

From the University of California, San Francisco

Frontotemporal Dementia and Mania

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Case Presentation

"Ms. V," a 60-year-old college-educated woman, was brought by her daughter to the emergency department at a teaching hospital for the evaluation of heart palpitations. Ms. V had personality changes and mood swings with aggressive verbal and physical behaviors that had progressively worsened over the past year. A psychiatric consultation was requested to evaluate these emotional outbursts. On the day of admission, Ms. V had had a court hearing for assaulting her brother, who is disabled due to mental retardation. One month before presentation, she had held a pillow over his face in front of the brother's social worker, who then called the police. After this event, her brother, who has been dependent on others for self-care since childhood, disappeared for several days. She was unconcerned about her legal situation and appeared cold and indifferent. She did not report that she did anything more than throw a pillow at her brother's face, and she laughed when she heard that he was missing. Ms. V's daughter reported that her mother had become increasingly irritable, with episodes of unprovoked shouting of profanities at strangers and family members. These behaviors were uncharacteristic of the patient's personality at baseline. She had had an increase in goal-directed activities, cleaning the house constantly, checking the locks, and checking the stove. Two years before, Ms. V was fired from her job as a school administrative assistant because of difficulties managing her relationships with the students' parents. Since then, she had not made any attempts to seek other employment. There was no history of head trauma, loss of consciousness, seizures, or previous contact with mental health providers.

Ms. V reported no new stressors but did report some "moodiness" over the last 6 months. She reported no an-

gry outbursts or violence but endorsed a decreased need for sleep (now 6 hours, down from 8, per night). Although she did not report feeling euphoric, she reported increased irritability, daytime energy, task-oriented behavior, impulsivity, distractibility, racing thoughts, and pressured speech. Ms. V did not report feeling depressed or experiencing anhedonia. She reported no anxiety or psychotic symptoms, substance use, or recent changes in medications. Ms. V did not report any specific memory complaints, word-finding difficulties, misplacing or losing objects, or problems using transportation, following directions, or navigating. Her family history was notable for a brother with mental retardation and a sister with unipolar depression. Ms. V's vital signs were within normal limits, and complete physical and neurologic examinations were unremarkable. A CBC, a Chem 10 (basic chemistries), liver function tests, tests of thyroid-stimulating hormone, free thyroxine, rapid plasma reagins, B₁₂, and folate, an ECG, a chest X-ray, and a head computerized tomography with and without contrast showed no abnormalities.

Mental Status Examination

Ms. V appeared a well-dressed and well-groomed woman with mild psychomotor agitation. She made good eye contact, although she rolled her eyes frequently when hearing her daughter discuss her emotional outbursts. She breached personal boundaries by touching the interviewer's name tag without asking. Her speech was fluent, rapid, and pressured. She reported that her mood was "good." Her affect was expansive, silly at times, and bordering on childish, and she often laughed inappropriately. Her thought process was rambling and circumstantial. Her thought content was without any overt auditory or visual hallucinations, paranoid ideations, and suicidal or homicidal thoughts. Her insight and judgment

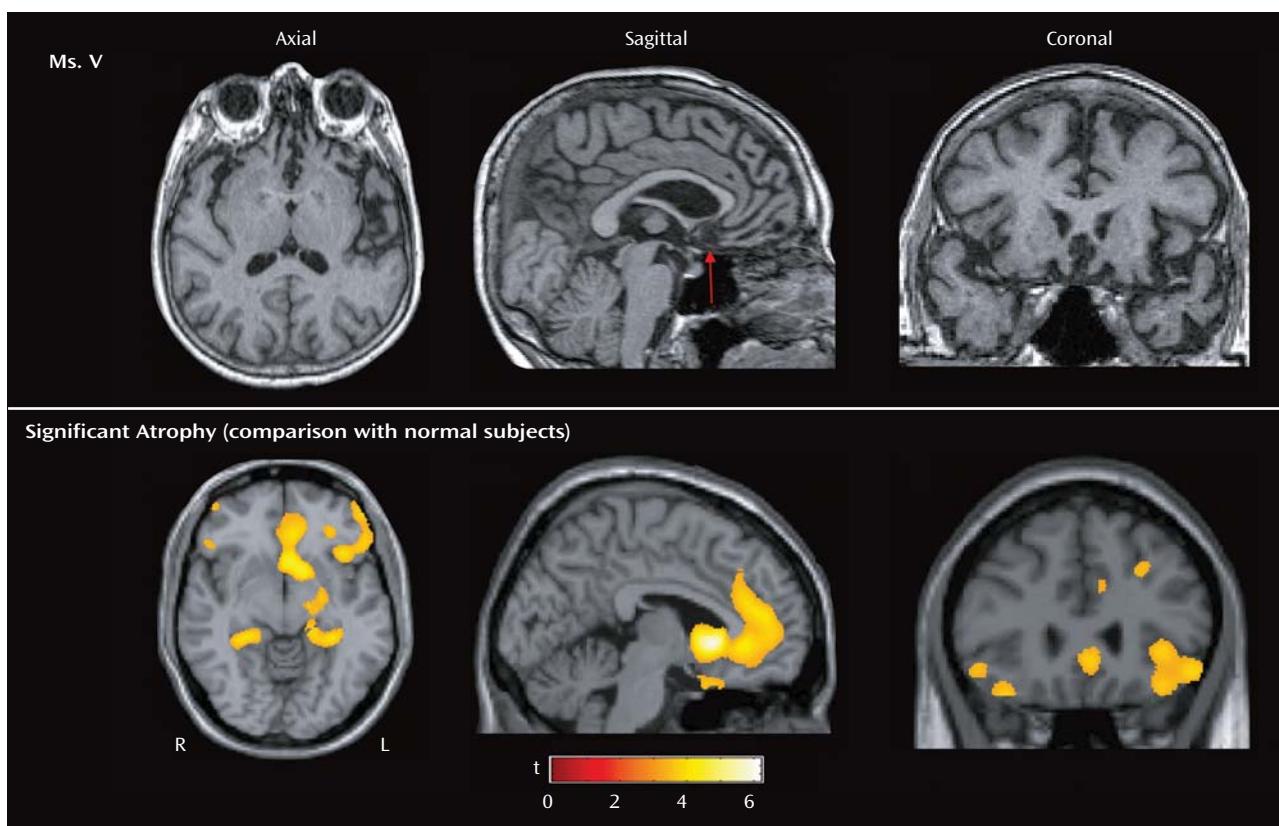
"One month before presentation, she had held a pillow over [her brother's] face in front of the brother's social worker, who then called the police."

were poor. On the Mini-Mental State Examination, Ms. V scored 30/30.

Differential Diagnosis

The insidious onset of behavioral symptoms in a woman of this age suggested a neurological process such as neurodegeneration, a silent cerebral infarct, or, less likely, an intracranial mass. Temporal lobe epilepsy as a cause of intermittent aggressive outbursts was also considered. Finally, a primary psychiatric disorder such as late-onset bipolar disorder or unipolar depression was also in the differential diagnosis.

FIGURE 1. Structural Magnetic Resonance Imaging (MRI) of Axial, Sagittal, and Coronal Sections Obtained From Ms. V Showing Atrophy in the Anterior Cingulate, Lateral Orbitofrontal Cortex, and Hippocampi^a



^a The red arrow indicates the area of most severe atrophy. Voxel-based morphometry on high-resolution T₁-weighted MRI images was used to identify brain regions that showed significantly greater voxelwise gray matter volume loss in Ms. V in relation to 94 normal comparison subjects (1, 2). The technique comprises an image-preprocessing step (spatial normalization, segmentation, modulation, and smoothing) followed by statistical analysis. Both stages were implemented in the SPM2 software package (www.fil.ion.ucl.ac.uk/spm) with standard procedures (2). Areas of significant atrophy are displayed on axial, sagittal, and coronal sections of a standard brain (bottom) and thresholded at $p<0.001$, uncorrected for multiple comparisons (coordinates: $x=-4.1$, $y=31.4$, $z=-6.2$). The most significantly atrophied area is the subgenual cingulate gyrus in the ventromedial orbitofrontal cortex ($p<0.05$, corrected for multiple comparisons). Other areas of less severe atrophy include the lateral orbitofrontal cortex, anterior cingulate, and hippocampi bilaterally.

Follow-Up Course

The psychiatric team determined that Ms. V was not at immediate risk of self-harm or violence, so she was discharged with close outpatient follow-up. Because of a strong suspicion for a neurodegenerative process, in particular frontotemporal dementia, she was referred to a neurology clinic that specializes in the treatment of neurodegenerative disease with a particular expertise in frontotemporal dementia. There it was noted that on direct questioning Ms. V had difficulty with object naming and short- and long-term memory.

Formal cognitive testing revealed deficits in visual and verbal memory, confrontation naming, word recognition, and executive function. An electromyograph showed no evidence of motor neuron disease, and homocysteine levels were within normal limits. Brain magnetic resonance imaging (MRI) showed moderate to severe symmetric atrophy of the bilateral frontal lobes and insula with relative sparing of the dorsal frontal regions. There was asymmetric anterior temporal lobe atrophy, left greater than right, though the amygdala were relatively spared and the hippocampi were moderately af-

fected (Figure 1, top). Using an unbiased, quantitative, image analysis technique (voxel-based morphometry), we compared her scan to those of 94 age-matched (mean=67, SD=10) female comparison subjects (Figure 1, bottom). This analysis revealed significant atrophy in the subgenual cingulate gyrus in the ventromedial orbital frontal cortex. Other areas that showed less severe atrophy included the lateral orbitofrontal cortex, anterior cingulate, and hippocampi bilaterally. Ms. V was given escitalopram, 10 mg/day, to which she had a transient favorable response, with a decrease in aggressive behavior. However, over several weeks, this effect diminished, and her disinhibition escalated. For example, during this time, she found her way into a private funeral, allegedly hit the hostess, whom she felt had insulted her, and in response was physically assaulted by other attendees of the service. The violence stopped when her daughter shouted to the crowd that her mother had Alzheimer's disease. The escitalopram was increased to 20 mg/day, and she was given quetiapine, titrating to 75 mg b.i.d., with improvement of her aggressive behavior.

Discussion

Although medical causes must always be ruled out in the case of new-onset mania, this is particularly important in the elderly. Older patients with new-onset mania are more than twice as likely to suffer from a comorbid neurological disorder (3), including silent cerebral infarcts (65% in new-onset versus 25% in chronic illness) (4). In addition to a standard history and a physical, these patients require a thorough neurologic examination, neuroimaging, and other selected tests (5). Reported neurological causes of late-onset mania include stroke, tumors, epilepsy, Huntington's disease and other movement disorders, multiple sclerosis and other white matter diseases, head trauma, infections such as neurosyphilis, Creutzfeldt-Jakob disease, and frontotemporal dementia (for a review, see references 6–8).

Ms. V's symptoms of irritability, pressured speech, expansiveness, decreased need for sleep, impulsivity, and psychomotor agitation all suggested mania. Clues that she had a neurodegenerative disease included her age as well as the chronic and progressive nature of her symptoms. The profound loss of sympathy and empathy for others, along with severe disinhibition and the repetitive motor behaviors (e.g., checking locks), suggested frontotemporal dementia. Frontotemporal dementia is a progressive neurodegenerative disease that affects the frontal and temporal cortices, has several clinical subtypes (for a comprehensive review, see references 9 and 10), and is a common cause of dementia in patients younger than 65 (11). The frontal lobe variant of frontotemporal dementia (also known as behavioral variant or social/executive disorder variant) is characterized by insidious behavioral and personality changes, and often the initial presentation lacks any clear neurological signs or symptoms. Key features include apathy, disinhibition, loss of sympathy and empathy for others, repetitive motor behaviors, overeating, and frontal/executive deficits on neuropsychological testing. Because of these features, in one series (12), patients with frontotemporal dementia were more likely to initially present to a psychiatrist than to a neurologist and often received erroneous psychiatric diagnoses before frontotemporal dementia was correctly diagnosed.

Affective blunting, loss of insight and social awareness, lack of concern about the disease process (so-called *l'a belle indifference*), coldness, and lack of empathy for family and friends were prominent symptoms in Ms. V and are common symptoms in frontal lobe variant frontotemporal dementia (9, 13, 14). Furthermore, damage to the ventromedial portion of the frontal cortex, as seen in Ms. V, leads to disinhibition, poor impulse control, and antisocial behavior in patients with discrete lesions (15) and frontotemporal dementia (16, 17). Similarly, atrophy to a frontotemporal circuit, including the ventromedial frontal cortex in frontotemporal dementia, has been linked to loss of empathy (18). Patients with frontotemporal dementia with asymmetric atrophy of the nondominant frontal lobe have also been shown to exhibit dramatic alterations in their self as defined by changes in political, social, or religious values (19). Stereotyped behaviors, such as compul-

sive cleaning, pacing, and collecting are also common in frontotemporal dementia; in addition to often presenting as acute mania (e.g., reference 20), patients with frontotemporal dementia frequently present solely with compulsive symptoms (21). In dementia, these repetitive motor behaviors are associated with atrophy in the right supplementary motor region of the frontal lobes (17). Ms. V was also apathetic (e.g., not seeking a new job), which is a common symptom in frontotemporal dementia associated with atrophy of the anterior cingulate and medial frontal lobes (22). This can be confused with depression, which is not common in frontotemporal dementia; patients with frontotemporal dementia are apathetic and emotionally withdrawn but not sad or suicidal. Often (up to one-third) of patients with frontotemporal dementia exhibit euphoria, which can take the form of elevated mood, inappropriate jocularity, and exaggerated self-esteem that can be indistinguishable from hypomania or mania (for a review, see reference 23). Gluttonous overeating is also common in frontotemporal dementia (24–26) and appears to be due to disruption of a right-side orbitofrontal-insular-striatal circuit (27, 28). Similarly, an exaggerated craving for carbohydrates has also been demonstrated in frontotemporal dementia by questionnaire (24, 25, 29) and laboratory (27) studies. The absence of these symptoms in Ms. V may be due to relative sparing of her right ventral insula and striatum.

Therapeutically, serotonin reuptake inhibitors are common first-line agents given the well-described serotonergic deficits in frontotemporal dementia (29, 30). A recent meta-analysis demonstrated these agents are effective in the treatment of frontotemporal dementia (31) (but see reference 32). Atypical antipsychotics and mood stabilizers can also be used to control the behavioral symptoms of frontotemporal dementia (33), although data on their efficacy is limited. Furthermore, patients with frontotemporal dementia are known to have dopaminergic deficits (31) and are particularly prone to developing extrapyramidal side effects (34). Although acetylcholine deficits are well described in Alzheimer's disease (35) and have led to successful therapeutic use of acetylcholinesterase inhibitors in this disease (36, 37), the acetylcholine system in frontotemporal dementia appears to be relatively intact (30, 31). In our and others' clinical experience, acetylcholinesterase inhibitors are ineffective in frontotemporal dementia and contraindicated since they can worsen patients' agitation, anxiety, behavioral alteration, and restlessness (34, 38, but see reference 39). The N-methyl-D-aspartic acid (NMDA) antagonist memantine has also been tried, and one small, open-label, uncontrolled study has shown it may be helpful for behavioral disturbances in frontotemporal dementia (40).

Historically, the clinical features of what would first be termed Pick's disease and later called frontotemporal dementia were first delineated by the German psychiatrist Arnold Pick in 1892 (41). He described a 71-year-old gentleman with progressive aphasia, apraxia, and behavior change in association with frontotemporal atrophy. In 1926, pathologists found that round intraneuronal inclu-

sions, when stained with silver, were characteristic of this illness (42). In honor of Arnold Pick, these inclusions were later called Pick bodies (43). More recently, these inclusions were found to contain aggregations of insoluble hyperphosphorylated tau protein. Thus, frontotemporal dementia came to be grouped in a class of neurodegenerative diseases called the tauopathies (others include semantic dementia, primary progressive aphasia, progressive supranuclear palsy, and corticobasal degeneration).

The understanding of frontotemporal dementia has improved over the past 15 years. During this time, large autopsy studies have found that the "classic" tau pathology of frontotemporal dementia is actually absent in 60% of patients with clinically diagnosed frontotemporal dementia. Instead, many of these patients' brains display ubiquitin-immunoreactive neuronal cytoplasmic inclusions and neurotic changes in the cerebral cortex and the hippocampus (44, 45). This neuropathologic pattern was labeled frontotemporal lobar degeneration with ubiquitin inclusions (46). Until very recently, both the identity of the ubiquinated protein that comprises the inclusions and the underlying pathophysiology of frontotemporal lobar degeneration with ubiquitin inclusions have remained a mystery.

A clue to better understanding frontotemporal lobar degeneration with ubiquitin inclusions lay in the fact that overall, frontotemporal dementia has a strong genetic component with up to 20% of cases showing a highly penetrant, autosomal dominant pattern of disease transmission (47–49). In 1998, in a subset of patients with frontotemporal dementia demonstrating classic tau pathology, mutations in the microtubule-associated protein tau gene on chromosome 17q21 were identified (50). These mutations remain relatively uncommon, even in familial forms of frontotemporal dementia (51).

In 2006, two back-to-back articles in *Nature* reported that mutations in the gene for a widely expressed growth factor called progranulin caused multiple cases of familial and even some cases of sporadic frontotemporal lobar degeneration with ubiquitin inclusions (52, 53). The investigators described a variety of frameshift mutations, initiation codon, and nonsense mutations, all leading to a null mutation in one of the two progranulin alleles, resulting in haploinsufficiency (i.e., loss of functional progranulin). In an apparent coincidence, the progranulin gene is also found in chromosome region 17q21, only 1.7 Mb upstream of microtubule-associated protein tau gene, explaining why a number of frontotemporal dementia families who had been shown to have mutations linked to the chromosome 17q21 region lacked any abnormalities in their microtubule-associated protein tau gene (54). Overall, progranulin mutations account for approximately 10% of frontotemporal dementia cases and approximately 20% of cases with a family history (53, 55, 56).

Progranulin is known to play systemic roles in development, wound repair, and inflammation through its effects on cell cycle progression and motility (57–59). In the CNS, it is most highly expressed in pyramidal neurons and activated microglia, but its specific role in the brain remains

unknown (60). Of interest, when progranulin is overexpressed, it has been linked to tumor genesis, possibly through induction of vascular endothelial growth factor (58, 59, 61), whereas in circumstances of haploinsufficiency, it leads to neurodegeneration.

Frontotemporal dementia patients are approximately evenly divided between those with tau or frontotemporal lobar degeneration with ubiquitin inclusions. In those with the frontotemporal lobar degeneration with ubiquitin inclusions histopathologic pattern, one subset has lentiform intranuclear neuronal inclusions. It is this subset of frontotemporal lobar degeneration with ubiquitin inclusions patients with both neuronal cytoplasmic inclusions and lentiform intranuclear neuronal inclusions that have been found to have mutations in the progranulin gene. Of importance, neuronal cytoplasmic inclusions and lentiform intranuclear neuronal inclusions do not stain for progranulin and instead were recently found to stain for another protein, TAR DNA binding protein-43 (62). This is consistent with the finding that the progranulin mutations that cause frontotemporal dementia are null alleles leading to a dearth of wild-type progranulin and little to no production of mutant progranulin protein or sometimes even its mRNA. In addition, the discovery that the nuclear protein TAR DNA binding protein-43 is found in the inclusions of all frontotemporal lobar degeneration with ubiquitin inclusions subtypes (i.e., in both neuronal cytoplasmic inclusions and lentiform intranuclear neuronal inclusions) suggests that a common pathogenic pathway unites frontotemporal dementia's disparate histopathologic forms.

There is great clinical variability, even within families sharing the same progranulin mutation (63, 64). Also, a recent study comparing patients with frontotemporal dementia with progranulin mutations to those with microtubule-associated protein tau gene mutations found few consistent phenotypic differences between the two groups (65). Previous work has shown that 15% of patients with frontotemporal dementia have clinical and electromyograph findings consistent with amyotrophic lateral sclerosis (66). However, in a large genetic survey, no patients with frontotemporal dementia–amyotrophic lateral sclerosis were found to have progranulin mutations, despite the fact that frontotemporal dementia–amyotrophic lateral sclerosis patients also develop a frontotemporal lobar degeneration with ubiquitin inclusions histopathology (67). Rather, the motor difficulties experienced by patients with frontotemporal dementia with progranulin mutations more frequently take the form of mild parkinsonism (65).

Can this clinical variability even among patients with frontotemporal dementia with progranulin mutations be explained by the many different progranulin mutations already identified? This explanation appears unlikely in light of the considerable intrafamily phenotypic variability as well as the fact that although many progranulin mutations have been described, they all seem to result in the same endpoint, which is decreased levels of wild-type progranulin. Rather, the phenotypic variability most likely arises out of the variable anatomic distribution of the

frontotemporal dementia pathology, which likely results from unknown genetic or environmental modifiers.

The recent advances in our understanding of the genetics and pathophysiology of frontotemporal dementia stimulate great hope for future research and therapies. In particular, the finding that insufficient levels of progranulin can result in frontotemporal dementia suggests a potential simple replacement treatment modality that awaits further investigation.

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