



## Primer on Frontotemporal Dementia

Your patient came to the UCSF Memory and Aging Center website looking for information about frontotemporal dementia (FTD). If your patient exhibits the features of FTD, here are some helpful points we like to consider when narrowing the diagnosis.

Once considered rare, FTD is now thought to be the most common cause of early-onset dementia, after Alzheimer's disease. Patients typically present when they are between 45 and 65 years of age, and a positive family history is found in 40% of cases. FTD has three different subtypes, each with a unique pattern of atrophy and early symptoms.

The frontal or behavioral variant of FTD (bvFTD) leads to impaired self-representation, manifesting as loss of empathy, self-monitoring, moral reasoning and theory of mind, as well as apathy, disinhibition, emotional blunting, overeating and repetitive motor behaviors. These deficits are accompanied by focal degeneration in the anterior cingulate (ACC) and frontal insular (FI) cortices, which anchor a specialized paralimbic emotional-autonomic processing network.

In contrast, patients with primarily left frontal tissue loss present with language disturbances including hesitant, agrammatical speech output, called progressive non-fluent aphasia (PNFA). Finally, when the early atrophy is limited to the anterior temporal lobes, patients lose the ability to recognize words and people, so-called semantic dementia (SD).

### Recommended Work Up

**Physical exam and patient history.** Because the first symptoms of FTD are sometimes constitutional, identifying the actual date of onset may require

some probing. Suggested questions to ask include:

1. Has there been a change in personality, creativity, emotional attachment to others, drive, organizational skills or social abilities?
2. Has there been a recent weight gain and is overeating a problem?
3. Does the patient offend others in public or behave in a disinhibited manner?

These are all symptoms of FTD that you should probe, although determining the exact time when these symptoms started is difficult. An assessment of the patient's ability to complete activities of daily living helps quantify disease severity. Ask about any family history of neurological or psychiatric disease (relatives may have been misdiagnosed; many patients with genetic forms of FTD are mistaken for other neurological or psychiatric disorders, including Alzheimer's, Parkinson's disease or atypical parkinsonian dementias).

**Lab tests.** You should get a measure of complete blood count, electrolytes, renal, liver and thyroid function and serum B12. All patients diagnosed with FTD should have at least an MRI to look for frontal and anterior temporal atrophy. Other laboratory and imaging tests may be required.

**SPECT.** HMPAO-SPECT shows bilateral frontal hypoperfusion in early

bvFTD and SD, which differentiates FTD from AD, where the hypoperfusion is posterior parietal and temporal.

**PET.** FDG-PET demonstrates frontal and anterior temporal hypometabolism in patients with FTD/Pick's disease. In patients with SD, FDG-PET shows anterior temporal hypometabolism. In progressive non-fluent aphasia the hypometabolism tends to be in the left fronto-insular region.

PIB-PET measures the presence of beta-amyloid, a protein that accumulates in the brain in AD but not in FTLD. PIB-PET can thus be helpful in distinguishing between AD (elevated PET signal in cortex) and FTLD (no cortical signal is seen).

**MRI.** On a T1-weighted MRI scan, look for atrophy in the ventromedial frontal cortex, bilateral posterior orbital frontal regions, bilateral insula, anterior cingulate cortex, dorsolateral frontal cortex and premotor cortex to support bvFTD.

SD patients often have severe bilateral, asymmetric anterior temporal atrophy ("knife edge atrophy") as well as medial temporal atrophy. In SD the amygdala, temporal pole, fusiform and inferolateral temporal gyri are more severely atrophic than in typical AD. Unbiased measurements of T1-weighted MRI scans suggest that atrophy in SD is much more significant in temporal than extra-temporal brain regions.

MRI scans of PNFA patients show atrophy of the left frontal, insular, anterior parietal, perisylvian and superior temporal cortices.

**Neuropsychology.** Patients with bvFTD tend to show executive function and working memory impairments. Unlike AD, memory and visuospatial skills are relatively spared. Patients may have difficulty with set shifting, concept formation, abstraction and reasoning, inhibition of over-learned responses, response generation, organization, planning, self-monitoring and using feedback to guide behavior.

While bvFTD patients tend to score well on the Mini Mental State Exam (MMSE), SD patients score lower due to their language difficulties. Despite these language problems, episodic memory for recent events is relatively spared. As the disease progresses, SD patients perform progressively worse on category fluency tests (i.e. the number of animals or musical instruments generated in one minute), picture naming (Boston Naming Test) and generating verbal definitions of words and pictures. Many SD patients also have concomitant dyslexia. Nonverbal testing of semantic memory may provide better results.

Like patients with bvFTD, PNFA patients tend to show executive function and working memory deficits while episodic memory, semantic memory and visuospatial function are preserved. Unlike bvFTD, PNFA causes specific language difficulties including agrammatism, phonemic paraphasias, anomia, stuttering, impaired repetition, apraxia of speech, alexia and agraphia.

## Differential Diagnosis

The first step in making an accurate diagnosis of FTD is to rule out other possible explanations of the symptoms, such as Alzheimer's disease, a primary

psychiatric condition or Parkinson's disease.

### Treatable dementias.

- **Reactions to medications.** Some medications have side effects that mimic the symptoms of dementia. Even a single dose of a medicine may trigger such a reaction in an older person or in someone whose liver fails to eliminate the drug normally. Interactions among two or more drugs may lead to reversible symptoms of dementia as well.
- **Metabolic abnormalities.** Decreased thyroid function (hypothyroidism) can result in apathy or depression that mimics dementia. Hypoglycemia, a condition in which there isn't enough sugar in the bloodstream, can cause confusion or personality changes. Pernicious anemia caused by an inability to absorb vitamin B-12 also can cause cognitive changes. Similarly, changes in blood sodium, calcium, heavy metals, or other compounds can cause a reversible dementia.
- **Nutritional deficiencies.** Chronic alcoholism can be associated with deficiencies of thiamin (vitamin B-1), which can seriously impair mental abilities. Severe deficiency of niacin (vitamin B-3) may cause pellagra, a neurological illness with features of dementia. Dehydration also can cause confusion that may resemble dementia.
- **Emotional problems.** The confusion, apathy and forgetfulness associated with depression are sometimes mistaken for dementia, particularly in older individuals. Similarly, bipolar disease, schizophrenia, and obsessive-compulsive disorder can be misdiagnosed as FTD

- **Infections.** Meningitis and encephalitis, which are infections of the brain or the membrane that covers it, can cause confusion, memory loss or sudden dementia. Untreated syphilis or Lyme disease can damage the brain and cause dementia.
- **Normal-pressure hydrocephalus.** If cerebrospinal fluid builds up in the ventricles of the brain, the brain tissue is compressed even though the fluid pressure remains normal. This may cause dementia. If this condition is identified in time, it may be treated by draining the excess fluid via a tube (shunt).

**Alzheimer's disease.** There can be significant overlap between Alzheimer's disease and frontotemporal dementia. In Alzheimer's disease disinhibition, overeating, loss of sympathy for others, and apathy are not usually prominent presenting features. More typical of Alzheimer's disease than FTD are the following:

- sparing of socially appropriate behavior,
- severe memory problems,
- difficulty with visuospatial tasks like navigation and
- a relatively normal neurological examination.

In FTD on neuropsychological testing, look for low performance on letter and category fluency tests, but better performance on the verbal memory subscales, block design test and drawing tests.

Use imaging to confirm orbitobasal (ventromedial) frontoinsular and/or anterior temporal atrophy versus parietal atrophy or more generalized atrophy.

**Psychiatric problems.** Many FTD patients show symptoms of obsessive-compulsive disorder and in particular,

repetitive compulsive behaviors are a core feature of FTD. Delusions and are euphoria are also common with FTD, sometimes leading to the misdiagnosis of either schizophrenia or bipolar illness. Depression is not common in FTD, but apathy and emotional withdrawal are and this can lead to the misdiagnosis of depression. Even though FTD patients often appear to be depressed, when you ask them about their mood, they often offer that they feel happy.

**Movement disorders.** Many patients with FTD develop, or even present with, Parkinsonian features. In classical Parkinson's disease (PD), a tremor is often present and the rigidity tends to involve the limbs, while in FTD, a tremor is often absent and the rigidity is usually axial. Falls at presentation or early in the disease course, poor response to levodopa, symmetry of motor signs, rapid progression, lack of tremor and early dysautonomia are signs that identify patients with forms of parkinsonism other than PD. A significant loss of smell suggests PD. Progressive supranuclear palsy (PSP) can cause difficulty with speech and swallowing, as well as depression and emotional difficulties. Alien limb suggests corticobasal degeneration (CBD) more than FTD or PD.

Like FTLT, confusion and memory loss similar to early Alzheimer's do not occur in people with PD until late in the disease. Language and thinking problems are likely develop in someone with CBD or dementia with Lewy bodies (DLB).

Formal eye movement recordings may be useful to distinguish PD and other forms of parkinsonism from FTD.

MRI and CT appear normal in PD, whereas the MRI of someone with FTLT will typically show some atrophy in the frontal and anterior temporal lobes. MRIs of people with

multiple system atrophy (MSA) may show abnormalities in the putamen (the so-called hot-cross bun sign). PET may show low levels of dopaminergic activity in PD.

Up to 50% of amyotrophic lateral sclerosis (ALS) patients also show loss of executive function and up to 20% have full-blown signs and symptoms of frontotemporal dementia. As a result, patients may lack the ability to fully understand the meaning of their illness, they may make poor decisions about their clinical care, or they may become agitated and difficult for caregivers who are trying to help them. They may have language problems that go beyond the expressive difficulties in ALS or show behavioral changes years before the ALS manifests.

## Diagnostic Criteria

**Nomenclature.** FTD nomenclature has evolved rapidly as our scientific understanding has improved. The term "frontotemporal dementia" (FTD) is used to refer to the clinical syndromes, such as behavioral variant FTD (bvFTD), progressive non-fluent aphasia (PNFA) and semantic dementia (SD). These syndromes are united by involvement of frontal and temporal brain regions. Previously, researchers sometimes used "FTD" to refer only to bvFTD, which has also been called "frontal variant FTD" (fvFTD).

FTD language variants are sometimes grouped under the umbrella term "primary progressive aphasia" (PPA). PPA has now been split into three subgroups: progressive non-fluent aphasia (PNFA), semantic dementia (SD) and logopenic progressive aphasia (LPA). Patients with LPA are often found to have Alzheimer's disease at autopsy. SD was previously referred to at times as "temporal variant FTD" (tvFTD).

Motor presentations of FTD include FTD with motor neuron disease (FTD-MND), corticobasal degeneration (CBD) – also sometimes referred to as corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP).

The term "frontotemporal lobar degeneration" (FTLD) is used to describe the specific pathological diseases that result in FTD syndromes. These too are united by their impact on frontal and temporal brain structures. Subtyping is based on the specific proteins found within neuronal inclusions. Most FTLT subtypes are either

1. tau-related disorders (tauopathies), such as Pick's disease, CBD and PSP or
2. FTLT with ubiquitin- and TDP-43-positive inclusions (FTLT-U/TDP-43).

### FTD (UCSF MAC)

In the diagnostic criteria we use at the UCSF Memory and Aging Center, one criterion must apply to all forms of frontotemporal dementia (FTD).

1. The patient must show a progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant).

Additional features not required for diagnosis but helpful to identify or eliminate concurrent illnesses include:

1. Onset before age 65
2. Presence of motor neuron disease (MND)
3. Motor symptoms and signs similar to CBS and PSP
  1. Asymmetric extrapyramidal syndrome
  2. Eye movement abnormalities
  3. Early falls
  4. Limb apraxia
  5. Dystonia
  6. Orobuccal apraxia
  7. Alien limb
4. Impaired word and object knowledge (disproportionate

deficits in confrontation naming, single word-to-object matching, semantic association tests)

5. Motor speech deficits (hesitant, effortful speech, apraxia of speech, dysarthria)
6. Significant grammatical deficits (grammatical deficits in language production (oral or written picture description) or comprehension of syntactically complex sentences (sentence-to-picture matching tasks or yes/no questions))

### **Possible bvFTD**

Exhibits three of the following six behavioral/cognitive symptoms.

1. Early behavioral disinhibition (one of the following must be present)
  1. Socially inappropriate behavior. (e.g., touching or kissing strangers, inappropriate sexual acts, public urination, criminal behavior)
  2. Loss of manners or decorum. Examples include a) crude or sexually explicit remarks, jokes or opinions which may be offensive to others; b) lack of response to social cues (e.g., will continue talking despite other's attempts to end a conversation); c) physical behaviors such as flatulence, touching private body parts, belching or spitting; d) poor hygiene or grooming (malodorous, stained, torn or inappropriate clothing), e) loss of respect for interpersonal space
  3. Impulsive, rash or careless actions. Impulsive behaviors which may or may not be performed in a social context (e.g., new-onset gambling, taking things, stealing (usually food or visually stimulating objects), buying or selling

property without regard for consequences)

2. Early apathy or inertia (one of the following must be present)
  1. Apathy. Loss of interest, drive or motivation (e.g., passivity, lack of spontaneity, does not engage in previously rewarding activities)
  2. Inertia. Decreased initiation of behavior (e.g., needs prompting to initiate or continue routine activities, less likely to initiate or sustain conversations)
3. Early loss of sympathy and empathy (one of the following must be present)
  1. Diminished response to other people's needs and feelings. Positive rating of this feature should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings – (e.g., hurtful comments, disregard for other people's pain, making jokes at a funeral)
  2. Diminished social interest, interrelatedness or personal warmth. General decrease in social engagement (coldness, lack of eye contact, etc.)
4. Early perseverative, stereotyped or compulsive / ritualistic behavior (one of the following must be present)
  1. Simple repetitive movements (e.g., tapping, clapping, rubbing, scratching, picking at skin or clothing, pursing lips, lip smacking)
  2. Complex, compulsive or ritualistic behaviors (e.g., counting and cleaning rituals, collecting, checking, repetitive trips to the bathroom, ordering objects, walking fixed routes)
  3. Stereotypy of speech. Repeating words or phrases

that have no communicative value

5. Hyperorality and dietary changes (one of the following must be present)
  1. Altered food preferences. Carbohydrate craving (particularly sweets) or food fads
  2. Binge eating, increased consumption of alcohol or cigarettes. Patient will continue to eat despite satiety (weight gain \_\_\_\_ lb); compulsive smoking, chewing tobacco or gum; or alcohol ingestion
  3. Oral exploration or consumption of inedible objects
6. Neuropsychological profile: executive / generation deficits with relative sparing of memory and visuospatial functions (all of the following must be present)
  1. Deficits in executive tasks. (i.e., Trails-B), generation tasks (letter fluency / design fluency) or presence of errors (e.g., perseverations or rule violations)
  2. Relative sparing of episodic memory
  3. Relative sparing of visuospatial skills (i.e., ability to copy simple line drawings)

### **Probable bvFTD**

1. Meets criteria for possible bvFTD
2. Exhibits a significant functional decline (by caregiver report or as evidenced by CDR and/or FAQ scores)
3. Imaging results consistent with bvFTD (one of the following must be present)
  1. Frontal and/or temporal atrophy on CT or MRI (disproportionate atrophy in medial frontal, orbital-insular

- and/or anterior temporal regions)
- 2. Frontal hypoperfusion or hypometabolism on SPECT or PET (disproportionate frontal or frontotemporal hypometabolism or hypoperfusion)

#### **bvFTD with Definite FTLD Pathology**

1. Meets criteria for possible or probable bvFTD
2. Meets one of the following
  1. Histopathological evidence of FTLD on biopsy or at post-mortem i.e., tauopathy, FTLD-U (TDP-43+ or TDP-43-), DLDH, NIFID
  2. Presence of a known pathogenic mutation i.e., MAPT, PGRN, CHMP2B, VCP

#### **Exclusion Criteria for bvFTD**

Criteria 1 and 2 must both be answered negatively for any bvFTD diagnosis. Criterion 3 can be positive for possible bvFTD but must be negative for probable bvFTD.

1. Pattern of deficits is better accounted for by other nervous system or medical disorder e.g., delirium, cerebrovascular disease, cerebellar disorder, systemic disorders (e.g., hypothyroidism), substance-induced conditions
2. Behavioral disturbance is better accounted for by a psychiatric diagnosis e.g., depression, bipolar disorder, pre-existing personality disorder
3. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process e.g., genetic mutations, extensive PIB binding, CSF markers, alternative imaging techniques

#### **Possible SD**

1. Early loss of word and object knowledge, particularly for unfamiliar items (both must be present)

1. Loss of word knowledge (disproportionate impairment on confrontation naming tests (e.g., BNT or other graded test); difficulty with single-word comprehension)
2. Loss of object knowledge (multimodal difficulty recognizing animate and inanimate objects; diminished performance on semantic association tests e.g. Pyramids and Palm Trees Test)
2. Early loss of semantics for socially relevant information (people and emotions) (all 3 must be present)
  1. Diminished knowledge of famous or familiar people (difficulty recognizing famous faces, diminished semantic associations with faces)
  2. Diminished perception of emotion (poor face-affect matching)
  3. Loss of empathy (positive rating of this feature should be based on specific examples that reflect a lack of understanding or indifference to other people's feelings – e.g., hurtful comments, disregard for other people's pain, making jokes at a funeral)

#### **Probable SD**

1. Meets criteria for possible SD
2. Exhibits significant functional decline (by caregiver report or as evidenced by CDR and/or FAQ scores)
3. Imaging results consistent with SD (one of the following must be present)
  1. Anterior temporal atrophy on CT or MRI (disproportionate atrophy in anterior temporal regions)
  2. Anterior temporal hypoperfusion or hypometabolism on SPECT or PET (disproportionate

hypometabolism in anterior temporal regions)

#### **SD with Definite FTLD Pathology**

1. Meets criteria for possible or probable SD
2. Meets one of the following
  1. Histopathological evidence of FTLD on biopsy or at post-mortem i.e., tauopathy, FTLD-U (TDP-43+ or TDP-43-), DLDH, NIFID
  2. Presence of a known pathogenic mutation i.e., MAPT, PGRN, CHMP2B, VCP

#### **Exclusion Criteria for SD**

Criteria 1-3 must be answered negatively for any SD diagnosis. Criterion 4 can be positive for possible SD but must be negative for probable SD.

1. Pattern of deficits is better accounted for by other nervous system or medical disorder e.g., delirium, cerebrovascular disease, hydrocephalus, systemic disorders (e.g., hypothyroidism), substance-induced conditions
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis e.g., depression, bipolar disorder, pre-existing personality disorder
3. Motor speech problem (non-fluent speech) – word-finding pauses may be present, but they do not affect fluency, grammar or prosody
4. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process e.g., genetic mutations, extensive PIB binding, CSF markers, alternative imaging techniques

### Possible PNFA

Either one of the following must be present:

1. Early motor speech deficits (2 of 3 must be present)
  1. Effortful speech: sound distortions, hesitations in initiation
  2. Apraxia of speech signs: inconsistent sequencing errors during multiple repetitions of multisyllabic words with consonant clusters, such as “catastrophy” or “primary”. When severe, they result in phonemic errors in any language production task (conversation, picture description, naming, repetition). i.e. “gingerjed” for gingerbread
  3. Dysarthria signs: slurring, hypernasality, breathiness
2. Early grammatical deficits (all must be present)
  1. Grammatical deficits in language production (oral or written picture description): short sentences (only single nouns in severe cases), omissions or errors in function words and verb usage (i.e. articles, pronouns: “car near house”)
  2. Deficits in comprehension of syntactically complex sentences (sentence-to-picture matching tasks or yes/no questions): difficulty with sentences such as “the girl is not being followed by the boy” but good understanding of simple sentences such as “the girl is pushing the boy”

### Probable PNFA

1. Meets criteria for possible PNFA
2. Exhibits significant functional decline (by caregiver report or as evidenced by CDR and/or FAQ scores)

3. Imaging results consistent with PNFA (one of the following must be present)
  3. Left or bilateral frontal-insular atrophy on CT or MRI (disproportionate atrophy in left or bilateral frontal-insular regions)
  4. Left or bilateral frontal hypoperfusion or hypometabolism on SPECT or PET (disproportionate hypometabolism in left or bilateral frontal-insular regions)

### PNFA with Definite FTLD Pathology

1. Meets criteria for possible or probable PNFA
2. Meets one of the following
  1. Histopathological evidence of FTLD or PSP/CBD on biopsy or at post-mortem i.e., tauopathy, FTLD-U (TDP-43+ or TDP-43-), DLDH, PSP, CBD
  2. Presence of a known pathogenic mutation i.e., MAPT, PGRN, CHMP2B, VCP

### Exclusion Criteria for PNFA

Criteria 1-5 must be answered negatively for any PNFA diagnosis. Criterion 6 can be positive for possible PNFA but must be negative for probable PNFA.

1. Pattern of deficits is better accounted for by other nervous system or medical disorder e.g., delirium, cerebrovascular disease, hydrocephalus, systemic disorders (e.g., hypothyroidism), substance-induced conditions
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis e.g., depression, bipolar disorder, pre-existing personality disorder
3. Impaired word and object knowledge (confrontation naming, single word-to-object matching, semantic association tests)

4. Logopenic progressive aphasia (progressive language disorder characterized by word finding pauses that result in decreased words per minute, phonological paraphasias and sentence repetition deficits, but spared motor speech with no grammatical errors in production and spared object and word knowledge.)
5. Predominant visuo-perceptual or memory disorder
6. Biomarkers strongly indicative of Alzheimer’s disease or other neurodegenerative process e.g., genetic mutations, extensive PIB binding, CSF markers, alternative imaging techniques

## Management of Symptoms

The essential first steps to treating someone with FTD are an accurate diagnosis and non-pharmacologic intervention. These steps should be followed by a review of all medications (prescribed, OTC, herbal, etc.) to look for contraindications, interactions, inappropriate prescription or inappropriate dosage. As of yet, there are no medications available to cure or delay the progression of FTD, but there are a number of medications that alleviate the symptoms. Medical management includes treatment of concomitant medical conditions such as infections, parkinsonian symptoms, seizures, pain and improving nutritional status. All medications the patient is taking should be fully reassessed for optimal response at the dose prescribed, and the patient should only be on necessary medications that are effective in treating the underlying conditions.

Of the reversible dementias, medication use is the most common cause. Furthermore, adverse drug events (ADEs) occur in 15 to 35% of older people, with 29% of those events

requiring health care services. An inappropriate or contraindicated medication can cause greater harm than good to the patient due to impaired liver metabolism, decreased renal function, increased body fat or increased sensitivity to CNS medications which can produce impaired memory and delayed psychomotor performance. While each individual varies in their sensitivity and precise condition, these general guidelines should be considered before prescribing certain medications.

## Clinical Trials and Research

The UCSF Memory and Aging Center runs multiple observational and interventional studies in FTD. If your patient is interested, we welcome your referrals. Please have them contact us so we can review the study protocol and consent with them and see if they meet the study criteria.

Current studies at the Memory and Aging Center include:

### Observational Studies

1. Attention/Executive Function
2. Domain Specific Tasks of Executive Function
3. Eye Movement Control in Normal Adults and Adults with Neurologic Disease
4. Frontotemporal Dementia: Genes, Images and Emotions
5. fMRI of Autonomic Physiology in Frontotemporal Dementia (FTD) and Alzheimer's Disease (AD)
6. New Approaches to Dementia Heterogeneity

### Interventional Studies

1. Double-Blind, Placebo-Controlled Trial of Memantine (10mg BID) for Frontotemporal Dementia and Semantic Dementia

## Contact Us

If you would like a consult or to refer your patient to our clinic, please call us at (415) 476-6880.

Mail the referral letter, insurance information and authorization, and medical records including lab results, diagnostic reports, clinical notes, and imaging from the past year to:

Attn: Clinic Coordinator  
 UCSF Memory and Aging Center  
 PO Box 1207  
 San Francisco CA 94143-1207

For more detailed information on anything you have read here, please visit us online at [memory.ucsf.edu/ftd](http://memory.ucsf.edu/ftd).