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Frontal and Temporal Lobe Dementia

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INTRODUCTION

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Background

Cases of elderly patients with progressive language deterioration have been described since Arnold Pick's landmark case report of 1892. This case study, "On the relationship between aphasia and senile atrophy of the brain", still serves as a frame of reference for apparently focal brain syndromes in diffuse or generalized degenerative diseases of the brain.

In 1982, Mesulam reported 6 patients with progressive aphasia, gradually worsening over a number of years, who did not develop a more generalized dementia. Since Mesulam's publication, numerous other cases have been reported. This disorder, which is currently termed primary progressive aphasia (PPA), has gained acceptance as a syndrome. Rarely, cases of isolated right frontal or temporal degeneration have been reported. These patients experience failure to recognize family members (prosopagnosia), failure to remember topographic relationships, and similar disorders.

In England, cases of frontal lobe dementia have been described with progressive dysfunction of the frontal lobes. In a series of case reports, Neary and Snowden outlined a syndrome with initial symptoms that were suggestive of psychiatric illness. However, the following frontal lobe behavioral abnormalities appeared over time: disinhibition, impulsivity, impersistence, inertia, loss of social awareness, neglect of personal hygiene, mental rigidity, stereotyped behavior, and utilization behavior (ie, tendency to pick up and manipulate any object in the environment). These descriptions included language abnormalities such as reduced speech output, mutism, echolalia, and perseveration.

In recent years, the condition described in the North American literature as PPA and that described in the European literature as frontal dementia have been combined under the diagnosis frontotemporal dementia (FTD).

Some North American authors have included under the FTD category cases in which artistic and musical abilities have actually emerged after the onset of the illness, usually in association with progressive language impairment.

Pathophysiology

The precise molecular causes of FTD and PPA remain elusive. Considerable progress has been made with regard to mutations in the tau protein that result in neurofibrillary tangles and neuronal degeneration. Other cases do not appear to have tau pathology and are more related to ubiquitin staining in the nervous system.

Frequency

United States

The exact prevalence of FTD is unknown. Some series based on brain pathology have estimated that FTD comprises as many as 10% of cases of dementia. In the United States, estimates are generally lower.

International

Studies on FTD from Lund, Sweden, and Manchester, England, estimate that FTD accounts for approximately 8% of patients with dementia. Probably the most accurate information comes from a Dutch study by Stevens et al, who reported 74 cases in a population of 15 million (ie, 5 cases per million). Among those aged 60-70 years, the prevalence was 28 cases per 100,000.

Mortality/Morbidity

FTD, like all dementing illnesses, shortens life expectancy. The exact influence on mortality is unknown. The rate of progression is variable. Patients with associated motor neuron disease tend to have much shorter life expectancy.

- The average age of onset is younger than that of Alzheimer disease (AD).
- The rate of progression from focal presentation to a more generalized dementia varies. Some patients experience only aphasia for periods exceeding 10 years, while others progress to dementia within a few years.
- In a subset of cases, motor neuron disease develops. This subgroup has a higher mortality rate from FTD than other affected patients. Swallowing difficulty and aspiration pneumonia are especially common in this subgroup of patients, but even patients with PPA can develop dysphagia late in the course of the illness.

Sex

FTD can develop at almost any age in either gender. The most complete review, compiled by Westbury and Bub, investigated 112 published cases prior to 1997; the series included 66% males and 34% females.

Age

FTD is generally believed to present at an earlier age than AD. In the 1997 review by Westbury and Bub, the mean age of onset was 59 years. The mode age was 64 years.

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History

- For the subgroup of FTD with PPA, the presenting symptoms involve a deterioration of language function. At first, other aspects of cognitive function and behavior may seem entirely normal. Patients who do not depend on their verbal skills for their livelihoods may continue to function at work. Artistic expressions may even increase or be taken on as new hobbies in these patients, although, according to Miller and Hou (2004), their productions are often compulsive in style.
    - The most common presenting symptom is word-finding difficulty. However, decreased fluency or hesitancy in producing speech, difficulty with language comprehension, and motor speech difficulties (eg, dysarthria) are also common. In general, the 2 patterns are (1) a progressive, nonfluent aphasia and (2) fluent aphasia with anomia.
    - The mode of presentation suggests a focal lesion of the left hemisphere language cortex, but a focal lesion, other than evidence of focal atrophy, usually is not found.
    - The course is progressive, with slowly worsening language function.
- Most patients have a nonfluent aphasia. Fluent aphasia at onset is a less specific finding than nonfluent aphasia. Some patients with progressive, fluent aphasia have AD.
- One area of controversy in PPA concerns whether a generalized dementia eventually develops in all patients

with PPA.

- The literature contains many cases of slowly progressive language dysfunction, developing over a period as long as 10-12 years, without obvious deterioration of other cognitive functions that would justify a diagnosis of dementia.
- The incidence of dementia in patients with PPA is unknown but likely approaches 50% over several years.

- One subgroup of the syndrome of PPA is semantic dementia, a disorder described by Hodges and colleagues in the United Kingdom. Semantic dementia is characterized by a progressive loss of naming ability and a loss of the ability to understand the meaning of words.
  - The aphasia is fluent, except for word-finding pauses.
  - The pathology underlying semantic dementia is variable. Most patients do not have the tau pathology often seen in persons with progressive nonfluent aphasia. Some patients have ubiquitin staining and nonspecific neuropathological changes such as neuronal loss and gliosis, and others have AD.

- In frontal lobe dementia studies, presenting symptoms often involve alterations in personality and social conduct.
  - Patients with the frontal variant of FTD may become disinhibited, developing a "witzelsucht," or fatuous sense of humor. Conversely, they may become apathetic, with little spontaneous speech or activity.
  - They tend to neglect personal hygiene and to lose sensitivity to the effects of their behaviors on others.
  - Some develop frank frontal lobe behavioral abnormalities such as hyperorality, utilization behavior (ie, picking up and manipulating any object in the environment, appropriate or not), and inappropriate sexuality.
  - In these descriptions, language function either is described as reduced in output (leading to muteness) or is characterized by perseveration, stereotyped responses, or even echolalia.

- A subgroup of patients with FTD develops signs and symptoms of motor neuron disease, such as fasciculations, muscle wasting and weakness, and bulbar symptoms. These patients have ubiquitin pathology. At least 2 genetic defects have been reported in patients with FTD and motor neuron disease. Another subgroup of patients with FTD experiences progressive right hemisphere dysfunction. Why reports of progressive right hemisphere degeneration have been so much less common than those of progressive aphasia is unclear. Finally, a genetic disease with combined inclusion body myopathy and frontotemporal dementia has been described.

- Diagnostic considerations
  - FTD is somewhat intermediate between focal disorders of the brain and more generalized neurodegenerative diseases.
  - The most important differential diagnoses for FTD involve focal pathologies such as brain tumors, abscesses, and strokes, as well as differentiation from the more common dementing illness, AD.
  - In distinguishing between FTD and other focal lesions, gradually progressive onset, usually over years, is the key feature.
  - Brain imaging studies are helpful in ruling out focal, destructive, or neoplastic lesions. Whitwell and colleagues used voxel-based morphometry on MRI to distinguish differing patterns of lobar atrophy in variants of FTD with and without motor neuron disease. PET studies have also been helpful in the diagnosis of FTD.
  - In distinguishing FTD from AD, the involvement of specific cognitive functions is the most important differentiating factor.
  - Grossman compared 4 patients with PPA to 25 patients with presumed AD.
    - PPA patients had preserved memory and visuospatial functions, while those with AD had nearly universal involvement of these functions.

- PPA patients performed worse than AD patients on syntactic and speech fluency tasks and had more severe impairment of attention (eg, digit span).
- In general, these differences between FTD or its PPA variant and AD reflect the pathologic involvement of the frontal and temporal lobes, particularly in the left hemisphere, as compared to the early involvement in AD of the hippocampi and parietal lobes.

Physical

Physical and neurologic examinations reflect mainly the mental status abnormalities described under History.

- Many patients have a nonfluent speech pattern, and virtually all have some degree of difficulty in naming or word finding.
- Behavioral alterations and frontal lobe symptoms have been previously outlined.
- Ideation tends to be concrete with poor abstraction and organization of responses and delayed shifting of cognitive sets.
- Visual and spatial functions and constructional tasks are much less affected, except as influenced by behavioral and organizational difficulties.
- Motor skills usually are spared, except for perseverative or inattentive responses and difficulty with temporal sequencing of tasks.
- Specific ideomotor apraxia is rare.
- Memory usually is preserved for orientation, although information retrieval may be difficult.
- Frontal release signs such as a positive glabellar sign, snout, grasp, and palmomental responses may develop.
- In a minority of patients, extrapyramidal signs, such as rigidity or even a full-blown parkinsonian syndrome of rigidity, akinesia, and tremor, may develop. An overlap also exists with the syndrome of corticobasal degeneration, in which rigidity and apraxia of the upper limbs may coexist with neurobehavioral symptoms much like those associated with the syndrome of PPA.
- Widespread muscle atrophy, weakness, fasciculations, bulbar signs, and hyperreflexia may ensue in patients with motor neuron disease. Muscle weakness is also seen in the rare variant with inclusion body myopathy.
- As mentioned earlier, some patients may show artistic or musical talents, sometimes with greater expression than before the onset of the illness.

Causes

The cause is unknown, but significant evidence supports a genetic component to these syndromes.

- As many as 40-50% of patients with FTD have an affected family member.
- In the Dutch study, 38% of the index cases of FTD had a first-degree relative with similar symptoms at an early age of onset.
- Many cases now have been linked genetically to markers on chromosome band 17q21-22, the gene locus for the tau protein.
- This gene marker has linked cases of FTD in several Dutch families, cases of hereditary dysphasic dementia reported in the United States, and a variety of other clinical syndromes called tauopathies, including familial

parkinsonism with dementia, corticobasal degeneration, Pick disease without Pick bodies, and progressive supranuclear palsy. Overlap cases with these other tauopathies have been reported. The pathophysiology involves abnormal tau proteins, leading to the new terminology of FTD as one of a series of tauopathies.

- In the words of an editorial by Wilhelmsen, the linkage of FTD with this gene site has put FTD "on the map" (ie, gene map). Many cases of familial frontotemporal dementia with specific tau mutations have now been reported. On the other hand, apolipoprotein E4 (apoE4), which increases the risk for late-onset, sporadic AD, does not appear to have increased frequency in patients with FTD or PPA. As mentioned above, however, not all persons with FTD have abnormalities in the tau protein; some have ubiquitin pathology, and still others have only nonspecific changes.

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DIFFERENTIALS

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WORKUP

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Lab Studies

- Routine testing (eg, blood, cerebrospinal fluid) is usually unrevealing.
- The genetic test for apoE4 is less useful in FTD than in AD. A study by Mesulam et al found no association between FTD and the apoE4 genotype. Other studies have had somewhat different results, but, in general, apoE4 correlates much better with AD than with FTD.

Imaging Studies

- Routine brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is usually remarkable only for cerebral atrophy.
    - Some patients show impressive localized atrophy in the frontal or temporal lobe on one or both sides.
    - On MRI, temporal lobe atrophy is especially easy to detect in the coronal projections. Cases differ as to the relative degree of atrophy in the frontal or temporal lobe and on the left versus right side. Whitwell et al reported in 2006 that cases associated with motor neuron disease have more paracentral atrophy by voxel-based morphometry on MRI.
- Functional imaging techniques, particularly single photon emission computed tomography (SPECT) and positron emission tomography (PET), detect focal lobar hypometabolism or perfusion with great sensitivity.
    - The Hammersmith PET facility in London published early studies by Tyrell et al, demonstrating that left temporal hypometabolism was observed in virtually all early cases of PPA.
    - More advanced cases also showed hypometabolism in the left frontal lobe and, occasionally, a lesser degree of hypometabolism in the right hemisphere.
- These patterns of cortical involvement have been confirmed in many subsequent studies.

- The pattern of frontal and/or temporal involvement is distinct from that of AD, in which both parietal lobes tend to show the earliest hypometabolism.

- New ligands used to bind to amyloid protein deposits (eg, Pittsburgh Compound B) are helpful in the diagnosis of AD but not FTD.

Other Tests

- The most specific tests for evaluating FTD, other than brain imaging studies, are neuropsychological testing and evaluation by a speech/language pathologist with standardized language batteries.
    - Such studies assess the specific pattern of language abnormality and the presence of other cognitive and memory deficits.
    - Preservation of many of these functions distinguishes FTD and PPA syndromes from AD.
- The EEG findings are commonly abnormal in FTD, often showing focal slowing of electrical activity over one or both frontal or temporal lobes. These findings are not sufficiently specific to be clinically useful, and, in general, EEG is less useful than functional brain imaging with PET and even lobar atrophy on MRI.

Histologic Findings

Various pathologic findings have been reported in patients with PPA and FTD. The central theme of these reports is that these syndromes have a non-Alzheimer pathology.

Considering first the cases of PPA, Pick disease was the first pathologic disease associated with this syndrome. This was reported with a description of the language syndrome in 1892. In the current era, several groups have reported cases of pathologically proved Pick disease. Pick disease is a lobar atrophy of the brain, involving the frontal and/or temporal lobes of one or both hemispheres. Microscopically, the key features are neuronal loss, gliosis, and large intraneuronal, silver-staining inclusions known as Pick bodies. Holland et al, Wechsler et al, and Graff-Radford et al have reported patients with pathologically proven Pick disease and progressive language deterioration. All patients described in these reports had slowly progressive language symptoms, with naming involved early. In all cases, enough cognitive functions were spared initially to make the disorder easily distinguishable from typical AD.

Many reported cases do not have Pick bodies but have the less specific findings of lobar atrophy, neuronal loss, gliosis, and microvacuolization. Such cases were reported by Kirshner and colleagues as a pathologic underpinning of PPA, but similar changes also have been reported by Morris et al under the term hereditary dysphasic dementia and by English authors Neary, Snowden, and colleagues under the term frontal lobe dementia. Some cases report positive staining for tau proteins, including those linked to chromosome 17. Patients meeting pathologic criteria for corticobasal degeneration have been reported. Other cases are negative for tau abnormality but show ubiquitin staining. Ubiquitin staining is also seen in cases associated with motor neuron disease. In terms of AD, the most common dementing illness, only a few cases of pathologically confirmed AD have been reported that presented with isolated aphasia, and most had fluent patterns of speech. A variant known as semantic dementia may also

beassociatedwith AD or with nonspecific pathology, usually with ubiquitin staining.

Three classes of histopathology have been described for FTD. The first is identical to the nonspecific changes reported in PPA, namely neuronal loss with spongiform change and gliosis. The second pattern involves more prominent gliosis, sometimes associated with swollen neurons and/or argentophilic inclusions (Pick disease). The third involves either of the first 2 patterns plus evidence of motor neuron disease in the anterior horn cells of the brain stem and spinal cord. Significant overlap exists in all of these pathologic patterns of PPA and FTD. The specific clinical syndrome reflects the specific area of the brain involved as opposed to the specific microscopic histopathology. Kertesz et al have suggested the term "Pick complex" to include these various non-Alzheimer pathologies, with or without Pick inclusion bodies and with or without motor neuron disease.

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TREATMENT

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Medical Care

To date, most efforts have concentrated on diagnosing FTD and understanding its pathogenesis. Medical treatment is largely nonexistent.

- Social interventions, counseling, and speech/language/cognitive therapy to facilitate the use of spared functions may make the condition easier to bear for the patient, caregivers, and family members. Treatment of depression with a selective serotonin reuptake inhibitor (SSRI), such as sertraline or escitalopram, is frequently helpful. Trazodone may be helpful for sleep. These agents have been shown effective in small clinical trials.

- Neurotransmitter-based treatments, analogous to the use of dopaminergic agents in Parkinson disease or anticholinesterase agents in AD, are in their infancy. Anecdotal experience, including that of the author, has not suggested a benefit similar to that of AD with anticholinesterase agents or memantine.

- All of the pharmacologic treatments listed below must be considered investigational and not recommended for general use.
    - Anticholinesterase therapy generally involves donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). As stated above, only occasional patients appear to respond. The same is true of attempted treatment with the drug memantine (Namenda), Food and Drug Administration (FDA)–approved in January 2004 for AD. This drug may prevent neuronal damage from excessive release of the excitatory transmitter, glutamate, with overstimulation of remaining cells.

    - Dopaminergic drugs have been tested in patients with transcortical motor aphasia secondary to strokes. Anecdotal experience with dopamine agonist agents such as bromocriptine (Parlodel), pergolide (Permax), pramipexole (Mirapex), and ropinirole (Requip) has been unimpressive.

    - Stimulant drugs such as amphetamines and antidepressant agents may benefit patients with frontal lobe syndromes. Large, randomized, double-blind studies are lacking, but a few small trials are cited in the references.

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MEDICATION

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All current pharmacologic treatments are unproven, but SSRI antidepressants and trazodone are widely recommended. As discussed above, the cholinesterase inhibitors and memantine have not been shown to be effective in PPA or FTD (see Treatment).

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FOLLOW-UP

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Patient Education

- For excellent patient education resources, visit eMedicine's Dementia Center. Also, see eMedicine's patient education articles Dementia Overview and Dementia Medication Overview.

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MULTIMEDIA

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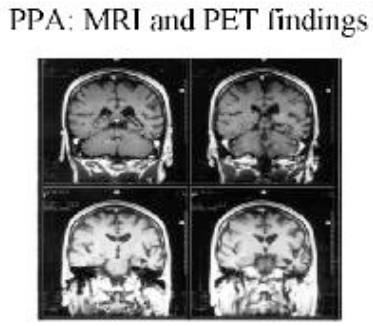
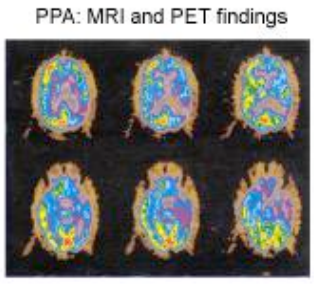
Media file 1: **MRI of a patient with progressive, nonfluent aphasia. Note the focal, left temporal atrophy. Reprinted from Neurology in Clinical Practice, 4th ed. Kirshner H. Language and Speech Disorders. Copyright 2004, with permission from Elsevier.**



View Full Size Image

Media type: CT

Media file 2: **Positron emission tomography (PET) scan from the same patient as in Image 1, indicating hypometabolism of glucose in the left hemisphere. Reprinted from Neurology in Clinical Practice, 4th ed. Kirshner H. Language and Speech Disorders. Copyright 2004, with permission from Elsevier.**



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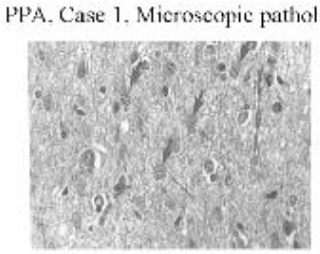
Media type: Image

Media file 3: **Hematoxylin and eosin stain of the left frontal cortex from a patient with primary**

progressive aphasia, showing loss of neurons, plump astrocytes (arrow), and microvacuolation of the superficial cortical layers. Reproduced with permission of John Wiley & Sons, Inc.



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