

The case of a 48 year-old woman with bizarre and complex delusions

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Background. A 48 year-old woman presented with an 18 month history of bizarre and complex delusions on a background of social, behavioral and cognitive decline over several years. Her psychosis progressed despite receiving high doses of antipsychotics. The patient's father also had a psychotic episode in his 40s. He subsequently developed motor neuron disease, which caused his death at 68 years of age.

Investigations. Physical examination, neuropsychological testing, nerve conduction studies, brain MRI and transcranial magnetic stimulation.

Diagnosis. On the basis of the patient's age at onset of the delusions, imaging findings and family history, a diagnosis of frontotemporal dementia (FTD) was favored over a primary psychotic disorder. The ubiquitin-positive and TAR DNA binding protein 43-positive inclusions that were found at autopsy confirmed the diagnosis of FTD.

Management. The patient was treated with various antipsychotics at high doses; however, her delusions continued to progress. No disease-specific treatments for FTD currently exist.

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Identify distinguishing features of frontotemporal dementia (FTD) when compared with schizophrenia.
- 2 Describe physical signs congruent with FTD in a patient with late-onset psychosis.
- 3 Describe pathologic findings associated with FTD.
- 4 Describe features of late-onset schizophrenia.

Competing interests

The authors and the Journal Editor H. Wood declare no competing interests. The CME questions author D. Lie has served as a nonproduct speaker for "Topics in Health" for Merck Speaker Services.

The case

A 48 year-old woman presented with an 18 month history of bizarre and complex delusions that involved intruders in her house. The patient believed that she had become pregnant following a 2 week sexual relationship with one of these intruders. Furthermore, she could hear the other intruders attempting to harass her by tapping their penises on the ceiling, and she could also smell semen in the house. These delusions persisted despite treatment with risperidone and, subsequently, olanzapine. Both antipsychotics were prescribed at a moderately high dose, although the patient's compliance with the medication regimens was variable.

The patient's medical history included thalassemia minor with mild anemia. In addition, her father had experienced a psychotic episode in his late 40s. He subsequently developed motor neuron disease (MND) and died aged 68 years. The patient also had two first cousins who were thought to have either schizophrenia or an autistic spectrum disorder.

When she was seen in the Cognitive Disorders Clinic, the patient displayed no insight regarding her delusions. Her family, however, provided a lucid history of her progressive social, behavioral and cognitive decline. The patient had collected approximately 300 cookbooks over the past decade and had become increasingly withdrawn socially and more rigid in her routines. She had also displayed progressive difficulty with spelling and comprehension over the past 5 years. The patient was still employed by a catering service, but her ability to work had been questioned. She had become increasingly disorganized

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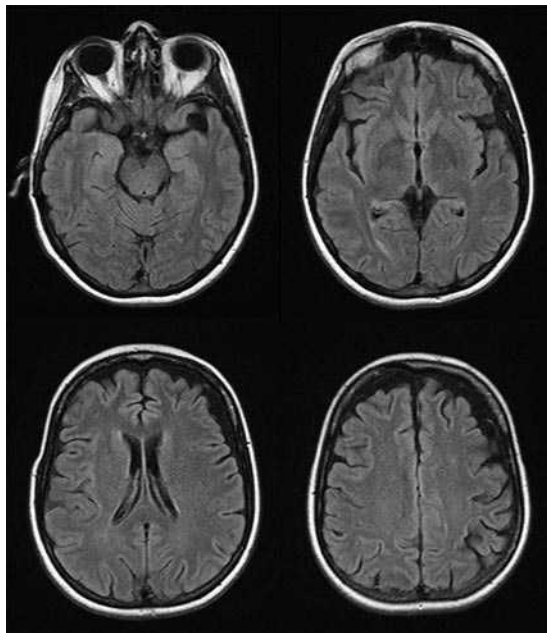


Figure 1 | MRI of the patient's brain. Mild frontal atrophy was observed on T2-weighted turbo inversion recovery magnitude sequences.

and was caught eating a portion of the ice cream that she was meant to deliver.

On examination, the patient was well groomed and cooperative, yet unduly passive. She was a poor historian and became mildly suspicious of the interviewer at times. The patient displayed a blunted affect, despite describing a euthymic mood. No evidence of a formal thought disorder after allowance for her cognitive deficits could be detected. She scored 26 out of 30 on the Mini-Mental State Examination, losing 1 point each on serial sevens, verbal recall, repetition and intersecting pentagons. She scored 75 out of 100 on the Addenbrooke's Cognitive Examination (revised),¹ and had letter and animal fluencies of 9 and 12 per minute, respectively. Bedside neuropsychological examinations were confounded by her impulsivity. Nonetheless, the patient exhibited impairment of frontal executive function (set-shifting, proverbs and planning) and also made mistakes with confrontational naming (semantic errors). Her episodic memory, however, was relatively preserved. The findings from the bedside neuropsychological assessment were consistent with the results of a formal neuropsychological examination that she underwent 10 months before the consultation.

Neurological examination of the patient revealed frontal release signs, as well as increased jaw jerk and generalized brisk limb reflexes. No fasciculations or muscle wasting could be detected, however. The patient had a normal EEG, a normal nerve conduction study and a negative pregnancy test, and no signs of denervation could be detected on electromyography. MRI revealed mild, bilateral atrophy of the frontal lobes, as demonstrated by widening of the inter-hemisphere fissure on axial images (Figure 1). Cortical hyperexcitability, as assessed using transcranial magnetic stimulation, can precede clinical symptoms in some individuals with familial MND.² Our

patient, however, demonstrated normal cortical excitability, without neurophysiological evidence of dysfunction involving the corticospinal tract.

Diagnosis

Initial diagnosis

The severity of the patient's psychosis brought to mind a primary psychotic disorder. Other features of the case, however, including the patient's social, behavioral and cognitive decline, her family history, and imaging findings, raised the possibility of frontotemporal dementia (FTD).

The presence of systemized delusions—defined as false beliefs that are firmly sustained despite strong and consistent evidence to the contrary—favored a diagnosis of schizophrenia. These delusions were accompanied by auditory hallucinations and social dysfunction in the absence of substance use or a pervasive developmental disorder. This cluster satisfied the Diagnostic and Statistical Manual of Mental Disorders criteria for schizophrenia when organic disorders were excluded.³

Evidence against a diagnosis of schizophrenia included the patient's age at disease onset, atypical hallucinations, cognitive dysfunction and imaging findings. Her age at onset was relatively late for a first episode of psychosis,⁴ and was more consistent with the age of onset for FTD. Our patient's hallucinations were not typical for schizophrenia: the nonverbal character of her auditory hallucinations and the presence of olfactory hallucinations suggested a secondary psychosis. In terms of neuropsychological deficits, the patient had predominantly executive dysfunction, which could have been consistent with either schizophrenia⁵ or FTD. Finally, the presence of frontal atrophy raised the possibility of an alternative diagnosis, as such atrophy is not traditionally regarded as a characteristic of schizophrenia. The atrophy exhibited by our patient was mild, however, and frontal gray matter volume of people with schizophrenia, as assessed by MRI, has been found to be reduced compared with controls.⁶ Thus, the imaging findings in our patient were perhaps not entirely inconsistent with a diagnosis of schizophrenia.

The patient's signs and symptoms also satisfied the clinical diagnostic criteria for FTD.⁷ She had an insidious onset of impaired social conduct, rigid behavior, and a pathological sweet tooth, and displayed poor insight and frontal release signs on examination. Her cognitive profile and imaging findings were also supportive of a diagnosis of FTD.

Psychosis has not been systematically studied in a prospective manner in patients with FTD, and might be more prevalent in this condition than was previously thought. In an autopsy series, 13% of patients with autopsy-confirmed FTD were found to have experienced delusions and hallucinations.⁸ A 3 year clinical series from a tertiary referral center reported a similar prevalence (14%) of these symptoms in such patients.⁹ In our experience, psychotic symptoms are more common in patients with FTD who later develop MND than patients with FTD who do not develop MND. Furthermore, patients with FTD are often resistant to treatment with antipsychotics,^{9,10} as seemed to be the case with our patient. A study involving a case series

Table 1 | Clinical features of late-onset schizophrenia and FTD

Clinical feature	Late-onset schizophrenia	FTD
Sex	Female predominance	Males and females equally affected
Premorbid personality	Higher proportion of patients exhibit a premorbid schizoid or paranoid personality with late-onset schizophrenia than with FTD	Personality more likely to be intact before symptom onset in FTD than in late-onset schizophrenia
Delusions	Bizarre delusions frequently present	Rarely present; when present, delusions can be indistinguishable in nature from those observed in late-onset schizophrenia
Hallucinations	Predominantly auditory hallucinations	Rarely present; when present, nonauditory modalities occur with a higher frequency in cases of FTD than in cases of late-onset schizophrenia
Course of psychosis	Eventually stabilizes and can ameliorate with time	Unknown; symptoms might progress with time
Antipsychotic response	Good	Unknown
Social interactions	Deterioration before reaching a plateau; social withdrawal and isolation are the predominant features	Progressive deterioration; disinhibition and socially inappropriate behavior are the predominant features
Cognitive function	Deterioration before reaching a plateau	Progressive deterioration
Insight	Poor	Poor

Abbreviation: FTD, frontotemporal dementia.

and a review of existing literature has drawn attention to the association between FTD with an onset before 60 years of age and the presence of schizophrenia-like psychosis.¹¹ In the case series, of the 17 patients with autopsy-confirmed FTD that developed before this age, five individuals had a psychotic prodrome and all were found to have ubiquitin-positive inclusions. Interestingly, two of the five patients who exhibited psychotic symptoms developed MND and another had a family history of FTD with MND. In their extensive review of the literature, the researchers found 46 cases of FTD that presented with a psychotic illness—6% of the total number of cases identified from 200 publications. In virtually all cases of FTD with psychosis, the age of onset was under 60 years of age (mean age 40 years). In Table 1, we have summarized the clinical features that might help distinguish late-onset schizophrenia from FTD.

The recognition that FTD and MND can co-occur in individuals and within families is increasing. Several kindreds with FTD–MND have now been linked to chromosome 9p,^{12,13} and our patient's family history was consistent with this 9p locus. Interestingly, psychosis has also been found in some of these kindreds.^{12,13} In all these kindreds with chromosome 9p-linked FTD–MND, immunohistochemistry has revealed ubiquitin-positive and TAR DNA-binding protein 43 (TDP-43)-positive pathology.

Taking into account her age at onset, imaging findings and family history, we favored a diagnosis of FTD over schizophrenia for this patient. FTD comprises a heterogeneous group of disorders—in terms of genetics, histopathology and clinical findings—that are unified by atrophy of the frontal and/or temporal lobes. Given our patient's family history of MND, we expected to find ubiquitin-positive and TDP-43-positive FTD pathology.

Final diagnosis

Over the 3 months following the initial presentation to our clinic, the patient's complex delusions continued to progress. She started snipping scissors in the air around

her to “cut away” the intruders, and placed steel wool in her underpants to “protect” herself. She was admitted for inpatient psychiatric care and became increasingly apathetic and distractible, and was barely able to speak in full sentences. Her delusions progressed despite treatment with olanzapine, amisulpride and, subsequently, a high dose of aripiprazole. She continued to believe that she was pregnant, and would pull down her trousers or lie on a table in a lithotomy position to ‘deliver’. The patient began cramming food without choking 2 months after admission. Neurological examination was limited by the patient's cooperation. She exhibited scalloping of the tongue, but no fasciculations or wasting in the limbs. The patient became progressively more agitated, experienced recurrent aspiration pneumonias and, eventually, stopped swallowing. She died of pneumonia 4 months after admission.

The patient was enrolled in a brain donor program and a brain-only autopsy was performed 26 hours after death. The brain, which weighed 1,112 g, was hemisected, and the right cerebral and cerebellar hemispheres and the right half of the brainstem were fixed in formalin.

As expected from our patient's family history, she was found to have FTD with ubiquitin-positive and TDP-43-positive pathology. Mild atrophy of the superior aspect of the anterior frontal lobe was evident on external examination (Figure 2a) and following sectioning in the coronal plane, although the atrophy was restricted to the prefrontal lobe (Figure 2b). In addition, the substantia nigra and locus ceruleus had a moderate pallor. Microscopy revealed scattered ubiquitin-positive and TDP-43-positive intracytoplasmic inclusions in the fascia dentate (Figure 2c). Such inclusions and dystrophic neurites were seen in the frontal, temporal and insular cortices (Figure 2d–f). Rare tau-positive neurons were seen in the CA1 sector of the hippocampus. Tau-immunopositive neurons and dystrophic neurites were also noted in the insular, but not in the temporal or frontal cortices. Mild superficial gliosis was seen in the insular cortex. The histopathology observed in

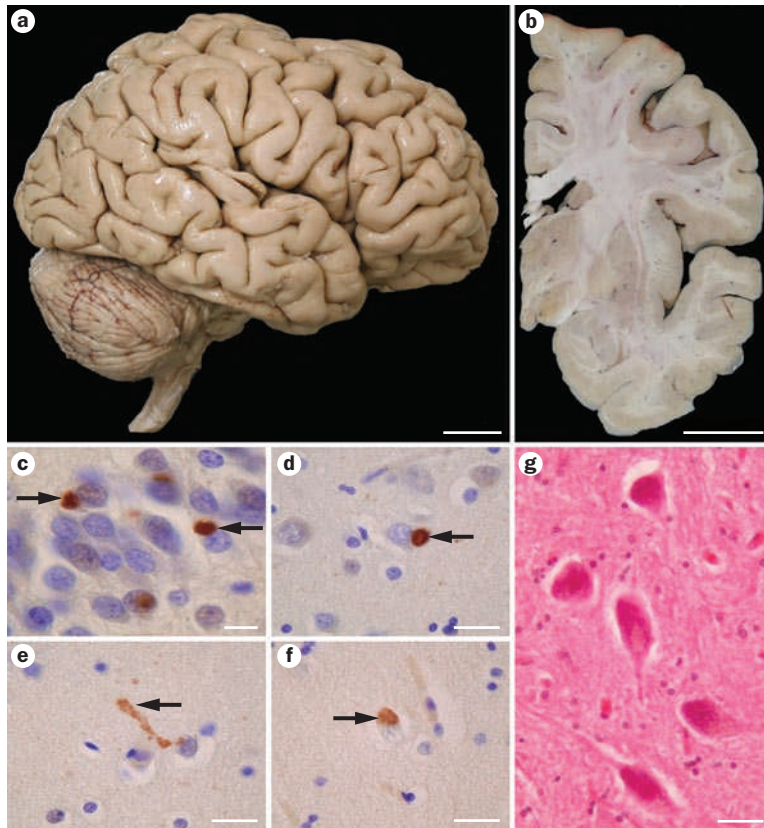


Figure 2 | Neuropathology of the patient's brain. **a** | Mild atrophy of the anterior frontal lobe could be seen on external examination of the right hemisphere (bar 2 cm). **b** | Motor areas of the posterior frontal lobe remained largely intact (bar 2 cm). Ubiquitin-positive intracytoplasmic inclusions (arrows) were observed in **c** | the dentate gyrus (bar 10 μ m) and **d** | the frontal cortex (bar 20 μ m). **e** | In the frontal cortex, ubiquitin-positive staining could also be observed in scattered dystrophic neurites (arrow; bar 20 μ m). **f** | Intracytoplasmic inclusions in this brain region also stained positive for TAR DNA binding protein 43 (arrow; bar 20 μ m). **g** | No loss of neurons from the hypoglossal nucleus was observed (bar 20 μ m).

the insular cortex of this patient was of particular interest, as the insula is usually preserved until later in the disease course of FTD.¹⁴ Activation of a number of brain regions, including the insular cortex, has been associated with hallucinations,¹⁵ and degeneration of this region might have accounted for some of the unusual features of our patient's clinical presentation. Examination of the primary motor cortex revealed a reduction in the number of Betz cells but no intracytoplasmic inclusions. A small portion of the upper cervical spinal cord was removed with the brainstem. This region of the spinal cord showed no obvious loss of anterior horn cells, or intracytoplasmic inclusions or pallor of the corticospinal tract. The hypoglossal nucleus was well populated (Figure 2g) and the substantia nigra showed mild pigment incontinence but no inclusions.

The vast majority of people with ubiquitin-positive FTD also exhibit TDP-43-positive inclusions; however, Neumann *et al.*¹⁶ identified a subgroup of patients who, while having no staining for TDP-43, were immunopositive for the fused in sarcoma protein (also known as FUS).¹⁶ Interestingly, a high proportion of the patients described by Neumann *et al.* also had psychosis. The age at onset of FTD in this subgroup, however, was approximately 38 years, and patients in this group did not have a family history of FTD or MND. Thus, these individuals constitute a group of FTD patients with psychosis that are separate from the familial FTD-MND subgroup to which our patient belonged. Given our patient's family history of FTD-MND, one might have expected her to develop MND. The brain autopsy, however, revealed little evidence of motor system degeneration. This finding was consistent with the normal cortical excitability demonstrated on transcranial magnetic stimulation.

Management and treatment

Regrettably, no disease-specific treatment exists for FTD.¹⁷ Part of the reason for the absence of therapies is the heterogeneity of FTD itself, in terms of both etiology and clinical features. Hopefully, with increasingly specific correlations between clinical findings and underlying etiology, improvements will be made in our capability to define etiologically homogeneous patient subgroups for future clinical trials. The heterogeneity in clinical features also renders outcome measurement in clinical trials difficult.¹⁸ Given that progressive lobar atrophy is a defining feature of FTD, the problems of disease monitoring might be partially overcome by advances in quantitative serial volumetric imaging.

Not surprisingly, given the familial nature of our patient's FTD, her family is concerned about other members developing the disease. In addressing the family's concerns, we sequenced the progranulin gene, mutations in which can cause FTD. Such mutations, however, are rare in families with FTD-MND¹⁹ and, as expected, sequencing of the progranulin gene did not identify a mutation in our patient. She might well fall into the group of patients with mutations in the yet to be discovered, chromosome 9p-linked gene for FTD-MND.^{12,13}

Conclusions

At times, the clinical differentiation between schizophrenia and FTD can be difficult. In our patient, however, a number of clues pointed to a diagnosis of FTD. These included her age at onset of the delusions, a family history of MND, the presence of atypical hallucinations and cognitive dysfunction, and brain atrophy on MRI. The autopsy confirmed the diagnosis of FTD with ubiquitin-positive and TDP-43-positive inclusions. Our patient is likely to fall into the group of individuals with chromosome 9p-linked familial FTD-MND.

1. Mioshi, E., Dawson, K., Mitchell, J., Arnold, R. & Hodges, J. R. The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int. J. Geriatr. Psychiatry* **21**, 1078–1085 (2006).
2. Vucic, S., Nicholson, G. A. & Kiernan, M. C. Cortical hyperexcitability may precede the

- onset of familial amyotrophic lateral sclerosis. *Brain* **131**, 1540–1550 (2008).
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR* (American Psychiatric Association, Washington DC, 2000).

4. Kessler, R. C. *et al.* Age of onset of mental disorders: a review of recent literature. *Curr. Opin. Psychiatry* **20**, 359–364 (2007).
5. Rajji, T. K. & Mulsant, B. H. Nature and course of cognitive function in late-life schizophrenia: a systematic review. *Schizophr. Res.* **102**, 122–140 (2008).

6. Mitelman, S. A. *et al.* A comprehensive assessment of gray and white matter volumes and their relationship to outcome and severity in schizophrenia. *Neuroimage* **37**, 449–462 (2007).
7. Neary, D. *et al.* Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology* **51**, 1546–1554 (1998).
8. Hodges, J. R. *et al.* Clinicopathological correlates in frontotemporal dementia. *Ann. Neurol.* **56**, 399–406 (2004).
9. Omar, R. *et al.* Delusions in frontotemporal lobar degeneration. *J. Neurol.* **256**, 600–607 (2009).
10. Bak, T. H., O'Donovan, D. G., Xuereb, J. H., Boniface, S. & Hodges, J. R. Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease-dementia-aphasia syndrome. *Brain* **124**, 103–120 (2001).
11. Velakoulis, D., Walterfang, M., Mocellin, R., Pantelis, C. & McLean, C. Frontotemporal dementia presenting as schizophrenia-like psychosis in young people: clinicopathological series and review of cases. *Br. J. Psychiatry* **194**, 298–305 (2009).
12. Luty, A. A. *et al.* Pedigree with frontotemporal lobar degeneration–motor neuron disease and Tar DNA binding protein-43 positive neuropathology: genetic linkage to chromosome 9. *BMC Neurol.* **8**, 32 (2008).
13. Vance, C. *et al.* Familial amyotrophic lateral sclerosis with frontotemporal dementia is linked to a locus on chromosome 9p13.2–213. *Brain* **129**, 868–876 (2006).
14. Kril, J. J., Macdonald, V., Patel, S., Png, F. & Halliday, G. M. Distribution of brain atrophy in behavioral variant frontotemporal dementia. *J. Neurol. Sci.* **232**, 83–90 (2005).
15. Hoffman, R. E., Anderson, A. W., Varanko, M., Gore, J. C. & Hampson, M. Time course of regional brain activation associated with onset of auditory/verbal hallucinations. *Br. J. Psychiatry* **193**, 424–425 (2008).
16. Neumann, M. *et al.* Frontotemporal lobar degeneration with FUS pathology. *Brain* doi:10.1093/brain/awp214.
17. Huey, E. D., Putnam, K. T. & Grafman, J. A systematic review of neurotransmitter deficits and treatments in frontotemporal dementia. *Neurology* **66**, 17–22 (2006).
18. Knopman, D. S. *et al.* Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. *Brain* **131**, 2957–2968 (2008).
19. Schymick, J. C. *et al.* Progranulin mutations and amyotrophic lateral sclerosis or amyotrophic lateral sclerosis-frontotemporal dementia phenotypes. *J. Neurol. Neurosurg. Psychiatry* **78**, 754–756 (2007).

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