Frontotemporal Dementia and Psychiatric Illness: Emerging Clinical and Biological Links in Gene Carriers

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Objective: *To describe psychiatric presentations in individuals with genetic mutations causing frontotemporal dementia (FTD).* **Design:** *Case descriptions from five carriers of FTD-related gene mutations with symptoms associated with non-neurodegenerative psychiatric disease.* **Setting:** *A comprehensive research program investigating genetic and non-genetic FTD at the University of California, San Francisco Memory and Aging Center.* **Participants:** *Three proband and two non-proband gene carriers.* **Measurements:** *Medical history and neurological examination, neuropsychological testing, magnetic resonance and/or positron emission tomography imaging, and a genetic analysis to screen for dementia-related mutations. Genetic status was unknown at the time of initial evaluation.* **Results:** *The chosen cases are illustrative of the variety of presentations of psychiatric symptoms in FTD gene carriers. In some cases, a non-neurodegenerative psychiatric illness was diagnosed based on specific symptoms, but the diagnosis may have been inappropriate based on the overall syndrome. In other cases, symptoms closely resembling those seen in non-neurodegenerative psychiatric illness did occur, in some cases immediately preceding the development of dementia, and in other cases developing a decade prior to dementia symptoms.* **Conclusions:** *Psychiatric symptoms in FTD gene carriers can be very similar to those seen in non-neurodegenerative psychiatric illness. Psychiatric symptoms with atypical features (e.g., late-life onset, insidiously worsening course) should prompt careful assessment for neurodegenerative disease. Guidelines for such an assessment should be established.* (Am J Geriatr Psychiatry 2015; ■:■−■)

Key Words: Frontotemporal dementia, C9ORF72, psychiatric disease

Frontotemporal dementia (FTD) is a neurodegenerative disease that causes changes in socioemotional behavior. The symptoms can overlap with those of psychiatric disorders, leading to erroneous diagnoses.[1−8] Better knowledge about the features that lead clinicians to attribute behavioral changes to

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non-neurodegenerative psychiatric syndromes could aid in early diagnosis of FTD.

Most data on psychiatric diagnoses in FTD come from retrospective studies in patients who have already received an FTD diagnosis.[7] It has been difficult to identify the reasons for the prior psychiatric diagnoses because detailed clinical and/or research data were not collected when symptoms began. Recent developments in the genetics of FTD offer an opportunity to revisit this issue. Because individuals who have FTD-related genetic mutations can be identified before they develop symptoms, these patients offer an opportunity to characterize psychiatric symptomatology during the earliest phases of illness. FTD gene carriers exhibit a high rate of psychiatric symptomatology, such as delusions and hallucinations, and have a high prevalence of psychiatric diagnoses in their families.[9–11] Although prior reports have highlighted psychiatric features, the degree to which the symptoms in such cases mimic typical, non-neurodegenerative psychiatric illness has not been well characterized.

We describe five individuals with disease-causing FTD mutations who received psychiatric diagnoses. These cases illustrate a variety of clinical presentations that led to psychiatric diagnoses and highlight the significant overlap in symptomatology that can occur between FTD and psychiatric disorders. In addition, they suggest that neurodegenerative diseases may lead to psychiatric symptoms through multiple biological mechanisms.

METHODS

Subjects

Patients were referred to the University of California, San Francisco Memory and Aging Center (UCSF) to participate in ongoing, longitudinal research on aging and neurodegenerative disease, and informed consent was obtained for their participation. Participants were not known to have an FTD-associated mutation at the time of their initial clinical assessment. During the research evaluation, mutations were identified in a laboratory specialized in FTD genetics. Based on the clinical presentations of patients being evaluated in the research program, it became clear that multiple types of psychiatric symptoms were present, with varying relationships to the other symptoms of neurodegenerative disease. The cases presented here were chosen as exemplars of three types of "psychiatric" presentation.

RESULTS

Case 1

Ms. A, a 62-year-old, right-handed woman, was referred for evaluation of 18 months of progressive cognitive and personality change, lack of empathy, and poor planning. At age 60, she displayed obsessive behavior, including rigid adherence to brushing her teeth after every meal, repeatedly organizing household items, and checking her e-mail compulsively. She was evaluated by a community physician and diagnosed with obsessive-compulsive disorder (OCD). Over the next 2 years, she became more withdrawn, apathetic, and exercised poor judgment. She lost money in an e-mail scam and posted a profile of herself on an Internet sex site. She made inappropriate political and racial remarks in public. She ate ravenously by shoveling food into her mouth. She became fixated on having three meals each day, sometimes eating immediately after a meal to satisfy the schedule.

Ms. A's family history included FTD in her sister and bipolar illness in her mother. Her 60-year-old sister was diagnosed at UCSF with behavioral variant FTD that began at age 50. At the time of evaluation, she spent hours transferring individual leaves into a bucket, wore layers of clothing in 38°C heat, and began hoarding. A second sister, still independent in her 50s, was also seen at UCSF with personality and behavior changes and hoarding behavior.

On exam, Ms. A was alert and cooperative but made inaccurate or vague statements. She had a tendency to move her mouth repetitively, had a fixed, open-eyed stare, square-wave jerks, and mild slowing of vertical saccades. She had mild cogwheel rigidity in the right hand and a mild action tremor. On cognitive testing, she scored 27 out of 30 on the Mini Mental State Exam (MMSE) but otherwise performed normally.

The magnetic resonance image (MRI) revealed mild-to-moderate frontal and anterior temporal lobe atrophy (Fig. 1). Her amyloid-positron emission