some further studies have reported somatic complaints including bizarre hypochondriasis as a common presenting or prominent feature in patients with FTD [9-11]. Furthermore, a changed response to

Somatic complaints in FTD

sensory stimuli, including both hyperalgesia and hypoalgesia, has been reported and it has been suggested that this is associated with different subtypes of FTD [9, 10, 12]. It has been postulated that FTD is characterised by a loss of awareness of pain and that the patients do not show appropriate response to painful stimuli [5, 9] since motivational-affective components of pain decrease [4]. In FTD there is an affection of frontomedian structures that are relatively spared in normal aging. The anterior cingulate cortex (ACC), a structure that often shows early changes in FTD, is also known to be related to the perception of pain and emotions [5, 13].

However, in contrast with other aspects of the clinical expression of FTD, the issue of somatic complaints and pain has not been thoroughly explored. It is well-documented that there is a co-morbidity between somatic complaints and depression in the general population [14], but this has not been studied in FTD.

The heterogeneous clinical and neuropathological features of FTD make it a complex disease to study. With our present knowledge and current biomarkers, the underlying neuropathological subtype can only occasionally be predicted during life. The term FTD is used for the clinical entities behavioural variant FTD (bvFTD) and the progressive aphasia; semantic dementia (SD) and progressive non-fluent aphasia (PNFA) whereas the term frontotemporal lobar degeneration (FTLD) is used to describe the typical underlying pathology of FTD [15-17]. FTLD is further subdivided based on protein pathology. Tau-positive pathology includes the classical Pick's disease and FTLD with tau-positive inclusions as well as progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD). The protein TDP-43, first found in ubiquitin-positive inclusions of tau-negative FTLD in 2006 [18], is now recognised as the second main pathological protein associated with FTD. Based on the distribution and morphology of TDP-43 inclusions, the TDP cases can be further subtyped as type A to D [19]. A minority of FTD cases that are both tau-negative and TDP-negative exhibit FUS-positive pathology instead. In the remaining few cases no inclusions or specific protein pathology can be detected [20].

In spite of relatively clearcut morphological subtypes, there is no conclusive explanation for

the underlying neuropathological basis of somatic complaints, generalised pain and hypo- or hyperalgesia in FTD.

We hypothesised that symptoms of somatic character with focus on pain may differ between subgroups with different protein pathology and/or regional neuropathology.

The study aimed to explore to what extent somatic complaints were present in FTD and whether the somatic presentations correlated with brain protein subclassification or brain pathology. Furthermore we carried out analyses to establish whether the patients with extensive somatic complaints showed more depressive traits.

Material and methods

Study population

We included cases with a neuropathological diagnosis within the FTLD complex from the brain bank at the Department of Pathology, Lund University. The study covers cases with a post-mortem examination performed between 1969 and 2013. All patients were earlier referred to and followed at the Memory Clinic (previous Psychogeriatric Department) in Lund. The majority of patients were included in one of two longitudinal prospective clinical studies (Lund Longitudinal Dementia Study [21] or Lund Prospective Frontotemporal Dementia Study) that included systematic clinical examinations including case history, physical examination, brain imaging and blood sampling during life. Only cases that fulfilled the clinical criteria for dementia were included, but a clinical FTD diagnosis was not a prerequisite for inclusion. All cases were neuropathologically diagnosed as FTLD. However, minor vascular lesions or minimal Alzheimer encephalopathy did not constitute exclusion criteria. Ninety-seven cases that fulfilled the inclusion criteria were identified. This study was approved by the Regional Ethical Board in Lund, no. 2014/286.

Data collection

The medical records for all patients (also including relevant clinical records from other hospitals and general practitioners) were systematically reviewed by two experienced MDs, first by each observer individually and then discussed

Somatic complaints in FTD

Table 1. Demographic variables in FTD patients with and without somatic complaints and/or abnormal pain response

	Total group n=97	Somatic complaints/ changed pain response n=39	No somatic complaints n=58
Age at onset*	58 (30-84)	56 (30-84)	60 (30-84)
Gender F/M	51/46	17/22	34/24
Disease duration*	8 (1-28)	8 (1-28)	7.5 (2-27)

*Median (min-max).

at a consensus meeting. The observers were blinded to all neuropathological findings when the clinical evaluations were made. Demographic data included gender, age at onset and disease duration. Age at onset was defined as the first time symptoms attributable to the disease were noted by relatives or by the patient.

We extracted information on clinical characteristics with special care devoted to somatic complaints, with emphasis on pain, both prior to dementia onset and during the course of dementia. An abnormal response to pain during the course was also noted. The symptoms were grouped into 4 major categories: (1) head, (2) gastrointestinal and/or urogenital, (3) musculoskeletal and (4) other. Somatic complaints were defined as repeated complaints of pain or discomfort that were subjective in nature, excessive and persistent over time and/or remained undiagnosed despite extensive investigations. Minor complaints, such as occasional headaches, were not considered to be sufficient in order to be regarded as positive in this item.

Descriptions of abnormal pain response during the course of dementia, with focus on indications of decreased (hypoalgesia) or increased (hyperalgesia) response to tactile sensory stimuli were noted. Possible information sources were either the patient-based information, caregiver history or the doctors' reports noted in the patients' clinical records.

Depressive traits during dementia disease were recognised and evaluated. Special note was taken of the expression of sadness, worthlessness and hopelessness. In order to be defined as having depressive traits there had to be a medical evaluation concluding that the patient suffered from depressive symptoms. Apathy/inertia (part of the FTD criteria) or mood

lability was not regarded as adequate evidence of depressive symptoms. The occurrence of suicidal behaviour, noted as present or not present, was assessed separately. This was defined as either expressing suicidal thoughts, suicidal plans or attempting or committing suicide.

Brain pathology

All cases had, prior to this study, been neuropathologically examined according to standardised clinical methods at the Department of Pathology. The procedure that includes whole brain assessment with entire bi-hemispheric coronal sections covering all major areas has been described in detail in a previous publication [22]. All clinical neuropathological assessments were carried out by one of two experienced neuropathologists.

All older cases were re-evaluated according to modern diagnostic methods. Complementary immunohistochemical stainings with tau, pTDP-43 and, in selected cases, ubiquitin and FUS were carried out in order to reach a pathological subclassification.

The diagnoses and regional atrophy patterns were reached based on a combination of the original clinical-neuropathological report, of new assessment from existing hematoxylin-eosin stainings and of complementary immunohistochemical stainings. The overall severity of degeneration was assessed as mild, moderate or severe according to the same definitions as described in detail previously [23]. Regional pathology was assessed and noted as predominantly frontal, temporal or equally frontal and temporal (frontotemporal) as well as predominantly left, right or symmetrical degeneration. If parietal pathology was present this was noted. Pathology was noted as present or not present in the cerebellum, thalamus, hippocampus, basal ganglia (defined as the caudate nucleus and the lentiform nucleus), substantia nigra, ACC, frontoinsula and the amygdala.

Protein pathology was assessed and all cases were subdiagnosed in the following diagnostic entities: Tau-positive (Pick, FTLT-tau, CBD or PSP), tau-negative (TDP-43 type A-D, FUS or FTLT with no identified protein pathology (FTLT-nipp)).

Somatic complaints in FTD

Table 2. Somatic complaints and pathology in FTD (n=39)

Case	Gender	Age onset	Duration	Headache	Gastr/uro	Musc/skel	Other	Abn pain	Predom pathol	Asymmetry	Diagnosis
1	M	59	9					+	F		Pick
2	M	47	17	bd		d			F		Pick
3	M	45	17	bd		d		+	F		Pick
4	M	59	12	bd	bd				F		Pick
5	F	84	2	d					FT	L > R	tau
6	F	58	4	d					T	R > L	tau
7	M	51	4	bd	d		b		F		tau
8	F	54	12	bd					FT		tau
9	M	63	6	d	d	d			F	R > L	tau
10	F	56	17		bd	bd			F		tau
11	M	70	9			d			F	L > R	tau
12	F	63	6	bd	d	d			FT		CBD
13	F	65	12		b		d	+	F		CBD
14	M	70	5			bd			FT	L > R	CBD
15	F	53	28	bd					T		PSP*
16	M	48	3	bd					F	L > R	TDP A
17	F	52	3	d					F		TDP A
18	F	50	5	d			d		F		TDP B
19	F	58	5	d		bd**			F		TDP B
20	M	52	7					+	F		TDP B
21	M	68	14					+	T		TDP B
22	M	70	15	b	bd	d		+	T		TDP B
23	F	52	18	d	d				FT	R > L	TDP B
24	M	46	17		d				F		TDP B
25	M	43	17	bd	b	bd			F		TDP B
26	M	46	6	d				-	F	L > R	TDP B
27	M	51	16	d		bd			FT		TDP B
28	F	75	10					+	T	L > R	TDP C
29	M	61	6	d					T	L > R	TDP C
30	F	56	15	d	bd			-	T	L > R	TDP C***
31	M	72	4					-	F	R > L	TDP D
32	F	35	7				b		F		FUS
33	M	30	8	bd					FT		FUS
34	M	54	10	d		d		+	T		0
35	F	69	1	bd					FT		0
36	F	49	26		bd	bd			F	L > R	0
37	M	75	7			d		+	F		0
38	F	69	2				d		F		0
39	M	51	10	bd					T	R > L	0

Gastr/uro=gastrointestinal/urogenital, Musc/skel=musculoskeletal, Abn pain=abnormal pain response, Predom pathol=predominant pathology, F=frontal, T=temporal, FT=frontotemporal, b=before, d=during, bd=before and during. +=hyperalgesia, -=hypoalgesia. 0=FTLD with no identified protein pathology (FTLD-nipp). *This patient also had TDP-43 inclusions, **History of whiplash injury, ***FUS-positive inclusions were found in addition to the predominant TDP-43 pathology.

Statistical analysis

The demographic data were described by number with percent or median with min/max values. Either the Fisher's exact test or the Mann-Whitney U-test was used to assess possible differences between groups. Exact calculations were performed. *P*-values below 0.05 were considered statistically significant. All statistical tests were two-sided. The statistical analy-

ses were performed in SPSS Statistics 22 for Mac (IBM Corporation, Somers, NY, USA).

Results

Patient characteristics

Basic demographics for the total group of 97 patients is shown in **Table 1** (51 females and 46 males). The median age at onset was 58

Somatic complaints in FTD

Table 3. Protein pathology in FTD (n=97)

Tau-positive n=30 (30.9%)		No of cases
Pick	9 (9.3%)	
FTLD-tau	12 (12.4%)	
CBD	8 (8.2%)	
PSP	1 (1.0%)	
Tau-negative n=67 (69.1%)		
TDP-43		
type A	8 (8.2%)*	
type B	38 (39.2%)	
type C	5 (5.2%)**	
type D	1 (1.0%)	
FUS	5 (5.2%)	
FTLD-nipp	10 (10.3%)	

FTLD-nipp=FTLD with no identified protein pathology, *Including three cases with type A/B pathology, **Including one case that also exhibited FUS positive inclusions.

(range 30-84) years and median duration was 8 (1-28) years. There was no difference in gender. Age at onset was 50-70 years in the majority of patients (70.1%). Sixty eight per cent of the patients presented younger than 65 years and only 6.2% were older than 70 years at symptom onset.

Somatic complaints

Symptoms of somatic character (either specific somatic complaints and/or abnormal pain response) were found in 39 patients (40.2%). These patients did not differ significantly from the total group with regard to gender, age at onset or duration (**Table 1**).

The 39 individuals with somatic complaints and/or abnormal pain response are presented in **Table 2**.

Headache was seen in 25 patients (25.8%), either prior to and during (14 cases) or only during dementia disease (11 cases). Gastro-intestinal/urogenital complaints were found in 12 (12.4%) and musculoskeletal pains in 14 patients (14.4%). Other complaints were seen in 5 cases and included one case with vague migrating pain, two cases with otorhinolaryngeal problems, one case with palpitations/chest pain and one with pruritus. The somatic complaints were all related to pain, except for the last case where the complaints consisted of severe pruritus that led to an excessive use of antihistamins. Seventeen patients (17.5%)

reported pain from more than one of the categories, e.g. both headache and gastrointestinal pain. When present during the course of dementia the somatic complaints were exclusively seen during the first half of the course of the disease.

In addition to the patients listed in **Table 2**, one patient suffered from migraine headaches for many years before dementia onset, but only until menopause about 10 years before dementia onset. Another patient was subjected to extensive medical evaluations, including explorative abdominal surgery, due to diffuse abdominal pain for which no explanation could be found, but this was about 10-15 years prior to dementia onset. In all other cases with somatic complaints prior to dementia the symptoms persisted until dementia onset.

Hyperalgesia was noted in six cases and hypoalgesia in three cases. In three cases the hyperalgesia was especially severe, for example making it impossible for the patients to have their nails or haircut. In one case the patient was described as having fallen to the floor in severe pain after a friendly touch on the shoulder. Among the cases with hypoalgesia, it was noted that two patients chewed on shards of glass without seeming to feel any pain or discomfort.

Depressive traits were present in 37 (38.1%) cases and did not correlate with somatic complaints. Suicidal behaviour was present in 17 cases (17.5%) and in 10 of these; suicidal behaviour was concurrent with symptoms of a somatic character. Thus 25.6% of the patients with somatic complaints showed suicidal behaviour compared to 12.1% of the patients without somatic complaints, the difference however, not reaching statistical significance ($p=0.1$). In 9 patients, suicidal behaviour was seen without any signs of depressive traits.

Hypochondriasis was noted in 16 out of the total 97 patients. Fourteen of these 16 patients also displayed somatic complaints.

Brain pathology

The total material (97 cases) consisted of 30 (30.9%) tau-positive and 67 (69.1%) tau-negative cases (**Table 3**). Among the tau-positive cases 9 were diagnosed with Pick's disease, 8

Somatic complaints in FTD

cases with CBD and one with PSP. The remaining tau-positive cases (n=12) had non-specific tau-positive pathology, FTLT-tau.

Among the tau-negative cases, 52 showed TDP-43 positive pathology (TDP-43 type A n=8, B n=38, C n=5, D n=1), 5 cases showed FUS-positive pathology and 10 cases could not be classified as either tau, TDP-43 or FUS positive (FTLD-nipp).

Headache was the most commonly reported type of somatic complaint, seen equally (no significant difference) in tau-positive (n=10, 33.3% of the tau-positive cases) and tau-negative cases (n=15, 22.3% of the tau-negative cases). The 12 patients with persistent pain from gastrointestinal or urogenital regions were found to be equally tau-positive (n=6) and tau-negative (n=6). Musculoskeletal pains were seen in 14 patients, equally common in tau-positive (n=7) and tau-negative cases (n=7). Other complaints were found in both tau-positive and tau-negative cases.

Hyperalgesia was found in both tau-positive (Pick n=2, CBD n=1) and tau-negative cases (TDP-43 type B n=3, type C n=1, FTLT-nipp n=2), whereas hypoalgesia was only found in TDP-43 cases (type B, C and D).

No obvious correlations were observed between somatic complaints and frontal/temporal pathology or asymmetric hemispherical atrophy. Nor were there any correlations between somatic complaints and regional degeneration including the cerebellum, thalamus, hippocampus, basal ganglia, ACC, frontoinsula and amygdala.

Discussion

In this study we analysed the prevalence of specific somatic complaints and pain in patients with FTD. Although these symptoms have been acknowledged earlier, not many studies have addressed the issue in neuropathologically verified cases [7-9, 11, 24]. Somatic complaints are not covered by the current diagnostic criteria for FTD [15, 25]. Recognising these symptoms and their association to FTD may be of diagnostic importance and have implications for treatment and care.

Somatic complaints were common in our material, present in about 1/3 of the cases. We did

not find any correlation with gender, age at onset or duration. There was no clear correlation between somatic complaints and protein pathology. This finding may not be surprising as the neurodegenerative pathology in FTD varies, even within the same pathological subgroup.

Pain processing and its relation to neuropathology is an intriguing and a complex issue. Many cerebral structures are involved in the expression and modulation of pain. Among the areas that have recently been discussed as specifically involved in the pain processes, including analgesia and hyperalgesia, is the amygdala complex [26]. No associations between pain and possible affected brain areas were found. However, the fact that our assessment of regional degeneration was too blunt to reveal any associations between pain and brain pathology cannot be ruled out.

The rather high prevalence of prominent and unexplained somatic complaints in FTD may have a neurobiological underpinning and may be associated with the disruption of pain networks. It is a recognised fact that pain circuits are closely related to pathways that regulate mood and cognition [1, 5, 13]. With regard to the complexity of the brain's pain circuits as well as to the combined physical, cognitive and emotional aspects of pain experience it may not be surprising that no obvious clinicopathological association was found in this study.

Interestingly, Chan et al found a marked somatic element in the clinical presentation in 35% of a clinical FTD cohort with predominantly right temporal lobe atrophy [12]. These findings are similar to our results in a general FTLT population. In our material we could not find any support that persistent pain without clear underlying disease is more common in temporal or predominantly right-sided variants of FTD.

An increased response to tactile stimuli was seen in six cases, which makes it seem less frequent in our material than in a study from Bathgate et al [9]. While this feature may be underreported in our study, it was often clinically prominent in the cases where it was reported. It has previously been suggested that an overreaction to sensory stimuli (or hyperalgesia) is associated with the clinical syndrome SD, whereas a reduced reactivity (or hypoalgesia) is commonly seen in bvFTD [27]. The under-

Somatic complaints in FTD

lying protein pathology of the clinical syndrome SD is most often TDP type C [28]. However, in our material we found hyperalgesia in all neuropathological subtypes. In our cases with TDP type C pathology we found both hypo- and hyperalgesia.

It is well documented that there is a comorbidity between somatic complaints and depression in the general population [14]. Interestingly our study did not indicate that FTD patients with somatic complaints or pain exhibited more pronounced depressive traits than those without, although depressive traits and/or suicidal behaviour were seen in 46 (47%) of the 97 patients.

Only a few studies have focused on the association between suicidal behaviour and FTD, although this issue has recently been addressed [29, 30]. In our study of 97 patients, 17.5% expressed suicidal ideations or behaviour. Although suicidal behaviour was more common in the group with somatic complaints, it did not reach significant levels. Somatic complaints can be considered a risk factor for suicidal behaviour in FTD, although other features such as disinhibition, impulsiveness, depression and social aspects might also play an important role.

We have no reason to believe that the extensive somatic complaints often observed in our patients could mainly be attributed to hypochondriasis. However, as hypochondriasis was noted in some patients we cannot rule out the fact that the two syndromes may partially overlap.

In a previous study we found that somatic complaints without any obvious medical explanation were highly prevalent in a family with FTD and the C9orf72 expansion [31]. Possible explanations for the altered states of bodily awareness and somatisation in FTD patients with this specific genetic background have been dealt with in a recent study [32].

In our study the somatic complaints were mostly observed in the early stages of dementia. This may be related to the gradual deterioration of expressive language, often reaching the state of mutism. As early as in the 1950's Robertson reported that both somatic complaints and hyperalgesia could no longer be

observed as the disease progressed. She concluded that it could not be determined whether this was the result of impaired communicative skills or a loss of ability to interpret the symptoms [7].

The strengths and limitations of this study need to be discussed. One major strength is that all patients were neuropathologically verified as FTLD. Furthermore, all patients had solid clinical records and all cases had clinical follow-ups. A limitation of this study, or any other retrospective study, is the possibility that symptoms were present but had not been verified, or that symptoms were not checked for or recognised. This might have resulted in underreporting and thereby underestimating the prevalence.

Findings from our longitudinal study show that many FTD patients display symptoms of a somatic character which cannot be attributed to any medical cause. The neuropathological data do not explain or resolve this issue. However, it is an important clinical issue that has to be recognised in order to optimize diagnostics and care. There is a need for prospective, longitudinally designed studies that also focus on symptoms not included in current criteria and with neuropathological follow up.

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Disclosure of conflict of interest

None.

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Somatic complaints in FTD

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Somatic complaints in FTD

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