Published in final edited form as:

Neurol Clin. 2016 February ; 34(1): 171–181. doi:10.1016/j.ncl.2015.08.007.

Frontotemporal Dementia

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Keywords

Dementia; Behavioral disturbance; Abulia; Inattention; Disinhibition; Impulsivity; Aphasia
neurodegenerative disorder

OVERVIEW

A major challenge in the detection of frontotemporal dementia (FTD) is the potential for subtle presentation, which can result in serious consequences for patients unless the confounding early manifestations are correctly identified.^{1–3} This point is illustrated in the following 3 case presentations:

Case Presentation 1

A 56-year-old right-handed man is brought to your office accompanied by his wife of 30 years. He is an accountant who is on administrative leave from his work because of increasing errors over the past several months. He has been described as a mild-mannered salt-of-the-earth type who regularly attends church and serves as a deacon. However, over the past year, he has made suggestive comments to several of his female coworkers, which is highly atypical for him according to his wife, and began looking at porn sites on his computer. This behavior is also viewed as highly atypical. He comes across as a bit reserved initially, and his wife provides much of his history. Generally, he has been in excellent health outside of hypertension of several years' duration and recently placed on a statin for dyslipidemia.

He has a college education, never smoked, drinks an occasional beer or glass of wine, and has never used illicit drugs. He has no history of sexually transmitted disease and has no history of significant head trauma. There is the question of dementia affecting his maternal grandfather in his 60s as well as a maternal uncle, but the specifics are not well known. There was an interesting recollection of a great uncle, described as a religious teetotaler, who ended up being killed in a brothel under mysterious circumstances.

The general examination is unremarkable. He does not come across as overly depressed and seems to cooperate fairly well with testing, often glancing over at his wife. On neurologic

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Disclosures: None.

testing, he is somewhat delayed in his responses, with 2 mistakes on serial 7 subtractions, difficulty reproducing a design, and scores 27 out of 30 on the mini-mental state examination. The neurologic examination is otherwise quite normal. You order routine laboratory tests along with a serum vitamin B12 and folate level and thyroid profile with all coming back normal. A computed tomography (CT) brain scan and MRI brain scan both reveal fairly prominent frontotemporal atrophy, especially on the right. An electroencephalogram (EEG) reveals some bifrontal slowing but no epileptiform activity.

Case Presentation 2

A 62-year-old right-handed woman comes to your office with her female partner. They have lived together for the past 12 years and both have worked as elementary school teachers. The patient has been noted to having some communication issues in recent months, and it is beginning to be picked up by other teachers as well as the students. She has word-finding difficulty, with speech hesitancy, and uses inappropriate word choices at times. She has complained of some reading difficulty as well, and this is of particular concern to her as she has been an avid reader.

She has been quite healthy all her life and was a marathon runner at one time as well as a state tennis champion. She has been on no medications and continues an active daily exercise program but is noticing diminished exercise tolerance in recent months. She is quite selective in her diet and has maintained a weight of 120 lb during her adult life with a height of 5 ft 3 in. However, her weight is recorded at 114 lb in your office. The patient is surprised by this, although her partner has noticed a reduction in her typically finely toned musculature over the past half year. She has never smoked, drinks a glass of wine each evening, and does not use recreational drugs. The family history is noncontributory as she is adopted.

On examination, she looks quite healthy but has some obvious speech hesitancy and the suggestion of a mild bulbar type of dysarthria at times. The general physical is quite normal. She has some difficulty with naming and repetition, although comprehension seems to be intact. Her palate elevates symmetrically, and her gag reflex is intact. Her tongue is not of full bulk with suggestion of fasciculations. There is fair rapid alternating movement of the tongue. Strength and tone seems to be normal on motor testing, with some atrophy of the shoulder muscles; scattered fasciculations are noted. She does well with cerebellar testing and with gait, and no sensory loss is noted. Deep tendon reflexes are 3+ in both biceps and triceps and 3+ to 4- at both knees with a crossed adduction response, and there are several beats of clonus at both ankles, with the Babinski response positive on both sides and with a 2+ jaw jerk.

Brain imaging reveals the suggestion of frontal lobe atrophy, more prominent on the left. Blood tests come back fine. The cervical spine MRI is normal. Electromyography reveals increased insertional activity in several muscles of the upper and lower extremities with denervation and reinnervation changes.

Case Presentation 3

This patient is a 60-year-old gentleman whose cousin has made this appointment. He is accompanied by the cousin who provides essentially all of the history. The patient was once the life of the party and had several wives in his younger years. He was a very successful car salesman and could sell ice to the Eskimos, as his cousin termed it. He was known to drink liberally in the past and was a former smoker. He was under treatment of gout and had been treated for a manic episode by a psychiatrist several years ago. He refused to take medication for this episode and was never the same, according to his cousin. A former wife tried to make contact with him recently and found him to be somewhat rambling and incoherent on the phone leading her to call the cousin to check on him.

The cousin had found the patient in a disheveled condition in his apartment. He had not been seen by neighbors for several days and typically ventured out at night to get some groceries. The apartment was in shambles with food scattered about. The patient was noted to have poor personal hygiene. He is initially quite passive and apathetic but becomes easily irritated with any attempt at questioning him. He was not cooperative in the examination. He responds, "I don't know," to most questions. The examiner makes note of facial blunting and obvious bradykinesia. No tremor is noted. There is the suggestion of resistance to passive movement versus actual rigidity during the limited motor testing that the patient allows. Strength is fairly good throughout with limited cooperation in assessment of dexterity or in cerebellar function. He walks with a somewhat stooped posture with limited arm swing. A bilateral grasp reflex and suck reflex is noted.

CASE DISCUSSION

The first case illustrates the not-uncommon presentation of the behavioral form of FTD. This gentleman demonstrates personality change, which is initially subtle but progressive. Such patients are often referred for psychiatric evaluation. However, the onset of symptoms, at this age, with no prior psychiatric history suggests the vagaries of the behavioral form of FTD. Impulsive behavior, with disinhibition, can lead to physical interactions as well as criminal activity. Pillars of the community may end up in illicit sexual relationships, which causes extreme embarrassment for the family. Recognition of the cause of such personality change is obviously of great value in determining how best to avoid such activity. On the other hand, some patients display increasing loss of initiative with apathy and are pretty much confined to a listless life-style based on their selective involvement by the pathologic process.

The second patient is an example of the primary progressive aphasia (PPA) form of FTD. The onset tends to be insidious and usually does not invoke acute stroke in the differential. However, an atypical subtle stroke presentation affecting the communication centers of the dominant cerebral hemisphere is a potential explanation in some patients as is a structural lesion, such as neoplasm, abscess, or subdural hematoma. This second case also illustrates the potential association of FTD and motor neuron disease.⁴ This relationship has been identified with the GGCCC (G₄C₂) repeat expansion of the C9orf72 gene, which is the most common cause for familial amyotrophic lateral sclerosis (ALS), FTD, as well as ALS-FTD.⁵

In addition, to the potential overlap of ALS and FTD, one can also see features of parkinsonism with FTD.⁶ The parkinsonism is typically of the akinetic-rigid type and is not generally responsive to levodopa. This type is illustrated in the third case. The overlap of FTD and parkinsonism has been linked to mutations in the gene encoding the microtubule-associated protein tau (*MAPT*; Online Mendelian Inheritance of Man [OMIM] + 157140) on chromosome 17.⁷ However, not all kindreds with this familial overlap presentation have been attributed to a tauopathy with *MAPT* mutations. Certain kindreds have mutations of the gene encoding progranulin (*PGRN*; OMIM *138945), which is in close proximity to the *MAPT* location on chromosome 17.⁸

MANIFESTATION KEY POINTS

- It is the most common cause of dementia in adults less than 60 years of age.⁹
- The most common age of onset is in the sixth decade.
- Most cases of FTD are sporadic.
- Up to 10% to 15% of cases are associated with an autosomal dominant genetic mutation.¹⁰
- The initial manifestations are often initially reported to psychiatrists, psychologists, marriage or addiction counselors, human relations officers, or those in the legal realm reflective of the potential for aberrant behavior.¹¹
- Semantic PPA type is characterized by impaired single-word comprehension and marked anomia but with fluent speech.¹²
- The nonfluent/agrammatic PPA type is characterized by limited speech production with grammatical and syntax errors.¹²
- The logopenic PPA type is characterized by intermixed fluent and nonfluent speech related to significant word-finding difficulty typically resulting in slow or delayed speech.¹²

DIFFERENTIAL DIAGNOSIS

The potential manifestations of FTD result in a bridging between psychiatric disease and other causes of dementia. The potential alternative explanations are outlined in Box 1.

GENOTYPIC AND PHENOTYPIC FACTORS

The phenotypic variability reflects genetic variations, which can include tau mutations, progranulin gene mutations, as well as repeat expansions (GGGCCC) of the *C9orf72* gene. Three subtypes of FTD have been designated based on the type of inclusions in brain tissue.¹³ These subtypes include tau protein, transactive response DNA-binding protein 43 (TDP-43), and RNA-binding protein fused in sarcoma (FUS). Such inclusions impact on the potential manifestations. Tau pathology is often associated with features of parkinsonism but typically not with ALS. On the other hand, TDP-43 and FUS are not uncommonly seen in combined FTD and ALS. In terms of frequency, roughly 50% of patients with FTD have

FTD-TDP as the major pathologic subtype,^{14,15} whereas FTD-tau accounts for roughly 45% of patients and FTD-FUS 5% or less.¹⁶

DIAGNOSTIC APPROACH KEY POINTS

- Clinicians must have a certain index of suspicion that the behavioral disturbance or communication deficit is not in the psychiatric realm but in the neurodegenerative realm.
- Atypical presentations can obviously be misleading, such as an unexpectedly young age of onset, such as in the 20s or 30s.
- Neuroimaging is key, with the finding of atrophy of the frontal and temporal lobes on either brain CT or MRI scan of key importance.
- The potential for familial predisposition can be an important clue.
- Coexistent manifestations, such as motor neuron disease or parkinsonism, can help in putting the clinical picture in proper perspective.
- As with other dementing illness, exclusion of other potential explanations with brain imaging, blood work, and possibly EEG can be elucidating.
- Special imaging techniques, such as ¹⁸fluorodeoxyglucose (FDG) PET scan, and new techniques, such as beta-amyloid and tau imaging PET scan as well as diffusion tensor MRI, can provide pertinent supportive or nonsupportive information.

The particular frontotemporal involvement can be demonstrated anatomically with CT brain scan or MRI brain scan as mentioned earlier (Fig. 1). Significant hypodensity changes in the subcortical white matter in the periventricular region on a CT brain scan or the corresponding signal hyperintensity changes on an MRI brain scan tends to reflect microvascular ischemic disease. One can readily exclude a significant component of communicating hydrocephalus on such scans as well as potential structural lesions or larger vessel cerebrovascular disease on such scans.

Cerebral PET scan with ¹⁸FDG can demonstrate hypometabolism in the frontotemporal region, which will help distinguish FTD from the fairly characteristic pattern for Alzheimer disease of biparietal hypometabolism earlier on in the course of this disorder. The fluorine 18 –florbetapir PET scan allows in vivo imaging of beta-amyloid plaque deposition within the brain and can be of potential value in determining a primarily Alzheimer component to the dementia.¹⁷ More recently, tau in vivo brain imaging with PET has become available with the potential to identify primarily tau-mediated neuro-degenerative disease.¹⁶ The potential for such advanced imaging in distinguishing one form of dementia from another was illustrated in a recent case report.¹⁸

Diagnostic biomarkers may also have utility in the diagnostic assessment. In Alzheimer disease, for example, there is a fairly consistent pattern of elevated total tau protein and diminished beta-amyloid-42 protein concentration in the cerebrospinal fluid.¹⁹ It is hoped that similar biomarkers will be identified for FTD. One potential biomarker for FTD is a

specific antibody for TDP-43 for patients with FTD who have a proteinopathy characterized by brain inclusions for transactive response DNA-binding protein of 43 kDA.²⁰

MONITORING OF DISEASE ACTIVITY

Obviously, the expected clinical course of a neurodegenerative disease is progression. However, the natural history of FTD, reflective of the significant variability in phenotypic expression, makes accurate prognostication for patients and family members challenging at best. Unlike Alzheimer disease, whereby the progression over 6- to 12-month intervals can be fairly accurately determined by reports of family members and simple office cognitive testing, the behavioral variant of FTD can be difficult to objectively quantitate with the not-unexpected fluctuation. Even for the language variant of FTD, it is not at all uncommon to see fluctuation in communication ability from day to day.

Volumetric analysis of dementia with modalities such as MRI can provide quantitative measurement of tissue loss, that is, atrophy, over time. Efforts have been made to distinguish the selective atrophy of FTD from the atrophy pattern seen with Alzheimer disease.²¹ In an MRI volumetric analysis of Alzheimer disease and FTD,²² the investigators reported some differentiation of the degree of atrophy for the hippocampus and amygdale in Alzheimer disease versus FTD but not for the cingulate gyrus. There has been a recent report of the potential value of longitudinal diffusion tensor imaging as a biomarker of disease activity in FTD.²³ This study was of the behavioral variant group with measurements at baseline and approximately 1.3 years later. Rates of change in fractional anisotropy and mean diffusivity suggested selective involvement over time of the pericallosal cingulate region, in the 23 patients as a whole, with *MAPT* carriers showing greatest change in the left uncinate fasciculus and sporadic and *C9orf72* carriers with the greatest change in the left uncinate fasciculus.

TREATMENT APPROACH

Addressing the underlying molecular pathology will eventually significantly impact the treatment approach.¹² There are presumably multiple pathways potentially involved, which lead to the progressive atrophic process within the frontal and temporal lobes as illustrated in Fig. 2. This patient was a case presentation of the case records of the Massachusetts General Hospital published in the *New England Journal of Medicine*.¹¹ The onset of personality change and progressive neurologic decline was at 28 years of age with death in a debilitated state, with manifestations of both dementia with behavioral disturbance as well as parkinsonism at 33 years of age. This case reflects the not-uncommon progressive impairment seen in a neurodegenerative-related dementia over a 5-year time frame. The pathology for this gentleman is illustrated in Fig. 3. Special staining reflected tau-based pathology, specifically tau-positive inclusions of the Pick disease subtype. This particular presentation was due to a *Gly389Arg* mutation. Unfortunately, no specific treatment is presently available for such a presentation outside of supportive care. Not uncommonly, such patients will be tried on cholinesterase inhibitors, memantine, and vitamin E supplementation, along with various mediations related to the behavioral disturbance variant.

In order to develop effective strategies against such proteinopathies, neuroscientists will need to elucidate the responsible network of RNA and protein interactions.²⁴ Biomarkers for specific disease identification and level of expression have significant potential in this quest.²⁵ Elucidation of genetic susceptibility, such as determination of low-frequency coding variants with intermediate effect size by genome-wide exom array multi-ancestral studies,²⁶ will also be important. An example of where such innovative research might take us, McMillan and colleagues²⁷ reported recently on the potential for *C9orf72* promoter hypermethylation to be potentially neuroprotective in disorders associated with inclusions of TDP-43. They surmised that such an approach could result in transcriptional silencing of mutant *C9orf72* and be a potential avenue for drug development in both FTD and ALS.

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Box 1 Differential diagnosis of FTD

1. Previously unrecognized bipolar disorder
2. Previously unrecognized schizoaffective disorder
3. Sociopathic personality disorder
4. Alzheimer disease
5. Dementia with Lewy bodies
6. Parkinsonism-dementia complex
7. Normal pressure hydrocephalus
8. Neoplastic disease of the brain
9. Remote effect of malignancy, such as limbic encephalitis
10. Anti-N-methyl-d-aspartate receptor encephalitis
11. Human immunodeficiency virus–related dementia
12. Spinocerebellar ataxia 3 (Machado-Joseph disease)
13. Epilepsy-related encephalopathy
14. Medication-induced encephalopathy
15. Metabolic encephalopathy
16. Endocrine-related encephalopathy, for example, Hashimoto encephalopathy
17. Neurosyphilis
18. Cryptococcal meningitis
19. Herpes simplex encephalitis
20. West Nile encephalitis
21. Chronic traumatic encephalopathy
22. Vascular dementia
23. Mercury toxicity
24. Methamphetamine/phencyclidine/cocaine/psychostimulant abuse
25. Late-onset metachromatic leukodystrophy
26. Late-onset Nasu-Hakola disease
27. Late-onset Niemann-Pick disease type C
28. Adult Tay-Sachs disease
29. Adult Gaucher disease
30. Adult neuronal ceroid lipofuscinosis

31. Adult polyglucosan body disorder

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KEY POINTS

- The initial description of this disorder is attributed to Arnold Pick in 1892.
- Involvement of the dominant hemisphere is characterized by primary progressive aphasia.
- The primary manifestations of the behavioral variant, reflective of nondominant hemisphere involvement, include the following: cognitive impairment including loss of initiative with apathy, abulia reflective of this loss of initiative including impaired executive function and lack of spontaneity, impulsivity, disinhibition, oral fixation, lack of sympathy and empathy, and repetitive behavior.
- There is well-recognized heterogeneity of clinicopathologic correlations.

Fig. 1.

(A) Fluid-attenuated inversion recovery MRI brain scan of 68-year-old gentleman with 5-year history of increasing difficulty with executive function, impulsivity, mood swings, and inattention, which displays frontotemporal region atrophy. (B) Coronal T1-weighted MRI demonstrating particular involvement of the temporal lobes.

Fig. 2. Brains sections at autopsy of a man in his 30s with progressive cognitive impairment, behavioral disturbance, and parkinsonism. (A) Demonstrates a moderate degree of frontal and temporal lobe atrophy. (B) Demonstrated evidence of cortical atrophy and ventricular enlargement. (C) Demonstrates selective atrophy of the frontal and temporal lobe region with relative sparing of the superior temporal gyrus (arrow). (From Miller BL, Dickerson BC, Lucente DE, et al. Case records of the Massachusetts General Hospital. Case 9-2015. A 31-year-old man with progressive personality changes and progressive neurologic decline. *N Engl J Med* 2015;372:1158; with permission.)

Fig. 3.

Microscopic neuropathologic images of the patient in Fig. 2. (A) Stain that reveals reactive gliosis and neuronal loss in the frontal lobe (Luxol fast blue [LFB] and hematoxylin and eosin [H&E]). (B) Demonstration of a Pick body (*arrow*) (LFB and H&E). (C) Demonstration of a Pick body (Bielschowsky silver method) (*arrow*). (D, E) Immunohistochemical staining with phospho-specific antibodies against tau reflective of tau protein-containing inclusions. (F) Stain demonstrating neuronal loss in the pars compacta of the substantia nigra (LFB and H&E). (G) Immunohistochemical staining for PHF1 shows cytoplasmic inclusions and neuropil threads, within the substantia nigra, which contain

phosphorylated tau. (*From* Miller BL, Dickerson BC, Lucente DE, et al. Case records of the Massachusetts General Hospital. Case 9-2015. A 31-year-old man with progressive personality changes and progressive neurologic decline. N Engl J Med 2015;372:1159; with permission.)

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