Psychotic Symptoms in Frontotemporal Dementia: Prevalence and Review

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Key Words

Frontotemporal dementia · Psychosis · Delusions · Hallucinations · Paranoia · Alzheimer's disease

Abstract

Background/Aims: Although most patients with frontotemporal dementia (FTD) present with neuropsychiatric symptoms, the frequency of psychotic symptoms is unclear. This study aims to determine the prevalence of psychotic symptoms in a large cohort of well-diagnosed and followed FTD patients compared to age-matched patients with Alzheimer's disease (AD) and to further review the literature on psychosis in FTD. **Methods:** Delusions, hallucinations and paranoia were evaluated among 86 patients who met consensus criteria for FTD, had frontotemporal changes on functional neuroimaging and were followed for 2 years. They were compared to 23 patients with early-onset AD on a caregiver-administered psychiatric questionnaire. **Results:** Among the FTD patients, only 2 (2.3%) had delusions, 1 of whom had paranoid ideation; no FTD patient had hallucinations. This was significantly less than the AD patients, 4 (17.4%) of whom had delusions and paranoia. Other investigations fail to establish a significant association of psychosis with FTD. **Conclusions:** These findings, and a literature review, indicate that psychotic symptoms are rare in FTD, possibly due to limited temporal-limbic involvement in this disorder.

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Introduction

Frontotemporal dementia (FTD) usually presents in middle age with neuropsychiatric symptoms [1, 2]. Alterations in interpersonal conduct and personal regulation are core features of FTD, and many of these patients present to psychiatrists with a suspicion of a primary psychiatric disorder [3, 4]. The development of disinhibition, socially inappropriate behavior, emotional disengagement, repetitive compulsive-like acts, poor insight and other behavioral changes can lead to a misdiagnosis of FTD as schizophrenia or another psychotic disorder [2–6].

The evidence is indecisive for a specific association of psychosis with FTD, particularly in comparison to other neurodegenerative dementias. There have been case reports, generally without confirmatory neuropathology, which describe delusions, hallucinations or paranoia in patients with possible FTD [7–19]. Other studies describe psychotic symptoms in FTD on informant inventories or questionnaires but do not further define the symptoms [20–24].

There are several problems with prior reports of psychosis in FTD. First, there is variability in the accuracy of their clinical diagnoses of FTD. In the absence of pathology, investigators must rigorously apply clinical criteria in the diagnosis of this disorder. Second, there is variability in the length of follow-up, which can affect the preva-

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lence of psychotic symptoms. Finally, investigators must distinguish significant psychotic symptoms from the often bizarre personality and behavior changes of FTD. This study reports the prevalence of significant psychotic symptoms among a large cohort of well-characterized and followed patients with FTD, compared to age-matched patients with Alzheimer's disease (AD), and critically reviews the literature.

Materials and Methods

Subjects

All 109 patients in this study presented for evaluation to university-affiliated specialty clinics in dementing disorders. All patients had the insidious onset and progression of behavioral or cognitive changes and were followed up over a 2-year period. These community-based, moderately impaired patients underwent an initial neurobehavioral evaluation, laboratory assessment and magnetic resonance imaging (MRI) of the brain. They were screened for preceding or premorbid mental illnesses and for other medical conditions that could result in psychosis. Finally, as part of the diagnostic evaluation, every patient underwent functional imaging with either single-photon emission tomography (SPECT) or positron emission tomography (PET). Study participation included written informed consent according to institutional review board guidelines for clinical information.

Patients were identified as having the behavioral variant of FTD by consensus criteria [1]. Those with other frontotemporal lobar degenerations, such as primary progressive aphasia and semantic dementia, were excluded. The necessary core features of consensus criteria included evidence of declines in social interpersonal conduct, regulation of personal conduct, emotional expression and insight. This study included 86 patients who continued to meet consensus criteria for FTD after 2 years of follow-up, had frontal or frontotemporal hypoperfusion or hypometabolism, and had not taken antipsychotic medications for more than 3 months for other than psychotic symptoms.

Patients were identified as having AD by research criteria for clinically probable AD [25]. In order to compare with FTD patients, whose ages of onset were usually in the presenium, the AD patients were included if they had ages of onset of 65 years or younger. Because of this early-onset restriction, this study was able to include only 23 patients who continued to meet criteria for clinically probable AD after 2 years of follow-up, had focal temporoparietal hypoperfusion or hypometabolism, and had not taken antipsychotic medications for more than 3 months for other than psychotic symptoms.

Procedures

The FTD and AD patients were routinely seen every 6 months and were assessed with the following psychiatric questions. (1) Has he/she had beliefs that others did not share and that are persistently held despite evidence that they are false (in other words, delusions)? (2) Has he/she seen, heard or had experiences that others did not share (in other words, hallucinations)? (3) Has he/she felt excessively suspicious or persecuted, or believed that someone was trying to hurt him/her (in other words, paranoia)?

Table 1. Patient characteristics: FTD vs. early-onset AD

	FTD	AD
Patients	86	23
Gender		
Male	44 (49)	10 (43)
Female	42 (51)	13 (57)
Education, years	14.91 ± 4.22	15.19 ± 2.91
Age at onset, years	56.70 ± 11.12	61.2 ± 9.92
Age at presentation, years	58.41 ± 10.50	63.52 ± 9.49
Duration at 2 years FU, years	4.82 ± 3.34	5.23 ± 4.24
MMSE on presentation	25.01 ± 6.21	23.59 ± 5.42
MMSE at 2 years FU	22.32 ± 6.44	20.91 ± 6.14
CDR on presentation	1.49 ± 1.01	1.33 ± 1.41
CDR at 2 years FU	1.99 ± 1.48	2.11 ± 1.12
Delusions score ^{1,2}	0.40 ± 0.96	1.11 ± 1.69
Hallucinations score ¹	0.19 ± 0.56	0.45 ± 1.12
Paranoia score ^{1,3}	0.17 ± 0.61	1.22 ± 1.79

Values are means ± SD. Figures in parentheses represent percentages. FU = Follow-up.

¹ Likert scale scores for presence of symptoms at any point from onset up to 2 years of follow-up.

² Significant group differences: $t = 2.53$, d.f. = 107, $p < 0.05$.

³ Significant group differences: $t = 4.37$, d.f. = 107, $p < 0.001$.

The clinic neurologists administered the questions after an interview with the patient's informant or caregiver. The investigators coded the psychiatric items on a 5-point Likert scale from 'not at all characteristic' to 'extremely characteristic.' After 2 years of follow-up, the presence of psychotic symptoms at any point in the course was judged significantly present if they attained Likert scores of 3 or more (moderately or extremely characteristic). Group differences were compared using 2-tailed t tests and χ^2 analysis as appropriate.

Results

The FTD and AD groups did not differ on demographic and dementia severity variables such as the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (CDR) Scale (see table 1) [26, 27]. There were no differences in the overall stages of their disease; both groups were evaluated during early to middle stages of progression.

The 2 dementia groups differed significantly on prevalence of psychotic symptoms. The overall Likert scores for delusions and paranoia were significantly different between the 2 groups (see table 1). From disease onset to the end of the 2-year period of follow-up, only 2 (2.3%) FTD patients had delusions, compared to 4 (17.4%) of the

AD group ($\chi^2 = 5.29$; $p < 0.05$). The persistently held false beliefs of the 2 FTD patients were: (1) being married to different movie stars at different times, and (2) the belief that her husband was dedicated to treating her poorly. Both of these delusions were investigated and found to be false.

All 4 of the AD patients had paranoid delusions, particularly spousal infidelity. One of the 2 FTD patients with delusions had paranoia, compared to all 4 of the AD patients with delusions. Hallucinations occurred in 1 additional patient in each dementia group. There were no correlations between the Likert scores for the 3 psychotic symptoms and the demographic or dementia severity (MMSE or CDR) variables. No clear pattern emerged suggesting correlation with other behavioral symptoms except that the AD patients had more memory deficits by definition than the FTD patients. Possibly significant is the fact that the one FTD patient with delusions and paranoia also had prominent memory difficulty.

Discussion

Clinicians often attribute psychotic symptoms to FTD. This report, however, does not document a specific tendency for delusions, hallucinations or paranoid ideation among a large cohort of patients who met clinical criteria for FTD and who were followed for 2 years. This is the first report expressly dedicated to evaluating psychotic symptoms among FTD patients. This study's findings are discussed in the context of a critical review of the medical literature.

Although FTD may resemble schizophrenia [28–31], many reports of FTD patients with delusions or hallucinations probably referred to alternative diagnoses. The original report was Goldstein and Katz's [7] (1937) analysis of the psychopathology of a 56-year-old woman with presumed Pick's disease. She had visual hallucinations and delusions of seeing her recently deceased brother, expressed agitation and distress over his 'going hungry' and had marked intellectual deterioration. A careful review of her history, however, suggested a psychotic depression precipitated by her brother's death or the presence of another neuropsychiatric disorder rather than FTD. Neary et al. [10] (1988) described 1 of 7 FTD patients with paranoid ideas, and Miller et al. [11] (1991) reported 1 of 8 FTD patients with the delusion that he was a messenger of God. This last patient, however, proved to have a left basal ganglia lacunar infarction and hypoperfusion in both parietal regions suggestive of AD. Similarly, Miller et al.

[12] (1993) described a 60-year-old depressed woman with possible FTD who complained that a dentist had inserted radioactive material into her mouth causing her teeth to crack and abscess, but she too had severe bilateral parietal hypoperfusion. Vanderzypen et al. [17] (2003) claimed that a 34-year-old man with psychotic symptoms might have FTD, but the patient had an abnormal neurological examination and a normal PET scan. Finally, Kerssens et al. [18] (2006) reported a 65-year-old woman with depression, personality changes and bizarre delusions with acoustic, haptic and gustatory hallucinations, but her other symptoms and course were more suggestive of psychotic depression than of FTD.

A further review of other case reports failed to establish an association of psychotic symptoms with FTD. Waddington et al. [13] (1995) described a 65-year-old woman with a schizophrenia-like psychosis who developed increasing cognitive deficits and the neuropathological hallmarks of Pick's disease on brain biopsy. She had begun with a personality change at the age of 25 and could have had a coincident association of 2 diseases. Kitabayashi et al. [14] (2005) had a similar patient with psychosis at the age of 24 and dementia from about the age of 62. Lamote et al. [15] (1998) described a 35-year-old woman with neuroimaging suggesting FTD who was diagnosed as having 'schizophrenic psychosis of the hebephrenic type', but she did not have delusions or hallucinations. Dell and Halford [16] (2002) reported a 37-year-old woman who, 10 months postpartum, began talking to pictures, counting ceiling tiles, naming inanimate objects and having 'odd thoughts', and had disproportionate frontal lobe atrophy on MRI. Despite marked loosening of associations, however, psychotic features were not reliably elicited.

There were 2 additional case reports that were reasonably convincing for a clinical course consistent with FTD with psychotic symptoms, but neither had pathological confirmation of the diagnosis. The first was a 56-year-old woman who developed depression and the false belief of having contracted AIDS from her husband [12, 32]. Her SPECT showed frontotemporal hypoperfusion, worse on the right than left. The second was a 53-year-old man who presented with hallucinations, both visual and auditory, and had frontotemporal atrophy on MRI and frontal hypometabolism on PET [19].

The more extensive FTD patient series did not include a full description of the psychotic symptoms. Among frontal variant FTD patients, investigators reported delusions and hallucinations in 5 and 2% of 68 patients and in 15 and 8% of 23 patients, respectively, without further

description or follow-up [33, 34]. In contrast, other series failed to find any psychosis among well-characterized patients with FTD [5, 35, 36]. On the Neuropsychiatric Inventory [37], informants have reported delusions in 5 and hallucinations in 0–3 patients from groups of 22 and 23 FTD patients (frontal or behavioral variant) [20, 21]. Although the number of delusions among the FTD patients was still fewer than among those with AD [20], it may still have been an overestimation. Informant responses on the Neuropsychiatric Inventory delusion question ('Does the patient have beliefs that you know are not true?') required clarification. For example, in a report of delusions among 8 (12.7%) of 63 FTD patients [24], none of these patients had true delusions after the informants' responses had been further clarified. Other investigators have documented few delusions among FTD patients in comparison to AD patients, whereas delusions and paranoia were common in the middle stages of AD [22, 23, 38]. Finally, 3 clinicopathological series with definitive frontotemporal lobar degeneration on autopsy found no psychosis among 19 patients [4], no hallucinations among 48 patients [39] and only 1 clearly defined paranoid-hallucinatory state among 20 patients [8, 9].

The infrequency of delusions, hallucinations or paranoia in FTD, particularly as compared to AD, is important for what it reveals about brain mechanisms of psychosis. In AD, delusions are worse with poor memory and cognitive function and are associated with frontal hypofunction, particularly on the right [40, 41]. Lesions in the right frontal cortex may facilitate delusions through poor mapping of internal feelings, such as paranoia, on observed reality, and inappropriate correction of any subsequent inaccurate conclusions and beliefs [42]. This conclusion is supported by the correlation of delusions in AD with the density of neurofibrillary tangles in midfrontal gyrus and other neocortical regions [43]. AD patients with psychotic symptoms, however, also have involvement of the mesiotemporal area [44, 45]. Lesions in the mesiotemporal area may result in de-

lusions that involve fear or a disturbed sense of threat or familiarity through disruption of limbic functions that link perception to emotional states [42]. FTD patients, in contrast to AD patients, have relative sparing of the temporal limbic system [46]. On the other hand, some FTD patients may have psychotic-like symptoms related to their compulsive tendencies or to coincident low B₁₂ levels [47].

There are several potential limitations of this study. First, there was no pathological confirmation. The FTD patients, however, met consensus criteria for FTD, had corroborative functional neuroimaging results, and were followed and monitored for 2 years. Second, the number of patients with significant psychotic symptoms was small. This study, however, aimed for greater specificity of the psychotic symptoms in order to distinguish them from the often bizarre personality and behavioral changes of FTD. Third, the number of patients with AD was also small. The number of AD patients was limited because of the need to have similar ages of onset and follow-up periods among AD patients in the same clinical program. Fourth, the one FTD patient with delusions and paranoia also had significant memory difficulty. She nevertheless met consensus criteria for FTD and had relatively isolated frontal hypometabolism on PET. Ultimately, a frontal variant of early-onset AD could not be ruled out in this patient.

In conclusion, the relative paucity of psychotic symptoms in FTD has several implications. First, there are important implications for differential diagnosis. In the past, as many as 21% of autopsy-verified FTD patients have been misdiagnosed with psychosis or schizophrenia [4]. Second, the findings in this report support minimizing the use of antipsychotic medications, particularly given an increased risk of neuroleptic side effects in FTD [48, 49]. Third, the lack of psychosis in FTD may indicate that the temporal-limbic system is necessary to develop unchecked paranoid false beliefs, as in AD. Further work is required in order to corroborate these findings, particularly among FTD patients followed to autopsy.

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