

Frontotemporal Lobar Degeneration

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Introduction

Pick's disease, a type of frontal lobe degeneration, was first recognized clinically in 1892.¹ However, frontal lobe degenerative dementia was considered rare until 1987 when 12.5% of autopsy cases from a series of patients with dementia were reported to have degeneration of the frontal lobes with non-Alzheimer's pathology.² Since then frontotemporal lobar degeneration (FTLD) has become recognized as the third most common cause of cortical dementia behind Alzheimer's disease and Lewy body disease. In 1998 the consensus guidelines for the clinical diagnosis of FTLD were published.³ This article will discuss the three-prototypical clinical syndromes in the consensus guidelines, followed by the presentation of a case of probable FTLD, and a review of the neuropathology and genetics of FTLD.

Clinical Criteria

Three of the prototypical clinical syndromes that have been extensively described and have consensus guidelines are frontotemporal dementia, progressive nonfluent aphasia, and semantic dementia. All of these subtypes must have an insidious onset and gradual progression of behavioral and cognitive change. See Table 1 for other core clinical diagnostic criteria.³

Frontotemporal dementia (FTD) is the most common clinical subtype of FTLD. It is characterized by personality change and impaired social conduct initially and throughout the disease course. Patients may also have emotional blunting and loss of insight. Other common features are

disinhibition, neglect of personal hygiene, mental rigidity, perseverative behaviors, voracious appetite and hyperorality. An example of disinhibition in one of our patients was an elderly woman with FTD who when at a restaurant would walk over to other tables and eat the food off another customer's plate. Another patient would constantly fill water bottles, up to 20 at a time, demonstrating perseverative behavior. As the disease progresses these patients often develop primitive reflexes such as the snout or grasp reflex. Patients with this subtype are considered to have the bulk of pathological changes occurring in the both frontal and temporal lobes.

Chronic progressive aphasia (CPA) is another subtype in which patients develop nonfluent speech. Their dialogue is dominated by short utterances that are agrammatic and often contain paraphasias. The paraphasias are usually phonemic in that patients get stuck on and mispronounce individual syllables or parts of syllables. For example, a patient may say "shoon" instead of "spoon". Comprehension is relatively normal although patients will likely have difficulty understanding complex grammatical sentences. These patients have asymmetric pathology affecting the dominant hemisphere more involving speech areas in the frontal, temporal, and parietal lobes.

A fluent progressive aphasia with severe anomia dominates the clinical picture of the third subtype, semantic dementia (SD). These patients have speech that is fluent but empty and conveys little meaning. The patient will seem vague because of the overuse of nonspecific terms such as "this thing" or "that place". They may also have semantic paraphasias using a word such as "knife" when meaning to use the word "spoon". These patients may later develop an agnosia when they not only can't name but don't recognize an object. For example, one of our patients attempted to use a handkerchief as a comb. This disorder of object recognition is not due to visuospatial impairment because these patients can copy drawings of complex objects and can match one object to another. Bilateral anterior temporal lobes, often worse on the left, are the areas of dysfunction in SD.

On presentation most patients can be classified into one of these three syndromes. However, these syndromes likely reflect the extent of pathology at the time of presentation and as the disease progresses the patient may develop symptoms and signs that overlap with more than one

Table 1. Core Clinical Diagnostic Features For FTLD

Frontotemporal dementia

- Early decline in social interpersonal conduct
- Early impairment in regulation of personal conduct
- Early emotional blunting
- Early loss of insight

Progressive nonfluent aphasia

- Nonfluent spontaneous speech with at least one of the following: agrammatism, phonemic paraphasias, anomia

Semantic dementia

- Language Disorder characterized by
 - Progressive, fluent, empty spontaneous speech
 - Loss of word meaning, manifest by impaired naming and comprehension
- Semantic paraphasias
- Perceptual disorder characterized by
 - Prosopagnosia: impaired recognition of identity of familiar faces
 - Associative agnosia: impaired recognition of object identity
- Preserved perceptual matching and drawing reproduction
- Preserved single-word repetition
- Preserved ability to read aloud and write to dictation orthographically regular words

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syndrome. A common feature supportive of the diagnosis of FTLD is onset before age 65. Exclusionary criteria include abrupt onset, onset related to head trauma, and multifocal lesions on neuroimaging.

Also, patients with progressive right frontotemporal degeneration have been described.⁴ These patients were similar in their presentation to the FTD subtype in that they had disinhibition and impaired social conduct in addition to a quite bizarre affect. On neuroimaging these patients had predominant involvement of the right frontal and anterior temporal lobes.

Besides the cognitive and behavioral symptoms, FTLD can also be associated with motor neuron disease and extrapyramidal signs. Clinical presentations when familial and associated with Parkinsonism have received numerous labels including disinhibition, dementia Parkinsonian complex with amyotrophy (DDPAC), rapidly progressive autosomal dominant Parkinsonism and dementia with pallido-ponto-nigral degeneration (PPND), familial multiple system tauopathy with presenile dementia (MSTD), and progressive subcortical gliosis.⁵

Case

A 63-year-old right-handed man presented to Mayo Clinic Jacksonville because of a four-year history of gradually increasing difficulty in finding names. He was able to describe events in general terms but was unable to specifically name individuals or objects. His memory was preserved in nonverbal terms; e.g. he drove without getting lost. However, he was impulsive and would run through traffic lights and had received a traffic ticket one week prior to evaluation. He lived on a farm and continued to work on lawn projects by himself. He also had a personality change in that he would seem to persist on certain tasks from which it was difficult to distract him. Family history was remarkable for his mother and maternal uncle having probable Alzheimer's disease that was of late onset.

On exam the patient scored 19 out of 30 on the Mini-Mental State Exam (MMSE) but received 8 out of 10 on orientation items. The patient was talkative with fluent speech and was difficult to interrupt. Comprehension was normal. On tests of current events he had great difficulty in remembering the names of political figures and in naming pictures of common objects. The rest of the neurologic and general medical exam was normal. He was evaluated by one of our neuropsychologist. On the Dementia Rating Scale he score 102/144 which reflects a moderate severity of dementia. He scored in the normal range on digit span forward and backward (tests of immediate attention), repetition, and judging line orientation and copying complex figures (tests of visuospatial skills). His comprehension was variable. He scored in the impaired range on tests of verbal and visual memory, naming and verbal fluency.

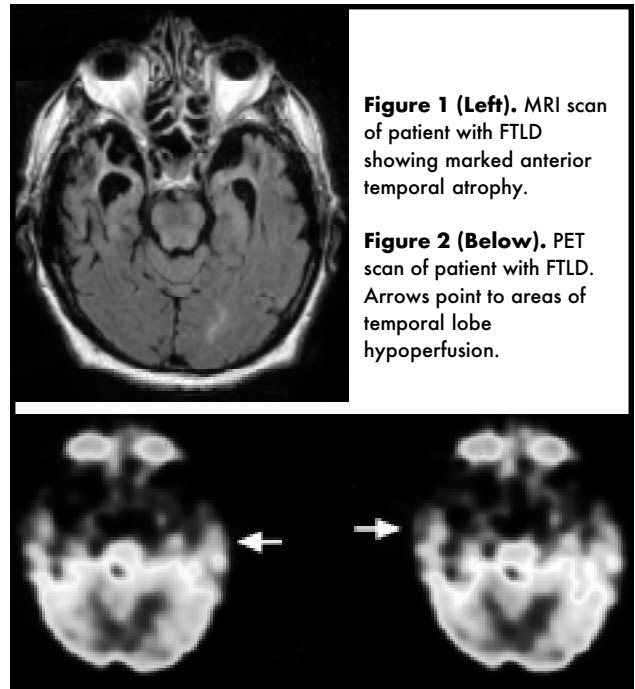


Figure 1 (Left). MRI scan of patient with FTLD showing marked anterior temporal atrophy.

Figure 2 (Below). PET scan of patient with FTLD. Arrows point to areas of temporal lobe hypoperfusion.

Verbal fluency is measured by the number of words in a certain category the patient can generate in one minute. Tests that require divided attention and problem-solving skills were also impaired. On magnetic resonance imaging (MRI) scan showed bilateral anterior temporal lobe atrophy greater on the right (Figure 1). A positron emission tomography (PET) scan showed severe hypometabolism of the bilateral temporal lobes (Figure 2).

Case Discussion

This patient illustrates several aspects of the FTLD clinical syndromes. First, presenile onset is common, i.e. before the age of 65. Also, the patient had some behavioral changes that were not striking but suggestive of the frontotemporal subtype. He had marked difficulty in generating names of people and objects and was noted to be vague, all of which are characteristic of semantic dementia. He was more impaired on semantic fluency than letter fluency, another finding in SD. As important as the impaired areas are his preserved areas of functioning and cognition. Despite the memory complaints by his wife and impaired memory on neuropsychology tests the patient probably has relatively preserved anterograde memory. Memory impairment in these patients is often due to lack of attention and language problems. Evidence that this anterograde memory is relatively preserved is his score on the orientation of the MMSE indicating he can remember where he is and what day it is. AD patients often are much more disoriented even early in the illness. The preserved memory is sometimes difficult to demonstrate on neuropsychology tests that require relatively preserved language and attention. Visuospatial skills are usually impaired in early in AD

but were normal in this patient. Driving without getting lost, his ability to find his way to the neuropsychology office, and normal copying of complex figures all support this assertion. Because of the preserved anterograde memory and visuospatial skills SD and CPA patients can often continue to function relatively well at home despite their cognitive impairments on neuropsychological testing. However, the converse may occur in the FTD subtype. These patients may have profound behavioral alterations, lack of insight and difficulty in planning causing difficulty in functioning at home and in social settings while at the same time they score well on neuropsychological tests that are not sensitive to frontal lobe impairment.

On neuroimaging patients often have atrophy of the frontal and temporal lobes. The anterior temporal lobe atrophy is readily apparent in this patient. Note the relative preservation of the medial temporal lobe that is often atrophied in AD patients. The PET scan demonstrates the temporal lobe hypometabolism. PET and single photon emission computed tomography (SPECT) scans can be useful in separating AD patients who usually have posterior brain (temporal and parietal) abnormalities from FTLN patients who have anterior (frontal and anterior temporal) brain abnormalities.⁶

Neuropathology

Circumscribed cerebral atrophy of the frontal and anterior temporal lobes, also called lobar atrophy, is the gross pathological hallmark of FTLN.¹ The rationale for grouping these clinical syndromes is that almost invariably these patients will have degenerative changes of the frontal and temporal lobes with one of several types of histologic change. At present it is impossible to predict prior to autopsy which of the histopathologies will be present unless there is a family history of the disorder with prior pathological confirmation. The first type of possible histology has prominent microvacuolar change in layer II and upper layer III of the cortical lamina. This type usually does not have specific histologic features meaning the absence of staining with immunohistochemical markers. Sometimes neurons stain with an antibody to a B crystallin.⁵ The other type has severe astrocytic gliosis with or without ballooned neurons and inclusion bodies (Pick type or Pick's disease).¹ The ballooned neurons and inclusion bodies of the Pick type will stain with antibodies directed against the tau protein. The ballooned neurons also stain for neurofilament protein. Therefore, frontotemporal dementia with Pick type pathology may represent part of a spectrum of diseases that have prominent tau pathology. Other examples of such diseases are corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP). Furthermore, CBD and PSP may start as clinical syndromes similar to the ones described above. Alzheimer's disease also has tau pathology in addition to amyloid pathology. Despite the many disorders that may have tau pathology there are differences in the

morphology and biochemistry of the tau deposits. This provides good reason to recognize all these disorders as separate entities but to keep in mind that they may have similar pathogenic mechanisms.

Genetics

In one study about 45% of FTLN patients have family members with a similar disorder.⁷ Genetic mutations in the tau protein on chromosome 17 have been identified in several families. Most of these mutations have been shown to increase the proportion of an isoform of tau called 4-repeat tau.⁸ However, it is clear that most cases in clinical practice don't have one of these mutations on chromosome 17. In fact in more than 50 consecutive cases, we have identified none with a chromosome 17 mutation. Apolipoprotein E4 allele (which has been shown to be a risk factor for AD) does not appear to be associated with FTLN.^{9,10}

Conclusion

Frontal temporal lobar degeneration is a form of degenerative dementia that presents clinically with profound alterations in behavior and social conduct or language impairments. In contrast to Alzheimer's disease these patients have relatively preserved memory and visuospatial skills. The areas of pathologic involvement are the frontal and anterior temporal lobes. Several types of histopathology are found at autopsy. The Pick type pathology is likely caused by an abnormality of the tau protein on chromosome 17. Some familial cases have been shown to have mutations in the tau gene. At present, there is no known treatment of the disorder except for the use of psychotropic medicines for the behavioral problems.

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