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Behavioral Disturbances in the Course of Frontotemporal Dementia

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Key Words
Frontotemporal dementia · Neuropsychiatric inventory · Behavioral disturbance · Apathy

Abstract
Background: Behavioral disturbances are prominent in frontotemporal dementia (FTD), and their occurrence has been the topic of several investigations. Nonetheless, the prevalence and severity of behavioral disturbances of patients with FTD in different degrees of dementia severity have rarely been studied. ***Objective:*** The aim of this study was to assess and compare the prevalence and severity of behavioral disturbances in patients with mild FTD and in patients with moderate/severe dementia. ***Methods:*** We included 21 outpatients with mild FTD [Clinical Dementia Rating (CDR) = 1] and 19 patients with moderate or severe dementia (CDR = 2 or 3) in this study. Behavioral disturbances were assessed using the Neuropsychiatric Inventory (NPI). ***Results:*** We found a statistically significant difference in the total NPI scores between patients with mild FTD and patients with moderate or severe FTD, the latter scoring higher. Apathy was the most prevalent symptom in both patient groups (90.5 and 100%). Except appetite and eating disturbance, which appeared in 77.8% of the patients with moderate/severe dementia, all other symptoms were clearly less common (<50%). ***Conclusion:*** The results highlight the variability of behavioral disturbances in mild and moderate/severe stages of FTD.

Introduction

For a long time dementia secondary to frontotemporal lobar degeneration (FTLD) was believed to be a very rare condition. Since the introduction of detailed consensus criteria in 1998 [1], however, it has become obvious that FTLD probably accounts for 50% of presenile cases of dementia [2, 3] and for 3–20% of all dementias [3–6]. The consensus criteria divide FTLD into 3 major subtypes: (1) frontotemporal dementia (FTD), a behavioral syndrome with selective involvement of the frontal and/or temporal cortices; (2) semantic dementia defined as a disorder of language, semantics and recognition of visual percepts caused by predominant anterior temporal pathology, and (3) progressive nonfluent aphasia, a syndrome associated with asymmetric degeneration of the frontotemporal cortex in the language-dominant hemisphere.

FTD is the most common clinical phenotype of FTLD [7]. Cerebral dysfunction predominantly in the frontal lobes [8] generates a clinical syndrome characterized by early decline in social behavior and personal conduct, emotional blunting, and early loss of insight [1]. Behavioral disturbances in most cases dominate the clinical picture in FTD, whereas impairment of cognitive abilities is less obvious, at least in the early stages of the disease [9].

The behavioral symptoms in dementia are extremely distressing for patients and carers. Studies in Alzheimer's

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disease (AD) and FTD found that behavioral disturbances are associated with increased caregiver burden, earlier nursing home admission and higher cost of care [10–13].

Several studies described behavioral disturbances in patients with FTLD [14–18], other investigators focused on FTD [13, 19, 20] or compared behavioral disturbances in FTD and AD [21–24]. The latter studies reported a wide range of behavioral abnormalities in FTD, including loss of insight, disinhibition, impulsivity, apathy, reduced empathy for others, frivolous behavior, mood changes, stereotypic and perseverative behavior, compulsions, aberrant motor behavior as well as changes in eating pattern [19, 21, 25].

Apart from one study, which described the changes of behavioral disturbances in patients with FTD during a 3-year course [24], and one very small investigation, which also studied behavioral disturbances in the course of FTD [26], in all studies patients with mild FTD were examined, or patients with mild, moderate and severe dementia were grouped together. Investigations on behavioral disturbances of patients with moderate and severe FTD are lacking. However, a better understanding of the spectrum of the behavioral disturbances of patients in different stages of dementia severity would aid in their assessment and treatment, and is a necessary condition for the design of clinical trials and the development of nonpharmacological interventions.

Objective of the Study

The aim of this study was to assess and compare the prevalence and intensity of behavioral disturbances of patients with mild FTD and patients with moderate/severe FTD.

Patients and Methods

We included 21 outpatients with mild FTD [Clinical Dementia Rating (CDR) = 1] and 19 patients with moderate or severe dementia (CDR = 2 or 3) in this study. The patients were diagnosed according to the revised Lund-Manchester criteria [1]. Cases with semantic dementia or progressive nonfluent aphasia were excluded. The diagnostic process consisted of history, psychiatric and neurological examination as well as laboratory screening. The patients underwent neuropsychological testing including the Mini-Mental State Examination (MMSE), the Consortium to Establish a Registry of Alzheimer's Disease Neuropsychological Battery (CERAD-NAB) and frontal executive tests (Frontal Assessment Battery [27], Color-Word Test [28], Trail Making Test [29]). Disease severity was assessed using the CDR [30]. The CDR is a clinical staging instrument that characterizes 6 domains of cognitive and functional performance: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. The information to make a rating of each domain is obtained through a semistructured interview of the patient and a reliable informant. In addition to ratings on a 4- and a 5-point scale, respectively, for each domain an overall CDR score is derived by standard algorithm. This score is useful for globally staging the level of impairment: 0 = no impairment; 0.5, 1, 2 and 3 indicate questionable/very mild, mild, moderate and severe dementia.

Every patient underwent cranial computed tomography or magnetic resonance imaging to exclude focal lesions. Efforts were made to increase the validity of the clinical diagnosis. First, cranial ^{18}F-FDG positron emission tomography was performed in 39 of the 40 patients, demonstrating frontal or frontotemporal hypometabolism typical of FTD [31–33]. Second, 17 patients with moderate or severe dementia had been examined at the same unit 1–7 years before the present visit, when the diagnosis of FTD was confirmed in every case. Third, in the remaining 2 patients reliable medical records on the early stages of the disorder were available, demonstrating the typical onset and symptoms of FTD.

Neuropathology was available in 3 patients, which confirmed the diagnosis of FTLD in all cases.

Assessment of Neuropsychiatric Symptoms

Reliability and validity of the Neuropsychiatric Inventory (NPI) have been established [34], and this instrument has been used in a variety of studies on AD and FTD [13, 35–37]. The NPI version we used assesses 12 categories of neuropsychiatric symptoms that commonly occur in dementia (see legend of table 2). The instrument examines whether behavioral disturbances were present in the past month. The informant is asked about the frequency of the symptoms in the domain on a 4-point scale from 1 (less than once a week) to 4 (more than once a day) and the severity of the behavior on a 3-point scale. By multiplying severity and frequency scores, each NPI symptom yields a domain rating with a range of 0–12, the total score is $12 \times 12 = 144$ points.

Of the 40 informants, 35 were spouses, 3 were children, and in 2 cases close friends were asked. The clinical diagnosis was made independently of the NPI, which was assessed by an independent psychologist (C.P.), who did not know the diagnosis and severity of dementia.

A few patients with moderate and severe dementia were receiving low-dose psychotropic medication at the time of examination. Explicit effects of medication on behavior were excluded by an interview of the caregiver. The patients would not have been considered in this analysis if the informants had described obvious changes of behavior following medication. However, this was not the case.

Statistical Analysis

Group comparison of demographic variables and results of the MMSE was performed using independent-sample t tests. To determine if the prevalence of the symptoms assessed by the NPI differed between the patients with mild FTD (CDR = 1) and moderate/severe FTD (CDR = 2 or 3), the χ^2 test was used. The Mann-Whitney U test was performed to analyze whether the mean scores of the single items of the NPI differed between early and later stages.

Table 1. Differences in demographic data and MMSE scores between patients with mild FTD and moderate/severe (CDR = 2 or 3) dementia

CDR	Patients	Female/male	Education years	Age years	Age of onset years	Duration of disease years	MMSE* years
1	21	4/17	14.1 ± 3.9	61.3 ± 10.0	57.3 ± 9.1	4.1 ± 2.8	23.2 ± 5.8
2 or 3	19	4/15	12.6 ± 3.2	64.6 ± 10.2	59.4 ± 9.4	5.8 ± 3.5	15.4 ± 6.9

Results are expressed as means ± standard deviation. * Significant difference ($p < 0.01$).

Table 2. Prevalence of the NPI symptoms across the stages of FTD

CDR	Del.	Hal.	Ag.	Depr.	Anx.	Euph.	Apa.	Dis.	Irrit.	Motor	Sleep	App.
1	19.0	0.0	47.6	28.6	19.0	38.1	90.5	42.9	47.6	33.3	40.0	47.6
2 or 3	10.5	0.0	52.6	47.4	21.1	36.8	100.0	47.4	47.4	52.6	36.8	77.8
p	0.58		0.75	0.22	0.56	0.94	0.17	0.78	0.99	0.22	0.61	0.11

Percentage of patients with a composite score >0. Del. = Delusions; Hal. = hallucinations; Ag. = agitation/aggression; Depr. = depression; Anx. = anxiety; Euph. = euphoria; Apa. = apathy; Dis. = disinhibition; Irrit. = irritability; Motor = aberrant motor behavior; Sleep = sleep disturbance; App. = appetite/eating disturbance.

Table 3. Mean domain scores in the NPI of patients with mild (CDR = 1) and moderate or severe dementia (CDR = 2 or 3)

CDR	NPI total	Del.	Hal.	Ag.	Depr.	Anx.	Euph.	Apa.	Dis.	Irrit.	Motor	Sleep	App.
1	20.3 (8.6)	1.2 (3.1)	0.0 (0.0)	1.2 (1.5)	0.9 (1.6)	0.5 (1.1)	1.0 (1.3)	5.9 (3.9)	1.6 (2.8)	1.9 (2.8)	1.6 (2.6)	1.6 (2.4)	3.0 (4.2)
2 or 3	32.5 (13.2)	0.2 (0.7)	0.0 (0.0)	2.0 (3.1)	1.4 (2.1)	0.7 (1.7)	1.2 (2.1)	9.5 (2.3)	2.6 (3.6)	2.4 (3.3)	4.1 (4.4)	2.2 (3.5)	5.2 (4.2)
p	0.002	0.38		0.65	0.33	0.80	0.82	0.002	0.8	0.78	0.06	0.91	0.07

The figures in parentheses represent standard deviation. NPI total = Total NPI score; Del. = delusions; Hal. = hallucinations; Ag. = agitation/aggression; Depr. = depression; Anx. = anxiety; Euph. = euphoria; Apa. = apathy; Dis. = disinhibition; Irrit. = irritability; Motor = aberrant motor behavior; Sleep = sleep disturbance; App. = appetite/eating disturbance.

Results

There was no significant difference between the patients with mild FTD (CDR = 1) and those with moderate/severe FTD (CDR = 2 or 3) regarding age and duration of the disease. The patients with moderate/severe FTD had significantly lower MMSE scores than the patients with mild dementia (table 1).

On the NPI, all subjects were shown to have at least 1 symptom. The prevalence of symptoms was not significantly different between the 2 groups in any NPI domain. The percentages of patients having each NPI symptom in the level of the CDR severity are shown in table 2.

The most common symptom in the group of patients with mild FTD was apathy (90.5%), followed by irritability, agitation/aggression, appetite/eating disturbance (each 47.6%), disinhibition (42.9%), sleep disturbance (40.0%), euphoria (38.1%) and aberrant motor behavior (33.3%). Depression (28.6%) and delusions (19.0%) were rare, and hallucinations did not occur in any patient.

In the group of patients with moderate or severe dementia, apathy was observed in all patients. More patients with moderate/severe FTD exhibited symptoms of depression, aberrant motor behavior and appetite/eating disturbance than patients with mild FTD. However, this difference did not reach statistical significance. Regard-

ing all other NPI symptoms, there were only minor differences between the groups.

The total score and the domain scores of the NPI are shown in table 3. We found a statistically significant difference in the total NPI scores between the patients with mild FTD (20.3 points) and those with moderate/severe FTD (32.5). Apathy was the symptom that attained the highest scores in the group of patients with mild dementia (5.9) as well as in the group with moderate or severe dementia (9.5). Except delusions and hallucinations, all mean scores were higher in the group of patients with moderate/severe FTD. However, only the difference in the apathy scores and no other difference reached statistical significance.

Discussion

We found that behavioral disturbances assessed with the NPI are increased in frequency and severity in patients with moderate/severe FTD compared to patients with mild FTD.

Of all NPI symptoms, apathy was the most prevalent one, not only in the patients with mild dementia but also in those with moderate/severe FTD. All other symptoms were clearly less common. Anxiety and delusions were rare, and hallucinations were not reported at all. Overall, these results are consistent with the findings of similar studies demonstrating a striking predominance of apathy in patients with mild FTD [37] and a great variability of other behavioral symptoms [18, 19]. The low prevalence of psychotic symptoms in FTD that we found in our study was also described recently [12]. A 3-year longitudinal study of behavioral disturbances in patients with FTD [24] found a slight but statistically not significant increase in behavioral symptoms over time. A detailed comparison of our results with these studies, however, is not possible due to different patient groups and assessment methods.

In the group of patients with moderate/severe dementia, the second most common symptom was appetite/eating disturbance. Almost 80% of the patients presented this symptom; similar results have been pointed out in other studies [12, 21]. Increased appetite is often difficult to manage and does not only cause weight gain, but excessive eating can lead to aspiration or choking [38].

The fact that all NPI symptoms apart from apathy and appetite/eating disturbance were observed in <50% of the patients shows that patients with FTD are a very heterogeneous group with respect to behavioral disturbances. Recent imaging studies suggest that different localizations of the neurodegenerative process might cause distinct neuropsychiatric symptoms [19, 25, 39] so that a typical profile of behavioral disturbances in FTD cannot be identified.

The most interesting result of our study is that apathy is the most prominent symptom – not only of the patients with moderate/severe FTD but also of those with mild dementia. Other authors have also described apathy as a very common change in FTD [19, 40]. In the NPI, apathy includes lack of interest, lethargy, social and emotional withdrawal and reduced speech output. Previous research on apathy in demented elderly individuals shows that it can contribute equally to disability in activities of daily living and can accelerate cognitive decline [41, 42]. In early stages of FTD, apathy and lethargic behavior – next to agitation, psychotic symptoms and irritability [13] – are the most distressing symptoms for caregivers [43]. While symptoms such as aggression or agitation can be treated successfully in some cases using antidepressants [36] or neuroleptics [44], there are barely any pharmacologic treatment options to modify severe apathetic behavior. The efficacy of nonpharmacological interventions, i.e. activity therapy [45] or cognitive behavioral therapy [46], has not been systematically studied. Thus, the results of our study underscore the need for investigations of pharmacological and nonpharmacological treatment options of apathy in FTD.

The present study has limitations.

(1) We did not compare behavioral symptoms in 1 patient group assessed at different points in the course of FTD. Of the patients with moderate/severe FTD, 17 had been examined at an earlier stage of the disease, but the NPI had not been performed at that visit. Thus, we compared cross-sectional data of 2 independent patient samples. However, both patient groups did not differ significantly with respect to years of education, male-to-female ratio and age of onset (table 1). Of even greater importance is that NPI informants were comparable between the 2 groups regarding relationship with the patient and frequency of contact. With the exception of 2 informants in the group of patients with advanced dementia, who were close friends and visited the patients several times a week, all other informants were either spouses or children (in 3 cases), who lived in the same household with the patient.

The CDR has not yet been shown to be associated with disease stage in FTD. Unlike in AD, in FTD the concept of mild, moderate and severe dementia does not correspond exactly to early, middle and late disease stages.

Thus, comparing 2 independent patient samples with different severity of dementia, the present study does not show up the changes of behavioral disturbances during the progression of FTD.

(2) A selection bias might have occurred, since the study population was recruited from memory clinic attenders. Patients with mild dementia may be more likely to be referred to this unit if they exhibit behavioral problems, which may have led to an overestimation of neuropsychiatric symptoms at this stage of the disorder. On the other hand, patients with moderate or severe dementia who show marked behavioral symptoms may have an increased risk of hospital or nursing home admission and therefore be less likely to present at a memory clinic, which would result in an underestimation of behavioral disturbances at that stage.

(3) An assessment bias must be taken into account, since the NPI was not specifically designed for the assessment of patients with FTD and does not include measures of stereotypic and ritualistic behavior, which is typical of FTD. Thus, we were not in a position to detect differences of prevalence and severity regarding these symptoms.

(4) A point of criticism is the danger of a tautology in the present study, as the CDR was used to measure dementia severity. Aggression, irritability and apathy probably cause higher scores particularly in the domains community affairs, and home and hobbies so that patients who present with severe behavioral disturbances receive a higher global CDR score. However, as the CDR was primarily developed for the use in patients with AD, it has a strong focus on memory and cognition-related functional ability. This goes along with our finding that patients with moderate/severe dementia (CDR = 2 or 3) had significantly lower scores on the MMSE than patients with mild dementia (CDR = 1). Furthermore, in patients with FTD the instrument has been demonstrated to reveal functional impairments in a wide variety of domains as well as to discriminate between global stages of FTD [47], and so far there is no alternative or even better instrument for measuring the severity of dementia in FTD.

Despite the shortcomings, our study has shown clear results, highlighting the variability of behavioral disturbances in FTD in mild and moderate/severe dementia, and the prominence of apathy. Future studies must be conducted to investigate neuroanatomical and particularly neurophysiological correlates of the neuropsychiatric symptoms. A better understanding of the cerebral alterations is the basis of the development of specific therapies and could possibly be transferred to other neurodegenerative diseases like AD or even functional psychiatric disorders.

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