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Psychotic Symptoms in Frontotemporal Dementia

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Abstract Although psychotic features have long been recognized in association with frontotemporal dementia (FTD), recent genetic discoveries enabling further subtyping of FTD have revealed that psychotic symptoms are frequent in some forms of FTD. Hallucinations and delusions can even precede onset of other cognitive or behavioural symptoms in patients with FTD. In this review, we explore the frequency and types of psychotic symptoms reported in patients with FTD, as well as in other neuropsychiatric disorders, to aid practitioners' consideration of these features in the diagnosis of FTD and related disorders.

Keywords Frontotemporal dementia · Psychosis · Hallucinations · Delusions

Introduction

It was recognized over 30 years ago that psychosis, including hallucinations and delusions, occurred in approximately 20 % of patients with frontotemporal lobar dementia (FTLD) [1]. In particular, a high incidence of psychotic features was appreciated in patients with frontotemporal dementia with motor neuron disease (FTD-MND) [2]. Recent genetic discoveries have prompted recognition of psychotic features in a high percentage of patients with FTD and C9ORF72 repeat expansions [3•, 4, 5•]. The knowledge that psychotic features may occur early in the disease course, prior to the onset of other typical symptoms of FTD, requires practitioners to further consider neurodegenerative diseases such as FTD when considering diagnosis in patients with psychosis. In this paper, we present a summary of the incidence and nature of psychotic symptoms in FTD from the literature to date and the experience in our center to highlight the overlap and differences between psychotic symptoms in FTD, schizophrenia, and other neurodegenerative dementias.

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Methods

A search was conducted on PubMed using terms "frontotemporal dementia," "psychosis," "hallucinations," and "delusions" limited to articles published in English before March 9, 2015. This generated 138 articles. The abstracts were used to further narrow the articles to those relevant to the topic. Additional articles were gathered from the reference lists of relevant review papers. This yielded 99 articles.

FTD and Psychosis

While psychosis has long been recognized as a symptom in FTD, there exists significant variability in the rate of psychosis reported among clinical FTD cohorts. In the clinical series with at least ~100 patients with clinical diagnosis of FTD (Table 1), the prevalence of hallucinations ranges from 0 to 50 %. The relative frequency of visual and auditory hallucinations also varies across series, from auditory being more common in some [6], visual in others [7•, 8, 9], and similar frequencies in others [10, 11]. The frequency of concurrent of

Table 1 Select case series reporting on psychosis in patients with FTD

Study	FTD patients #	Other comparison groups #	Pathology	Genetics	Measurement	Psychosis	Delusions	Hallucinations
Bathgate et al. [10]	FTD 30	AD 75 VCI 34	No	–	Caregiver questionnaire		Suspiciousness 30 % Delusions of theft 10 % people in home 10 % Misidentification 30 %	Visual 7 % Auditory 10 %
Engelborghs et al. [42]	FTD 29	AD 205, mixed dementia 39, DLB 23	No	–	BEHAVE-AD	21 %	17 %	7 %
Harciarek & Kertesz, [12]	bvFTD 119 PPA 101 SD 24 CBD 18	AD 392 DLB 36 PD 26 PSP 8	No	–	Clinical interview		Misidentification SD 8.3 % bvFTD 0 %	
Landqvist Waldo et al. [7•]	FTLD 97		Yes (97)	–	Chart review		Total 17.5 % Persecutory 11.3 % Erotomania 1.0 % Somatic 3.1 % Uncategorized 2.1 % Paranoid ideas 20.6 %	Total 17.5 % Visual 14.4 % Auditory 3.1 % Tactile 2.1 % Olfactory/gustatory 1.0 %
Leger & Banks, [13]	FTD 149	578 AD	Yes (149)	–	NPI		Clinical FTD ~27 % Pathological FTD ~23 %	Clinical FTD ~23 % Pathological FTD ~20 %
Lillo et al. [2]	bvFTD 43 FTD-MND 18		Yes (25)	–	DSM-IV		bvFTD 19 % FTD-MND 50 %	bvFTD 12 % FTD-MND 28 %
Mendez et al. [28]	FTD 86	Early onset AD 23	No	–	Original set of questions		2 %	0 %
Mendez et al. [53]	bvFTD 48		Yes (1)	–	Not specified	False reports 8.3 %		
Mendez et al. [14]	bvFTD with FTLD 74	bvFTD with AD pathology 21	Yes (95)	–	Form B9 NPI		bvFTD with FTD pathology 14.9 % bvFTD with AD pathology 38.1 %	bvFTD with FTD pathology 8.1 % bvFTD with AD pathology 33.3 %
Omar et al. [8]	FTD 56		Yes (2)	–	DSM-IV		14 %	Total 9 % Auditory 2 % Visual 5 % Tactical 4 %
Passant et al. [29]	FTD 19		Yes (19)	–	Chart review		0	0
Schoder et al. [6]	FTD 100	AD 100	No	GRN 5 % VCP 3 % MAPT 2 %	NPI FBI		FTD 26.3 %	FTD: Auditory 21 % Visual 5.3 %
By mutation								
Boeve et al. [18]	bvFTD 210 FTD-MND 51 ALS 195		Yes (14) C9ORF72: bvFTD 9.0 %, FTD-MND 21.6 %, ALS 6.7 % MAPT: bvFTD 7.6 %, FTD-MND 0 %, ALS 0 % GRN: bvFTD 4.8 %, FTD-MND 0 %, ALS 0 %		Chart review		C9ORF72 45 %	C9ORF72 50 %

Table 1 (continued)

Study	FTD patients #	Other comparison groups #	Pathology	Genetics	Measurement	Psychosis	Delusions	Hallucinations
Dobson-Stone et al. [17]	FTD 89 FTLD 22		Yes (22 FTD-TDP)	C9ORF72 Total 15.7 % Clinical 10.1 % Pathological 40.9 %	Cambridge Behavioural Inventory	C9ORF72 56 % Non-carriers 14 %		
Hsiung et al. [16]	30 pts from 16 C9ORF72 families		Yes (21)	C9ORF72 55 % GRN 24 %	Chart review	3.3 %	3.3 %	0 %
Galimberti et al. [36]	FTD 651	CBD 21 PSP 31 Control 222	Yes (1 C9ORF72 case)	C9ORF72: FTD 6 % CBD 0 % PSP 0 %	DSM-IV	C9ORF72 30.3 % Non-carriers 8.1 %	C9ORF72 15.2 %	C9ORF72 12.1 %
Mahoney et al. [15]	FTD 273 (probands 256)	Controls (number not specified)	Yes (6)	C9ORF72 7.0 % MAPT 5.9 % GRN 6.6 % VCP 0.4 %	Chart review		C9ORF72 12.5 %	C9ORF72 6.3 % (somatic)
Simon-Sanchez et al. [64]	bvFTD 262 PPA 101 FTD-MND 38	Controls 522	Yes (10 C9ORF72 cases)	C9ORF72 11.9 %	Chart review		C9ORF72 0 %	C9ORF72 5 %
Snowden et al. [5•]	bvFTD 211 PNFA 66 SD 53 Mixed dementia 68		Yes (78 total; 5 C9ORF72 cases)	C9ORF72 8 % of total population	Chart review	C9ORF72 38 % Non-carriers < 4 %	C9ORF72 53 %	C9ORF72 19 %
Kertesz et al. [11]	62 FTD		Yes (8 C9ORF72)	C9ORF72 11 %	Chart review	C9ORF72 75 %	C9ORF72 37.5 % Non-carriers 18.2 %	C9ORF72: all 50 % Visual 37.5 % Auditory 37.5 % Non-carriers: all 4.5 %
Le Ber et al. [9]	fvFTD 352 FTD-MND 52 PPA 6 CBD 30		Yes (5 GRN cases)	GRN: fvFTD 5.7 % FTD-MND 0 % PPA 4.4 % CBD 3.3 %	NPI FBI		GRN 6 %	GRN: Visual 25 % Auditory 3 %
Le Ber et al. [19]	bvFTD 489		–	C9ORF72 24.2 % GRN 7.1 % MAPT 4.7 %	NPI FBI			C9ORF72 7 % GRN 25 % MAPT 9 % No identified mutation 1 %
Sha et al. [3•]	FTD 648	PCA 8 MCI 72 AD 171 DLB 5	No	C9ORF72 4.7 % of total population	Chart review NPI		C9ORF72: bvFTD 21.4 % FTD-MND 18.1 % Non-carriers: bv FTD 0 % FTD-MND 10.5 %	

FTD frontotemporal dementia, *FTLD* frontotemporal lobar dementia, *fvFTD* frontal variant FTD, *tvFTD* temporal variant FTD, *bvFTD* behavioural variant FTD, *FTD-MND* FTD and motor neuron disease, *ALS* amyotropic lateral sclerosis, *PPA* primary progressive aphasia, *PPA-nf* PPA non-fluent, *PPA-sv* PPA semantic variant, *CBD* corticobasal degeneration, *LPA* logopenic aphasia, *SD* semantic dementia, *PPNA* progressive non-fluent aphasia, *AD* Alzheimer's disease, *DLB* dementia with Lewy bodies, *PSP* progressive supranuclear palsy, *PD* Parkinson disease

auditory and visual hallucinations is not typically reported in the larger series.

The rates of delusions in patients with clinical diagnosis of FTD in the larger case series are converge around 25 % [6, 13]. Delusion types include paranoia and persecutory, erotomania, somatic, Cotard's type, and delusions of reference (Table 2).

In patients with pathologically confirmed FTD, frontotemporal lobar degeneration (FTLD), the rates of psychosis are typically slightly lower than in clinical cohorts. This has been attributed to a higher rate of delusions in patients with pathologic diagnosis of AD [13, 14]. In the largest series of 97 neuropathologically confirmed cases of FTD, 32 % had psychotic symptoms, 20.6 % had paranoid ideas, 17.5 % had hallucinations, and 17.5 % had delusions [7•]. The identified pathology in the whole cohort included ~31 % tau positive, 54 % TDP positive (type A 8 %, B 40 %, C 5 %, D 1 %), 5 % FUS, and 10 % FTLD with no identified protein pathology. Psychotic symptoms were identified in all the pathological subtypes. Hallucinations included visual, auditory, tactile, olfactory, and gustatory, with visual (14 %) and auditory (3 %) being reported as the most frequent. Delusions were most commonly paranoid or persecutory followed by erotomania. There were no significant differences in the demographics, gender, age at onset, and disease duration in patients with FTD with and without psychosis [7•].

C9ORF72 and Psychosis

The discovery of the C9ORF72 hexanucleotide repeat expansion as the most common genetic mutation associated with familial FTD-MND was soon followed by reports of high rates of psychosis and delusions in cohorts of patients with C9ORF72 mutations and FTD or FTD-MND. The prevalence of the mutation in FTD varies depending on the population studied and ranges from ~5 to 35 % [3•, 15]. In cohorts of patients with clinical diagnosis of FTD and C9ORF72 repeat expansions, the prevalence of psychosis ranges from 3 to 56 % compared to ~4 to 14 % in non-carriers [5•, 11, 16–19]. Hallucinations occur in up to 50 % [20] and can include visual, auditory, and somatic. Delusions are present in up to 53 % [5•] and most commonly include paranoid, persecutory, or somatoform delusions.

In clinical cohorts, the rates of psychosis in patients with FTD-MND are typically higher than those of patients with FTD without MND, likely due to a higher prevalence of C9ORF72 mutations in the FTD-MND cohorts. However, one series found that in patients with FTD-MND, those with C9ORF72 repeat expansions vs. non-carriers had similar rates of delusions as a presenting feature (18.1 and 10.5 %, respectively) [3•]. A relatively high incidence of somatic delusions and hallucinations has been noted in patients with C9ORF72 expansions [5•] (Table 1). In our own clinical cohort, in addition to somatic delusions, we have been struck by the number of patients with C9ORF72 repeat expansions who specifically endorse visual hallucinations of faces or partial faces ~25 %. Patients have typically experienced these in the evening at bedtime and reported concomitant auditory hallucinations of the faces talking to them. In two siblings, these visual and auditory hallucinations of faces were humorous and preceded the onset of FTD or FTD-MND by approximately 10 years; however, for other patients, the talking faces were perceived as threatening.

GRN and Psychosis

Mutations of the progranulin (GRN) gene on chromosome 17 represents another common cause of autosomal dominant FTD, accounting for approximately 5–11 % of all FTD cases and 6.8–23 % of familial FTD [19, 21–23]. Hallucinations are reported in 25 % of FTD patients with progranulin mutations and delusions in ~6 % [9]. In patients with FTD and GRN mutations, the nature of visual hallucinations may overlap with those in C9ORF72, with reports of hallucinations of faces, or with those of Lewy body disease including hallucinations of small animals. Delusional jealousy, delusions of persecutions/paranoia, and Fregoli's delusions with misidentifications have all been reported in FTD patients with GRN mutations.

MAPT

Mutations of the microtubule-associated protein tau (MAPT) gene represent the third most common cause of autosomal dominant FTD, accounting for 2–11 % of FTD cases [24, 25]. In patients with FTD and MAPT mutations, 9 % of patients have been reported to experience hallucinations [19]. There are fewer details on the nature of psychotic symptoms in MAPT carriers. One case report describes a bizzare delusion in a 35-year-old patient with FTD who claimed she was a park ranger who saved a girl from a rattle snake by picking it up and kissing it [26].

Psychosis in Schizophrenia vs. FTD

Increased recognition that patients with FTD may present with psychosis, including persecutory delusions and auditory hallucinations, potentially complicates distinctions between FTD and late-onset schizophrenia. In some series, up to 30 % of patients ultimately clinically diagnosed with FTD were initially diagnosed with a psychotic disorder (bipolar disorder, schizophrenia, or schizoaffective disorder), with a diagnosis of dementia coming an average 5 years later [27]. Similarly, FTLD has been confirmed on autopsy in up to 21 % of cases initially diagnosed with schizophrenia or psychosis [28, 29]. This is not surprising, given that the overlap of FTD and other key diagnostic features of schizophrenia includes disorganization of behavior and speech and apathy, in addition to delusions and hallucinations [30]. Based on current detailed symptom descriptions to date, there exists a significant overlap in the nature

Table 2 Types of delusions and hallucinations reported in patients with FTD

Term	Definition	Example in patients with FTD
Delusions	"Fixed beliefs that are not amenable to change in light of conflicting evidence" [60]	
Persecutory delusions	"Belief that one is going to be harmed, harassed, and so forth by an individual, organization, or other group" [60]	People at work where planning to poison him [8]; had knife and gun for self defense and called police for protection [5•]
Grandiose delusions	"When an individual believes that he or she has exceptional abilities, wealth, or fame" [60]	He had won the Purple Heart for courage in Vietnam and the Nobel Prize for discovering a way to generate gravity without rotational movement; he believed that he was a well-known TV personality [8]
Erotomanic delusions	"When an individual believes falsely that another person is in love with him or her" [60]	She believed she was married to different celebrities [28]; belief that she married a priest and had children with him [65]; looking for children she had with other man
Cotard's delusion	"Nihilistic delusions concerning one's own body" [62] "Typically, patients believe they have lost organs, blood or body parts, or even that they are dead" [61]	Belief that organs (lung, stomach) did not exist and feeling of having repeatedly died [55]; belief her arm had acutely been amputated
Somatic delusions	"Preoccupations regarding health and organ function" [60]	Belief that a device was implanted in the spine; plastic emanating from the head, weakness of gluteal muscles or pain [5•]; patient had holes in the top of her skull that caused water to run down her back for years
Bizarre delusions	"If they are clearly implausible and not understandable to same-culture peers and do not derive from ordinary life experiences" [60]	Claimed she was a park ranger who saved a girl from a rattle snake by picking it up and kissing it [26]
Fregoli's delusion	"Mistaken belief that some person currently present in the deluded person's environment (typically a stranger) is a familiar person in disguise" [63]	Recognizing strangers as acquaintance, despite lack of any resemblance [59]
Hallucinations	"Perception-like experiences that occur without an external stimulus…They may occur in any sensory modality" [60]	Visual hallucinations of faces or partial faces talking to patient [11]; Satan voice ordering to harm daughter [8]; pruritus caused by infects and snakes on skin [8]

of hallucinations and psychosis observed in patients with FTD and schizophrenia [5•, 11, 31]. Thus, at present, it may be difficult to distinguish between the two disorders based solely on the presence or nature of the psychotic symptoms. Further complicating the distinction is the finding that patients with FTD are more likely to have a family history of schizophrenia than those with Alzheimer's disease [6]. The implications of this finding are unclear, and it is suggested the association could represent a common etiology or alternatively could arise because patients with familial FTD were more likely to be misdiagnosed with schizophrenia. Although there are several case reports of patients presenting with classical features of schizophrenia who are found to have FTD mutations (C9ORF72, GRN, MAPT, VCP) [10, 11, 32, 33], genotyping of typical clinical cohorts of patients with schizophrenia for FTD-causing mutations including C9ORF72 and GRN has typically identified only a very small percentage (<1–2 %) of patients carrying FTD mutations [33–36].

While the onset of schizophrenia tends to occur at an earlier age than FTD, in the second to third decade of life compared to the fifth or sixth decade of life for FTD [37], an estimated ~25 % of schizophrenia presents after 40 years of age [31, 38]. The course of symptoms can be instructive, as the course of disease tends to stabilize in schizophrenia but in FTD a continual decline occurs [37]. The hyperorality observed in FTD, particularly for sweets, is also noted to be uncommon in schizophrenia [26, 37]. Neuroimaging features may also aid in the diagnosis, as the frontotemporal atrophy and hypoperfusion/hypometabolism of bvFTD are typically more extreme that that observed in schizophrenia (Fig. 1) [31, 39].

Psychosis in FTD vs. Lewy Body Disease

A key feature of dementia with Lewy bodies is the presence of hallucinations, classically visual hallucinations of people or animals [40, 41]. In a series of ~100 patients with probable DLB, 70 % had visual hallucinations, 10 % had auditory hallucinations, and 41 % had delusions [40]. Of interest, 2 % of patients diagnosed with DLB were found to have the C9ORF72 expansion. DLB patients were noted to have greater incidence visual hallucinations compared with delusions, the opposite pattern of that seen in FTD patients with C9ORF72. Older series have reported a higher prevalence of delusions in DLB of up to 61 % [42], though the series

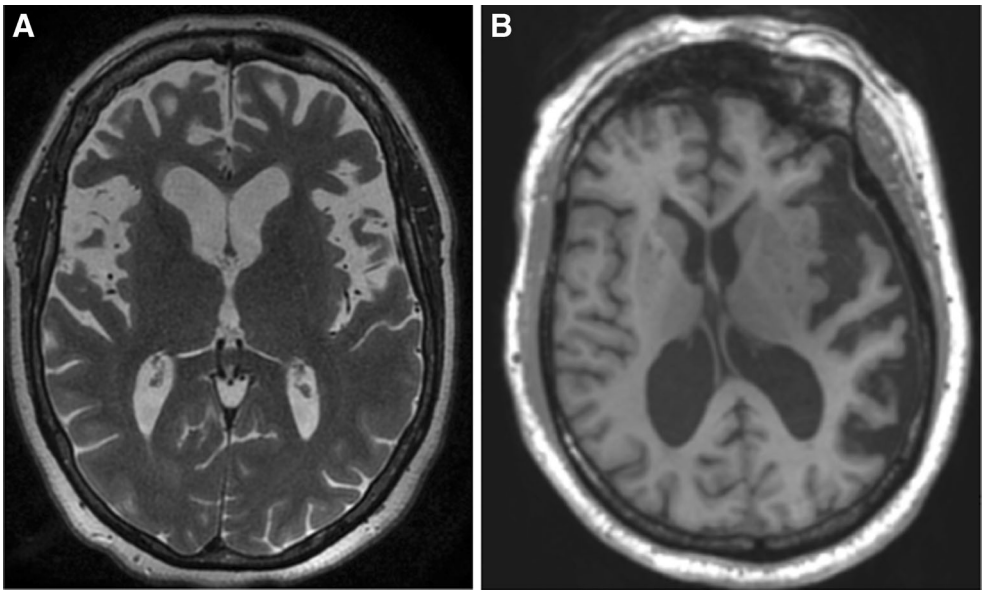

Fig. 1 Example MRI scans in patients with FTD and psychosis. A range of atrophy patterns can be observed in FTD patient with psychosis. **a** MRI scan from a patient with sporadic bvFTD with recent delusions she had won the lottery. **b** MRI from a patient with C9ORF72 expanded repeats and FTD who had persecutory visual hallucinations beginning 40 years earlier

predates knowledge of the C9ORF72 mutation. In our experience, early in the symptom course, patients with DLB may have good insight into the hallucinatory nature of these experiences and do not converse with hallucinatory images of people, or may simply tell them to go away, while some of our patients with FTD have been amused at the visual hallucinations of faces and described carrying on pleasant two-way conversations with the images [11]. The most common types of delusions also differ in LBD and FTD, with somatic delusions more frequent in FTD and rarely reported in DLB, while delusions related to misidentification of people and places are more common in DLB [40].

Psychosis in FTD vs. Alzheimer's Disease

The occurrence of psychotic symptoms in Alzheimer's disease is well documented. Approximately 50 % of patients with AD will experience delusions and ~30 % will experience hallucinations [43, 44]. Within delusions, the most common subtypes include paranoid delusions of theft, bodily harm, or spousal infidelity, and misidentification delusions in which the patient feels their spouse or family member is someone else (Capgras) or that their home is a copy of their real home (reduplicative paramnesia). Within hallucinations, the most common subtypes are auditory, experienced by 10–20 % of patients with AD, and visual hallucinations, seen in approximately 20 % [43, 45]. While delusions and hallucinations have sometimes correlated with low MMSE scores [46] and accelerated decline, the symptoms can be present in early stages of the disease, typically within 30–36 months of disease onset [43]. However, some of these reports pre-date the discovery of the C9ORF72 mutation, which can present with an Alzheimer-like clinical and neuropsychological profile. In our experience, it is rare for patients with Alzheimer's disease to develop hallucinations in early stages of the disease, and thus, the presence of early visual hallucinations is more commonly associated with FTD or Lewy body disease. While the specific nature of delusions in FTD and AD may overlap, review of the case series and our clinical experience indicates that patients with AD are more likely to have delusions that their spouse is having an affair, while patients with FTD more commonly falsely believe they themselves are having affairs or personal relationships with famous individuals [2, 8, 47]. Finally, somatic delusions and hallucinations are more common in patients with FTD and in our experience are rare in patients with Alzheimer's disease [5•].

Neuroanatomy and Imaging Findings in FTD with Psychosis

The occurrence of psychosis in patients with FTD with focal neuropathology offers a valuable opportunity to study the anatomic underpinnings of psychotic symptoms. In a cohort of patients with FTLD without a known genetic status, the presence of psychotic symptoms was associated with predominantly right-sided brain degeneration (76.9 % with psychotic symptoms) compared with symmetric degeneration (29.8 %) or predominately left-sided atrophy (13.0 %) [7•]. An association between right-sided temporal atrophy and visual hallucinations was also found in a smaller series of patients with temporal predominant FTD [48]. Although others have speculated that regions specifically affected by C9ORF72 mutations such as the thalamus or cerebellum may be important for the emergence of psychotic symptom, in one of the largest FTLD series to examine this question, no specific associations were found between psychotic symptoms and atrophy in the cerebellum, thalamus, hippocampus, basal ganglia, anterior cingulate gyrus, frontoinsular cortex, or the amygdala [7•].

The finding of increased psychotic symptoms in patients with right brain predominant FTLD is consistent with findings in patients with Alzheimer's disease. Atrophy of the right frontal lobe is most commonly associated with delusions in Alzheimer's disease; however, associations have also been reported with the hippocampus, superior temporal gyrus, parietal cortex, and other more specific regions of the frontal cortex such as the cingulate gyrus or orbitofrontal cortex [7•, 49–51]. The variability in results to date is likely due to several factors including the lack of specific subtyping of psychotic symptoms or delusions in many studies, variable neuroimaging techniques and data analysis, small sample sizes (generally between $n=5$ and $n=23$ patients with delusions or psychosis), and lack of multi-modal approaches [52].

Treatment

There have been no randomized controlled trials specifically for treatment of psychosis in FTD. A few cases in the literature have reported some improvements in symptoms when antipsychotics were initiated [53–55]. Patients with FTD are sensitive to the side effects of antipsychotics, with extrapyramidal symptoms occurring in 33 % and severe in 21 % [56]. Two case reports discussed the use of electroconvulsive therapy to treat psychosis after antidepressants and antipsychotics failed to control symptoms. In one, ECT was successful, but in the other, the effects were short-lived and the delusions continued to fluctuate [55, 57]. The treatment refractory nature of psychosis in FTD is in contrast to the more frequent improvement in such symptoms in response to antipsychotic medications in patients with schizophrenia [8, 58].

Conclusions

Psychotic symptoms are increasingly recognized as a presenting or early feature of frontotemporal dementia. In patients presenting with psychosis, consideration of the specific nature of hallucinations, the presence or absence of other hallmark features of FTD such as disinhibition or hyperorality, genetic screening, and neuroimaging can aid in the diagnosis of FTD and distinction from other disorders classically featuring psychosis including late-onset schizophrenia, Lewy body dementia, and Alzheimer's disease.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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