INTRODUCTION

Professor Arnold Pick first reported, in 1892, a 71-year-old patient with progressive language and cognitive decline, and grossly visible anterior temporal lobe atrophy post-mortem.1 This is thought to be the first report of a patient with what was later called semantic dementia by Professors John Hodges and Julie Snowden. Professor Alois Alzheimer subsequently described the microscopic histologic abnormalities that were later called “Pick’s disease” by Drs. Onari and Spatz. Professor Schneider published a detailed report on clinical course of the disease, highlighting the insidious early changes in behavior and personality and—in contrast with Alzheimer’s disease (AD)—the typical relative preservation of memory and orientation.2 Through most of the rest of the century, patients with behavioral-comportmental dementias were usually diagnosed as having “Pick’s disease.” In the 1980s and 1990s, Professors Marsel Mesulam, Sandra Weintraub, John Hodges, Julie Snowden, Andrew Kertesz, and others reignited the interest of the behavioral neurology and neuropsychiatry field in progressive aphasias.3–5 In the 1980s, the Lund6 and Manchester7 groups reported important early studies generating renewed interest in the behavioral phenotype of frontotemporal dementia (FTD), soon thereafter proposing clinical and pathological diagnostic criteria.8 In the late 1990s, in the Lund8 and Manchester9 groups reported important early studies generating renewed interest in the behavioral phenotype of frontotemporal dementia (FTD), soon thereafter proposing clinical and pathological diagnostic criteria.10 In the late 1990s, the Lund9 and Manchester10 groups reported important early studies generating renewed interest in the behavioral phenotype of frontotemporal dementia (FTD), soon thereafter proposing clinical and pathological diagnostic criteria.11 In the early 2000s, interest in the syndromes we now call FTDs surged, leading to the development and evolution of clinical and pathological criteria for the diagnosis and, more recently, an explosion in scientific understanding of this family of diseases, as well as a robust international clinical-scientific organization devoted to the diseases (http://www.isftd.org) with biannual international conferences sparking tremendous collaborative energy.12 Important advances were formalized in 2011 when new consensus diagnostic criteria were published for primary progressive aphasia (PPA)13 and the behavioral variant of FTD (bvFTD).14 These criteria were then largely incorporated with some simplification into the fifth edition of the American Psychiatric Association Diagnostic and Statistical Manual in 2013.

Although terminology remains confusing in this family of diseases, we continue to recognize the syndromes of bvFTD, semantic variant PPA (svPPA), and nonfluent or agrammatic variant PPA (nfvPPA) to present in the context of a neuropathological family of diseases termed frontotemporal lobar degeneration (FTLD). The third major subtype of PPA, the “logopenic” variant, is usually associated with AD pathology. FTLD is a loosely knit group of neurodegenerative diseases that preferentially affect the frontal and anterior temporal lobes, with relative sparing of other cortical regions in many cases, and often affecting basal ganglia and in some cases basal forebrain and brainstem nuclei. Largely for reasons of pathological overlap, several other diseases have also now been included in this clinical and pathological spectrum, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and FTD with motor neuron disease or amyotrophic lateral sclerosis (FTD-MND or FTD-ALS).

EPIDEMIOLOGY

FTLD is thought to be the third most common degenerative cause of dementia, after AD and Lewy body disease (LBD), accounting for 5–15% of dementias. FTLD often causes early-onset dementia, typically affecting people in their mid-40s to mid-60s. In people younger than 65 years old, it is thought to be the second most common cause of dementia. Nevertheless, pathologically confirmed cases have been reported with age of clinical symptom onset as young as age 2113 and as old as age 85.14 Some epidemiologic studies raise the question of whether it is being substantially underreported,15 suggesting that it may be more common than previously thought, including in the elderly.16,17

The incidence and prevalence rates of FTD have received little study with widely ranging results, from a prevalence of ~1.1 per 100,000 cases in a study from the Netherlands18 to 15–17...
of pathologically unclassified FTLD cases were determined to be immunoreactive to the fused in sarcoma (FUS) protein. Therefore, except for a very small number of cases, the majority of FTLD neuropathology is now possible to classify as (1) FTLD-tau (~40–50% of cases), (2) FTLD-TDP-43 (~40–50% of cases), or (3) FTLD-FUS (~5% of cases), and several other rare proteinopathies.

Meanwhile, Professor William Seeley identified the selective loss of the von Economo neuron (VEN), a specific cell type found in the anterior cingulate and frontoinsular cortex of evolutionarily advanced mammals. This spindle-shaped neuron appears to be reduced substantially in these brain regions in patients with FTLD but not in patients with AD. Remaining VEN neurons showed pathologic features in FTLD, but appeared morphologically normal in AD. So-called fork cells are also selectively vulnerable to FTLD pathology. Further research on selectively vulnerable cell types in FTLD may reveal new insights into the mechanisms of neuropathology and the predilection for certain brain regions in these diseases.

**GENETICS OF FTLD**

In the mid- to late-20th century it became clear that Pick's disease could be observed in multiple generations. Approximately 20–40% of cases of FTLD exhibit a family history of a similar or related condition, and 10–20% of cases have a family history consistent with an autosomal dominant inheritance pattern. When linkage studies identified loci on chromosomes 3, 9, and 17, the hunt for specific genetic mutations was on.

In 1998, mutations of the microtubule-associated protein tau (MAPT) gene on chromosome 17q21 were reported, with many patients in the initially reported families also exhibiting parkinsonism, leading to the term FTD-parkinsonism linked to chromosome 17 (FTDP-17). More than 44 MAPT mutations have been reported in over 100 families in the world. MAPT mutations are toxic gain-of-function abnormalities that reduce the ability of the tau protein to bind to and stabilize microtubules. The clinical phenotypes of patients with MAPT mutations include bvFTD, PSP syndrome, corticobasal syndrome (CBS), or rarely PPA. A fascinating aspect of this and other forms of autosomal dominant FTD is that patients within the same family with the same genetic mutation may present with distinct clinical phenotypes, including PPA, CBS, or bvFTD.

Despite these advances in understanding, it became apparent that there were a number of families with autosomal dominant FTLD with linkage to chromosome 17q21 who did not have MAPT gene mutations—none of the cases in these families that came to autopsy had tau pathology, but instead demonstrated what was originally described as DLDH and subsequently FTLD-U. The cause was elucidated in 2006 with reported mutations in the progranulin (GRN) gene, which is also on 17q21 and very close to the MAPT gene. GRN mutations are associated with FTLD-TDP-43 pathology. More than 70 GRN mutations have been reported, which are thought to result in a degraded protein whose function is lost (“loss of function”) due to haploinsufficiency. Mutations in GRN are the second most common...
genetic cause of familial FTLD (4–26% of familial FTLD). Age of symptom onset averages between ages 53 and 64, but varies widely, from as young as age 35 to as old as 88. The clinical phenotypes of GRN carriers include bvFTD (most common), PPA, CBS, and a progressive amnesic syndrome similar to that associated with AD. GRN mutation carriers who present with bvFTD tend to exhibit apathy, executive dysfunction, and social withdrawal rather than disinhibition or compulsive behavior. Those with PPA usually present with a nonfluent form, but may have logopenic features. Parietal degeneration is common, more prominently than in most other forms of FTLD, and frequently giving rise to limb apraxia, spatial disorientation, and related symptoms. Extrapyramidal features are also common, and psychosis is more common than in sporadic FTLD. Importantly, a common variant in the gene TME106B modifies the expression of GRN, delaying age of onset.66

Another major discovery in the genetics of FTLD was made in 2011. Families with members affected with FTD or ALS or both (FTD-ALS) had been reported with linkage to chromosome 9p, but the responsible gene remained unknown until reports of an expanded GGGGCC hexanucleotide repeat in the chromosome 9 open reading frame 72 gene (C9orf72).37.38 This important finding brought the FTD and ALS research communities together to investigate common biological mechanisms. It has since become clear that C9orf72 repeat expansions are the most common genetic cause of FTD (29% of familial FTD), ALS (38% of familial ALS), and FTD-ALS (88% of familial FTD-ALS). In patients without a family history of FTD or ALS, expansions in C9orf72 are occasionally found, that is, patients with sporadic FTD or ALS are rarely determined to have this genetic abnormality.59 Age of symptom onset averages between ages 50 and 64, but—like GRN—also varies widely, from as young as age 27 to as old as 83. As with GRN, variants in TME106B seem to protect against FTD due to C9orf72 but does not influence ALS in the same way.60 The clinical phenotypes of C9orf72 include bvFTD, ALS, and FTD-ALS, with bulbar symptoms appearing to be more common than in sporadic ALS. Psychosis and other neuropsychiatric symptoms, including anxiety, are much more common than in sporadic FTD. Memory loss is common, as are language symptoms, although primary amnesic or aphasic phenotypes without behavioral symptoms are relatively uncommon. Extrapyramidal features are not as more common than in sporadic FTD.

Tank-binding kinase 1 (TBK1, located on chromosome 12) was discovered in 2015 as the third most common cause of FTLD in a large Belgian cohort, after GRN and C9orf72.61 TBK1-related disease has been noted to cause bvFTD with prominent disinhibition, and, in a series of cases, with memory loss as an important associated symptom in the initial phase of the disease.62 Some patients exhibit ALS. Neuroimaging has demonstrated widespread frontotemporal atrophy. Neuropathology in two patients demonstrated TDP-43 type B pathology.62

Very rarely, familial FTLD can be associated with mutations in other genes, such as CHMP2B63 and valosin-containing protein (VCP).64 In 2009, mutations in the FUS gene were discovered in association with familial ALS,65,66 but nearly all FTLD-FUS cases examined to date do not appear to be associated with FUS mutations or other known genetic abnormalities (i.e., they appear to be sporadic).67

Detailed clinical and clinicopathologic studies of families in which FTLD is associated with particular genetic mutations have revealed important heterogeneity. Members of families with the same genetic mutation can develop pathology localized in different brain regions, and therefore present with different clinical phenotypes. This was first described clearly in families with MAPT mutations.52,53,68 Although the major clinical phenotype association with MAPT mutations is a behavioral-dys-ecutive syndrome, some patients present with extrapyramidal dysfunction, CBS, or PPA. This phenotypic heterogeneity was later also observed in families with GRN mutations, with some patients developing bvFTD, some PPA, and some CBS or other phenotypes.69 Note that CBS is much more common in patients with GRN mutations (~4%) than it is in patients with MAPT mutations (~2%). A few GRN cases have even presented with a posterior cortical atrophy syndrome.70,71 Families with the C9orf72 mutation are now the prototypical example of markedly different clinical phenotypes, with some patients exhibiting bvFTD, others with ALS, and others with FTD-ALS. The bvFTD phenotype associated with C9orf72 mutations is also unusual in that psychosis is much more prominent than in typical bvFTD; bizarre delusions are commonly a symptom very early in the course of the C9orf72 bvFTD phenotype.72 A growing research effort is being devoted to trying to understand this genetic-clinical heterogeneity. Families such as this imply the presence of modifying influences on the initial localization of pathology; some of these are likely genetic but it is also possible that some are developmental or environmental.

Genetic Counseling and Testing in FTD

The clinical practice of genetic counseling and testing in patients and families with FTD is complex; we and other specialty groups follow an approach similar to that summarized in several reviews.53–55 The foundation for genetic counseling is a confident diagnosis of the likely etiology of the patient’s syndrome, since the likely molecular pathology dictates genetic considerations. When we begin working with a patient and family we start by evaluating our confidence in the diagno-sis. Then, we carefully obtain a family history ideally encompassing three generations, recording each blood relative’s age of death, cause of death if known, and general cognitive/behavioral/neuropsychiatric status in later life (Figure 24-1). We summarize with the family that FTD and related conditions were often not diagnosed or may have been misdiagnosed in prior generations. If the family chose to have an autopsy performed, valuable information can be obtained, but in prior generations brain autopsy is relatively infrequent. If there is a potential family history of FTD or related disorders, we ask the family to try to obtain additional information or records about the affected relatives, and to consider meeting with our group’s genetic counselor. If there is clearly not a family his-tory of FTD or related disorders, and family members lived past typical age of onset, there is usually a low likelihood of the presence of a genetic mutation.64 If family history information is unavailable or blood relatives died at a younger age, we suggest that the patient/family work with our genetic counselor to discuss the issues involved. In a patient with FTD with age of
FTD gene mutation that runs in their family, their lifetime risk
duced with FTD. If individuals test negative for the pathogenic
gene and are best discussed with a genetic counselor experi-
and each offspring has a 50% chance of inheriting the genetic
disease protocol for performing this kind of counseling and
selor. Most genetic counselors follow the so-called Huntington’s
somatic genetic testing under the guidance of a genetic coun-
Asymptomatic blood relatives can choose to undergo presymp-
mation. If a patient with FTD is found to have a pathogenic
additional affected or unaffected family members if available.
The identification of a positive test result for a known, patho-
genic FTD gene mutation in a patient usually has a powerful
impact on the family and patient. A genetic counselor can guide
families in planning the disclosure of results to other family
members. In some families, such results may provide relief in
explaining a mysterious familial condition, while in other fam-
ilies this kind of result may lead to fear and stigma. Genetic
counseling plays an important role in helping family members
with this complex and emotionally challenging medical inform-
ation. A direct history with a spouse or adult child informant in
private is essential, and it is often helpful to obtain documenta-
tion through medical records or other notes of concerns at
the time of symptom onset. Although time-consuming, this
approach facilitates an open discussion of symptoms (infor-
mants may be uncomfortable discussing some issues in front
of the patient) and enables the clinician to evaluate insight and
concern in the patient separately from influence by informants.
Lack of awareness or concern is often a core element of the clini-
cal presentation in patients with bvFTD. Since many of the early
symptoms are related to changes in affect or personality, it is
not surprising that patients may first present to psychiatrists or
other mental health professionals.

Behavioral Variant FTD

FTLD neuropathology is often associated with a clinical pheno-
type involving the insidious development of changes in inter-
personal and emotional behavior, commonly accompanied by
executive dysfunction. This clinical syndrome has historically
been referred to as “Pick’s disease” but is now called bvFTD.
Based on a variety of concerns regarding prior criteria, new
international consensus diagnostic criteria were published in
2011 (Table 24-1).12 BvFTD appears to be the most common
syndrome associated with FTLD. The specific symptoms of
this variant depend on the particular regions of frontotempo-
cortical and frontostriatal brain systems involved and their
laterality.

Disinhibition is a common early symptom, and can manifest
as socially inappropriate behavior such as overly familiar inter-
actions with strangers; loss of manners or violations of social nom-
imate behavior, commonly accompanied by executive dysfunction. This clinical syndrome has historically
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Disinhibition is a common early symptom, and can manifest
as socially inappropriate behavior such as overly familiar inter-
actions with strangers; loss of manners or violations of social norm-
ivements may suggest that bvFTD may present as a “disinhibited”
or “inert” (apathetic) subtype80 while many patients present with
intermixed symptoms of both types.83 Atrophy in the anterior cin-
gulate cortex, dorsolateral prefrontal cortex,84 and striatum86 has
been observed in association with apathy in bvFTD.
TABLE 24-1  •  Diagnostic Criteria for bvFTD.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible bvFTD (at least 3 of the following must be present early (&lt;3 years) in the course)</td>
<td></td>
</tr>
<tr>
<td>Behavioral disinhibition</td>
<td>Socially inappropriate behavior; loss of manners or decorum; impulsivity</td>
</tr>
<tr>
<td>Apathy or inertia</td>
<td></td>
</tr>
<tr>
<td>Loss of sympathy or empathy</td>
<td>Diminished response to other people’s needs and feelings; diminished social interest</td>
</tr>
<tr>
<td>Perseverative, stereotyped, or compulsive behavior</td>
<td>Simple repetitive movements; complex compulsive or ritualistic behavior; stereotypy of speech</td>
</tr>
<tr>
<td>Hyperorality and dietary changes</td>
<td>Altered food preferences; binge eating or increased consumption of alcohol or cigarettes; oral exploration of inedible objects</td>
</tr>
</tbody>
</table>

| Neuropsychological profile of executive dysfunction with relative sparing of episodic memory and visuospatial skills |

| Probable bvFTD | |
| Meets criteria for possible bvFTD |
| Exhibits functional decline |

| Imaging results consistent with bvFTD | Frontal and/or anterior temporal atrophy or hypometabolism or perfusion |

| bvFTD with definite FTLD pathology | |
| Meets criteria for possible or probable bvFTD |
| Histopathological evidence of FTLD on biopsy or autopsy |
| Presence of a known pathogenic mutation |

| Exclusionary criteria for bvFTD | |
| Pattern of deficits is better accounted for by another neuromedical disorder |
| Behavioral disturbance is better accounted for by a psychiatric disorder |
| Biomarkers strongly indicative of Alzheimer’s disease or another neurodegenerative process |

Source: Rascovsky et al.2

Loss of empathy or sympathy toward the spouse, other family members, and friends is very common and can be subtle in some cases, depending in part on premorbid personality traits.97–99 These behavioral changes may concern family members for some time before it becomes obvious that something is wrong, which often occurs when the patient exhibits a highly unusual response to an event that almost universally provokes a vigorous, uniform emotion in most people, such as the death of a close friend or family member, or the birth of a child. Even under these circumstances, the behavior is commonly attributed to depression or another psychiatric illness or to stress or a mid-life crisis. Right anterior temporal cortex, anterior insula, and striatal abnormalities have been most consistently identified as related to loss of empathy.90,91

Compulsive, ritualistic, or repetitive behaviors are common in bvFTD, often early in the illness, and can be very distressing to family members.92,93 In some cases, they may be the presenting symptom.94 Examples of these symptoms include repetitive “projects” (e.g., stereotyped writing of greeting cards), chores (e.g., repeated emptying of trash), or playing of card or computer games or repetitive watching of a particular television show.95 Speech patterns may be stereotyped (e.g., catch phrases, telling of stories as if by a script). Some of these symptoms appear similar to those of obsessive-compulsive disorder (OCD) but usually bvFTD patients do not describe obsessive thoughts or any relief of such thoughts by a compulsive activity, as is typically described in primary OCD. Some patients have very rigid routines that must be performed identically each day (often at a particular time, associated with “clock watching”); if these routines are disrupted, some patients become very upset. These symptoms may change as the disease progresses, in some cases becoming simpler. Simple repetitive behaviors include tapping or moving a limb, licking lips, picking skin, grunting, or moaning. These may appear similar to choreiform movements seen in dyskinetic movement disorders or tardive dyskinesia. Anatomic abnormalities associated with compulsive behaviors include striatal and anterior temporal atrophy.96–98

Changes in eating behavior are common and may include altered food preferences (such as an increased sweet tooth or a rigid stereotypy in the foods eaten from day to day) or gluttonous or binge-like eating.95,99 This may—but does not always—result in substantial weight gain. Normative social eating conventions are often violated, including rapid eating or stuffing food in the mouth, taking food from others’ plates, or belching. Patients may exhibit changes in the consumption of alcohol or cigarettes, sometimes resulting in extreme intoxication or vomiting. Occasionally early, but more often later, in the course of the disease patients may explore inedible objects by placing them in their mouth similar to the behavior seen in Klüver-Bucy syndrome. The neurobiological basis of changes in eating behavior in FTD appears to involve right lateralized ventral anterior insula, striatum, and orbitofrontal cortex on structural MRI voxel-based morphometry,100,101 as well as degenerative changes in the hypothalamus.102,103

Executive dysfunction (problems with organization, planning, sequencing, decision making, multitasking, or monitoring performance) is very common in bvFTD.104 Symptoms described by family members often include difficulty with financial management, poor decision making, inability to complete tasks (particularly novel tasks), or not recognizing or correcting mistakes. Despite the report of these symptoms in daily life, patients may still perform within normal limits on neuropsychological tests of executive function.104 Progressive impairment of executive abilities may lead to job loss or disastrous mismanagement of money. In many cases, it can be difficult to determine which problems in daily life are caused by executive dysfunction as opposed to apathy. This is not surprising given that constructs of the executive functions usually include initiation or “energization” as a component process. Although executive dysfunction is typically thought of as being caused by dorsolateral prefrontal cortical involvement, it can originate in anterior cingulate.
Another important clinical feature of bvFTD is lack of insight. This symptom was considered a core element of the Neary et al.\(^9\) diagnostic criteria but was not included in the new international consensus diagnostic criteria because it was thought to be too difficult to ascertain consistently. Nevertheless, it is well established that many patients with bvFTD, and some patients with semantic dementia (SD), have a striking lack of insight\(^{105-107}\) even when confronted with obvious impairments. Clinically, this can be particularly challenging when the patient refuses to make office follow-up visits because he or she is convinced there is not a problem. Lack of insight in FTD has been associated with right-lateralized ventromedial prefrontal atrophy.\(^{108}\)

Another core feature of bvFTD is personality change. Alterations in personality can be prominent in bvFTD and also in SD.\(^{109}\) Although questionnaire-based instruments to assess classical dimensional personality traits are readily available, changes in personality might be best understood clinically by considering more specific process-oriented functions contributing to personality traits. When faced with a family member who says “my spouse is not the person I married, his/her personality is completely different,” it is incumbent upon the clinician to probe further to ascertain the specific changes being described. Some symptoms may include changes in the expression or comprehension of emotion, social withdrawal or disinhibition, or loss of empathy. In some cases, a previously gruff or aggressive individual becomes docile. The patient’s insight into these changes is often poor. We have reported on a bvFTD patient who developed the Geschwind syndrome of hyperreligiosity, hypergraphia, irritability, and other symptoms.\(^{109}\) Other symptoms that may also be described as personality changes include obsessive-compulsive behaviors, such as hoarding, and those involving changes in appetitive drives, such as sexual, eating, or drinking behaviors.

Despite the inclusion in the 2011 bvFTD diagnostic criteria of “the relative preservation of memory,” memory impairment can be a prominent early feature in some cases of bvFTD,\(^{111,112}\) including those that are pathologically proven.\(^{113}\) In some cases, memory symptoms are reported by the patient and/or family but test performance is normal; this may reflect executive contributions to memory encoding or retrieval in daily life which may be relatively controlled in the office setting.\(^{114}\) In other cases, day-to-day memory is preserved but psychometric test performance is impaired due to the magnitude of executive or semantic deficits, thereby resulting in an overestimation of memory impairment. In our clinical practice, we do not avoid the clinical diagnosis of bvFTD in a patient with well-documented amnesia if the remainder of the clinical presentation is consistent with bvFTD, especially if supported by neuroimaging test results.

Unlike the language-dominant types of FTLD, language may be relatively intact early in the course of bvFTD. This is particularly true on basic neuropsychological tests of language performance. Higher-order language abilities at the level of discourse,\(^{115}\) as well as emotionally laden forms of communication including prosody, irony, sarcasm, and humor, are often abnormal early in the course of bvFTD.\(^{115,116}\) As the disease progresses, semantic and other impairments often become prominent.\(^{117}\) Psychosis has been thought unusual in bvFTD, but the discovery of the C9orf72 expansion has highlighted the common presence of psychosis in patients as well as non-demented family members with this genetic mutation.\(^{118-119}\)

### Progressive Aphasic Subtypes of FTLD

The other major clinical phenotype associated with FTLD involves a primary language disturbance. According to the Neary et al.\(^9\) diagnostic criteria, such a patient would have been diagnosed as having a language-predominant form of FTD (and likely FTLD), and further subtyped into progressive nonfluent aphasia (PNFA) or SD. At present, the approach suggested by the recent international consensus diagnostic criteria for PPA\(^1\) focuses on determining the precise clinical phenotype without reference to the presumed underlying pathology. Three canonical clinical phenotypes of PPA are currently recognized: the nonfluent/agrammatic variant (nfvPPA, which likely captures most of the patients formerly diagnosed with PNFA), the semantic variant (svPPA, which likely captures most of the patients formerly diagnosed with SD), and the logopenic variant (lvPPA). Some patients with clinical phenotype consistent with SD do not meet criteria for svPPA because they present with prosopagnosia or visual object agnosia or with relatively prominent behavioral symptoms and thus do not meet core criteria for PPA. lvPPA is most frequently associated with biomarkers of underlying AD and ultimately AD pathology, and thus would not be considered a major clinical subtype of FTLD. Nevertheless, a minority of lvPPA patients do not demonstrate biomarkers of AD pathology in vivo\(^119\) and in fact have solely FTLD neuropathology post-mortem (usually FTLD-TDP-43).\(^120\) Thus, while lvPPA is often considered nearly synonymous with an atypical language variant of AD, these recent observations support the inclusion of this clinical phenotype as a part—if small—of the FTLD spectrum.

As its name implies, PPA is a disorder that can only be diagnosed when language is the sole of major dysfunction early in the illness, usually considered to be at least 2 years (Table 24-2); when other cognitive dysfunction is clearly present, such as loss of memory for daily events, visuospatial dysfunction, or behavioral symptoms, the diagnosis of PPA cannot be made.\(^121-123\) In some patients, language dysfunction can slowly progress and be the principal impairment for as long as a decade, but in many patients, impairments in other cognitive functions emerge after the first few years.\(^124\)

Although patients with progressive aphasias may have personality, comportmental, and social symptoms, they are, by definition, less prominent than the language impairment early in the course of the disorder. The presence of prominent early neuropsychiatric or behavioral symptoms is generally considered exclusionary for PPA. In spite of this distinction, which is particularly important for clinical research on these disorders, some patients whose diagnosis would be best considered as PPA have prominent early neuropsychiatric or behavioral symptoms (a point discussed briefly in the 2011 diagnostic criteria). Many others have relatively mild but notable symptoms, particularly as PPA progresses to involve abilities beyond language.\(^125\)
Nonfluent/Agrammatic Variant PPA

The core features of nfvPPA are an impairment of grammar and, commonly, defective motor speech production. The characteristics of nonfluent speech are typically an effortful and halting speech with sound errors and distortions, with agrammatism in language production and/or comprehension.141,142 Agrammatism is characterized by omissions of grammatical words and morphemes, reduced production of verbs,128,129 incorrect argument structures, and decreased utterance length and complexity, often with reduced mean length of utterances and fewer embedded structures, and decreased utterance length and complexity, often associated with distorted sound substitutions and additions with length or complexity effects, while "pure" AOS or nfvPPA with prominent AOS are characterized by syllable segmentation and lengthened intersegment durations. Some patients also exhibit limb apraxia or other elements of an extrapyramidal (parkinsonian) syndrome.137 Many others develop these symptoms or others consistent with a CBS or a PSP syndrome as the illness progresses.

The localization of symptoms in nfvPPA is typically linked to the prefrontal rolandic operculum, anterior insula, and possibly the opercular portion of Broca’s area. The diagnosis of imaging-supported nfvPPA indeed requires focal left-sided perisylvian regions involvement, particularly of the inferior posterior frontal gyrus and insula.11,138,139 The involvement of the "dorsal" language pathways appears to be responsible for syntactic dysfunction.140 AOS is associated with neurodegeneration in the left posterior inferior frontal lobe or supplementary motor area, while orofacial apraxia is associated with neurodegeneration in the left middle frontal, premotor, and supplementary motor cortical; and limb apraxia is associated with left inferior parietal lobe damage.137,141

In nfvPPA, neuropsychiatric symptoms are less frequent initially, but as the illness progresses it becomes increasingly common to see apathy, depression, or irritability. In some cases these symptoms are present early in the illness, which may lead to misdiagnosis as a primary psychiatric disorder (often depression).

Semantic Variant PPA

Patients with svPPA develop prominent word-finding difficulty in spontaneous speech, maintaining fluency but with a tendency to rely more on high (rather than specific low) frequency nouns, and exhibiting severe anomia in confrontation naming tasks. As semantic memory loss progresses, it impairs single-word comprehension, impacting the differentiation between within-category subordinate words,142 As the disease progresses, between-category words are affected and concepts become blurred, although speech may still be fluent. Impaired reading of words with irregular spelling is also typical of this disorder.143 Syntactic processing is typically preserved.144 Nonverbal skills are usually minimally affected in the early stages.142

The dominant hemisphere anterior temporal lobe is often prominently atrophic even at initial presentation, with varying degrees of bilateral involvement.143,144 The atrophy predominantly involves inferior and middle temporal gyri, anterior fusiform gyrus, perirhinal cortex, amygdala, and hippocampus,145–149 but the most prominent atrophy appears to be at the tip of the left temporal pole.150 Preserved motor speech and syntactic function reflect the integrity of the dorsal language regions and of the corresponding white matter connections.146,151

SvPPA patients commonly exhibit neuropsychiatric symptoms, often relatively early and in a fairly stereotypical fashion. Many of these symptoms are similar to those of bvFTD, including loss of empathy, changes in eating behavior, compulsive
behavior, and disinhibition. Although these symptoms are highly consistent with FTD, depending on when they begin and how they are reported by informants, it may be difficult for the clinician to be confident in assigning a subtype diagnosis (i.e., bvFTD vs. svPPA vs. SD). The Neary et al.'s diagnostic criteria for FTD included loss of sympathy or empathy and narrowed preoccupations (mental rigidity) as diagnostic features. A aberrant motor behavior is also reported as common in some studies; in our experience this often includes elaborate kinds of movements related to repetitive or compulsive behaviors. Depression is also reported as common in svPPA in some studies; in our experience, however, at least some patients say certain phrases repetitively (i.e., “catch phrases”) that appear to express negative emotion (e.g., “I feel so stupid,” “I used to know that and now I just don’t know anything”), but with minimal affective behavior consistent with depression, and a structured interview with some of these patients’ caregivers reveals little behavior in daily life that appears consistent with a diagnosis of depression. As the degeneration progresses, both anterior temporal lobes as well as the ventromedial and posterior orbital frontal cortices, the insula, anterior cingulate cortex, and amygdala often become involved, overlapping with the imaging features of bvFTD patients.152

Some patients present with semantic impairment that is more prominent for objects, people, or environmental sounds rather than words, suggesting a right-lateralized syndrome that is otherwise very similar to svPPA but likely best classified as SD.153 SD is a broader diagnostic construct that can be considered an umbrella term for patients with svPPA and patients with agnostic and/or amnesic impairments as well as semantic memory loss.

Logopenic Variant PPA

Patients with lvPPA present with variably hesitant speech and typically without articulation deficits, but with many false starts and phonological errors, long word-finding pauses, impaired sentence comprehension and naming, with spared single-word comprehension and nonverbal semantics.150 Patients with this syndrome typically exhibit a conduction aphasia-like deficit in repetition that is attributed to impaired phonological loop functions which is considered a core element of the syndrome.153,154 Since all patients pause when they are attempting to retrieve low-frequency words, and many patients make speech-sound errors and have difficulty understanding of grammatically complex sentences, they may be misdiagnosed as having nfvPPA. But in fact their unconstrained, spontaneous speech is often fluent, the speech-sound errors are phonologic rather than articulatory, and grammatical production and comprehension is not impaired when sentences do not exceed their limited auditory-verbal working memory capacity (or when they are reading or writing). Thus, fluency in lvPPA has been described as “intermediate”154; we prefer to describe them as “variably” fluent. Note that some authors have used the term anomic aphasia to describe patients who fulfill lvPPA criteria but whose repetition is normal.

The localization of neurodegeneration in lvPPA typically involves the left posterior superior and middle temporal gyri, and inferior parietal lobule,126,138,150,154 consistent with the hypothesis of a phonologic short-term memory impairment as the core cognitive deficit. As will be discussed below, this clinical phenotype is usually associated with underlying AD pathology rather than FTLD.

In lvPPA, neuropsychiatric symptoms are relatively infrequent early but increase as the illness progresses and include agitation, anxiety, irritability, and apathy. In many cases we have seen, the clinical phenomenology of neuropsychiatric symptoms appears similar to that seen in typical clinical forms of AD.

DIAGNOSTIC ASSESSMENT OF SUSPECTED FTLD

As with all neurodegenerative diseases, a careful clinical history taken from the patient and a knowledgeable informant is usually the single most important element of assessment. Specific FTD symptom inventories,80,95 such as the Cambridge Behavioral Inventory,153 the Frontal Behavioral Inventory,156 and the Neuropsychiatric Inventory (NPI),157 are very useful in ascertaining symptoms of FTD in a structured manner. Some of these instruments can be given to caregivers in advance as questionnaires, or used to structure an office-based interview. We have developed structured assessment scales for patients with FTD and related disorders that provide semiquantitative ratings of the types and severity of specific language impairments—the Progressive Aphasia Severity Scale (PAS)159—and social impairments—the Social Impairment Rating Scale.158 As mentioned above, we believe it is essential to interview the patient separately from informants. The interview with the patient should include a psychiatric evaluation of mood and affect, thought content (e.g., is there evidence of psychosis?), and insight. Some instruments, such as the Everyday Cognition (Ecog) scale,159 have both patient and informant forms which allows for an assessment of insight by comparing the two.

An important step in history-taking is to try to determine whether the symptoms are interfering with independent function or not (i.e., does the patient have a clinical stage of impairment consistent with dementia or mild cognitive impairment?). Some patients with PPA present with no or minimal functional impairment (problems performing activities that had previously been routine for the person, such as occupational activities or community or household activities). If function is impaired in PPA, by definition it should be attributable to compromised language and not to impairments in other domains of cognition or behavior. We have seen many patients with a progressive agrammatic multidomain syndrome, with prominent aphasia but also impaired executive function, memory, or other functions. It may be possible to clearly document by history or through medical records that such a patient would have met PPA diagnostic criteria previously, but they cannot be diagnosed with PPA currently if these other domains are impaired. In other patients, it may be impossible to determine whether they ever fit into the construct of PPA, and they are best described as having a multidomain dementia with prominent aphasia (we often call this “aphasic dementia” to differentiate it from amnesic dementia).

Because the core symptoms relate to socioaffective function, many patients with bvFTD present after having lost social or occupational function, and therefore would be diagnosed with dementia even if cognitive examination and/or
When a patient is suspected of having PPA, or when communication or speech symptoms are present, it can be very helpful to obtain a consultation with a speech-language pathologist. An evaluation by a speech-language pathologist offers an opportunity to clarify the diagnostic formulation, may provide ideas to develop compensatory strategies, or may help identify and monitor speech or swallowing impairments. Speech pathologists offer a growing array of approaches to the development of treatment approaches for patients with PPA or other forms of FTD (Kortte & Rogalski, 2013).

Neuroimaging and Other Diagnostic Tests

Neuroimaging is an important part of the diagnostic workup of FTD, and has made valuable contributions to our understanding of the specific subtype disorders. Both structural (MRI) and functional (PET, SPECT) neuroimaging may be valuable for the investigation of anatomic, metabolic, or perfusion abnormalities in the spectrum of FTD.

MRI is critical in the diagnostic workup of suspected FTD for both the exclusion of other potential causes of slowly progressive frontal lobe syndromes, such as tumors, cerebrovascular disease, or the newly identified “sagging brain syndrome,” and for the identification of abnormalities consistent with FTD neurodegenerative syndromes. Frontal and/or anterior temporal atrophy is the typical finding, and is often more prominent in the right hemisphere in bvFTD and the left hemisphere in PPA (Figure 24-2A). Metabolic or perfusion imaging can be useful in addition to MRI for the identification of abnormalities when anatomic changes are subtle or undetectable (Figure 24-2B). In some cases, both structural and functional neuroimaging may be normal early in the course of what ultimately declares itself over time as FTD. Electroencephalography is not commonly recommended in the diagnostic evaluation of suspected FTD, but may demonstrate anterior or focal slowing consistent with frontal neurodegeneration.

Cerebrospinal fluid (CSF) biomarkers are being investigated in the clinical conditions thought to be due to FTLD pathology, but are not yet mature enough for use in clinical practice. In some cases, the exclusion of an atypical form of AD can be
helpful by analyzing CSF for amyloid-β and tau. General CSF investigation may be valuable to rule out other neurologic disorders if the patient has atypical features or a more rapid course.

If clinical evidence of motor neuron disease is present, especially if it is subtle, electromyography can provide valuable information regarding the presence of upper or lower motor neuron dysfunction, which may be critical for prognosis (Figure 24-3).

**In Vivo Neuroimaging of Neuropathologic Markers**

With the advent of neuroimaging tracers that bind to specific pathologic molecules, such as Pittsburgh compound B (PiB) for fibrillar beta-amyloid and a growing number of putative tau-binding ligands, it is possible to investigate clinically-pathologic relationships in vivo. Extensive efforts are underway to develop tracers specific for additional pathologic markers. This will surely lead to a revolution in our understanding of the spectrum of FTD. In the first study of FTD with PiB, a comparison was made between PiB tracer uptake in 12 FTD cases, 7 AD cases, and 8 controls. The FTD cases included five patients with behavioral FTD, two with FTD/ALS, four with SD, and one with progressive aphasia. The results indicated that all AD patients had “positive” PiB PET scans, 7/8 controls had negative PiB scans, while 8 of 12 FTD cases had negative PiB PET scans.

Although this initially seemed to be a high number of amyloid-positive FTD cases, it may not be particularly surprising in light of several autopsy studies showing the presence of AD pathology in 20–30% of FTD cases, with or without the presence of additional FTLD-type pathology. The distribution of PiB tracer uptake in these four cases was similar to that typically seen in AD. Two of the cases carried clinical diagnoses of bvFTD, and the other two were clinically diagnosed with SD. Of note, some elements of the cognitive profiles and the FDG-PET metabolic deficits of these four cases showed features more often associated with AD than FTLD. Of the two FTD patients who have come to autopsy in this series, one had a tauopathy and one had a ubiquitinopathy: both were PiB negative.

A large multicenter study of more than 1200 patients with PPA demonstrated that more than 85% of lvPPA patients exhibited amyloid pathology, while only 20% of lvPPA patients demonstrated amyloid pathology and 16% of svPPA patients showed amyloid pathology. At least some cases of likely underlying FTLD pathology in PPA patients may exhibit dual pathology, and thus may have a positive amyloid PET scan.

**CLINICAL COURSE OF FTD**

The early symptoms help determine the major subtype of FTD, but as the disease progresses, involvement of other frontotemporal and subcortical brain regions often result in the development of symptoms characteristic of the other subtypes of the diseases. For example, patients with svPPA may develop disinhibition, compulsivity, and other behavioral symptoms, while
FIGURE 24-3. A 59-year-old man presented with loss of empathy, aggression, lack of insight, executive dysfunction, and word-finding difficulties. Within 1 year of symptom onset he developed dysarthria and dysphagia and was found to have clinical evidence of motor neuron disease with bulbar predominance (tongue weakness, fasciculations, lip weakness, as well as mild shoulder weakness and fasciculations with lower extremity hyperreflexia and extensor plantar responses). Electromyography showed sharp waves, fibrillation potentials, and fasciculation potentials in cervical, thoracic, and lumbar myotomes with long duration, high amplitude, polyphasic potentials with reduced recruitment and rapid firing. (A) MRI demonstrated bilateral (left greater than right) frontal atrophy, quantified with a map of cortical thickness compared to controls. His clinical syndrome lasted 3.5 years from first symptoms to death. (B) Post-mortem examination revealed the expected TDP-43 Type B pathology (TDP-43 immunohistochemistry of dentate gyrus of hippocampus).

CASE VIGNETTE 24.1

A 50-year-old man presented with depression and left-hand apraxia without rigidity, alien hand syndrome, or eye movement abnormalities, followed shortly by executive dysfunction, word-finding difficulty, and memory loss. When he was first evaluated, the neuroimaging examination revealed markedly asymmetric dominant hemisphere FDG-PET hypometabolism and atrophy extending from peri-Rolandic and dorsal parietal cortex into perisylvian cortex and ventral temporal cortex, with relative preservation of frontal cortex and striatum (Figure 24-4). Initial clinical syndromic diagnosis was CBS. Dopaminergic treatments did not change symptoms, as is often the case in CBS. He was treated with occupational therapy, speech-language therapy, as well as psychosocial support and multidisciplinary care planning with him and his family. Surprisingly (given his motor impairments), he was able to enjoy skiing and playing pool as well as a variety of other social and hobby-related activities for several years. His symptoms gradually progressed to include severe asymmetrical hand apraxia with rigidity (resulting in a complete loss of function of his dominant hand), and he also exhibited an increasingly prominent aphasia with dysarthria. Symptoms progressed to include episodic and semantic memory impairment, compulsive behavior, impulsive eating, and agitation. Some of these behavioral symptoms responded to antidepressant and anticonvulsant treatments, and additional behavioral strategies and education and support helped his family develop a structured care plan with the involvement of home health aides and companions. Along with the progression of symptoms, atrophy progressed over a 4-year interval to include ventral and anterior temporal, insular, and posterior frontal cortex (Figure 24-4). Eventually the disease progressed into a terminal phase of severe rigidity with dementia lasting about a year, and he finally passed away in home hospice after an 8-year clinical course. We expected to find CBD pathology, but neuropathological examination identified Pick's disease (FTLD tau pathology, Pick's type). Given the absence of a family history and the identification of this pathology, we counseled the family that this is typically a sporadic condition for which other family members are not likely at elevated risk. To confirm this prediction, sequencing of the MAPT gene was performed and did not reveal any abnormalities.
FIGURE 24-4. A 50-year-old man with a clinical syndromic diagnosis of corticobasal syndrome. The first neuroimaging examination revealed markedly asymmetric dominant hemisphere FDG-PET hypometabolism (A, B, C, left column) and atrophy (A, B, C, right column) extending from peri-Rolandic and dorsal parietal cortex (A) into perisylvian cortex (B) and ventral temporal cortex (C) with relative preservation of frontal cortex and striatum. Along with the progression of symptoms, atrophy progressed from parietal and posterolateral temporal over a 4-year interval to include ventral and anterior temporal, insular, and posterior frontal cortex (D). Although this man's clinical and imaging features pointed toward corticobasal degeneration as the likely etiology, histological examination revealed Pick bodies (E, left) and tau immunoreactive pathology (E, right) consistent with pathological Pick's disease (frontotemporal lobar degeneration tau pathology, Pick type).

bvFTD patients may develop speech, language, and/or semantic deficits.

Overall, survival after diagnosis is typically 6–10 years, with PPA-semantic variant patients having the longest survival. A more recent study suggests a slightly better prognosis for bvFTD patients, with a median survival of 4.2 years from diagnosis. The development of early motor symptoms or signs is a poor prognostic feature in all forms of FTD, as is early language impairment in bvFTD. Recent data suggest that SD patients may commonly have a very slow progression, with 50% of patients alive at 12.8 years after diagnosis in a large cohort of 100 patients. The ultimate development of markers of the specific form of neuropathology may be important for prognostication, with one autopsy study of 71 patients indicating that tau pathology was associated with shorter (3 years) survival than non-tau forms of FTLD pathology (8 years).

In our practice, we always discuss the value of autopsy with family members and with patients if possible (see the Case Vignette as an illustration of the value of autopsy). Despite continued improvements in the use of clinical and biomarker data for probabilistic prediction of FTLD or non-FTLD pathology, every specialized center continues to observe surprising cases. Not only is autopsy information important for providing family members with the greatest detail possible about the patient’s disease, it also contributes in extremely valuable ways to ongoing research efforts.

TREATMENT OF AND CARE PLANNING FOR PATIENTS AND FAMILIES WITH FTD

Once a diagnosis of one of the forms of FTD is made, the clinician unfortunately needs to deliver the news that, at present, there are no disease-modifying therapies for FTD (as is the case for all other major neurodegenerative diseases). Nevertheless, despite the fact that we are not yet able to reverse or slow the progression of FTD and related disorders, these diseases are treatable if we approach the patient and family using a biopsychosocial model of care plan development. Treatment includes empiric pharmacologic management of symptoms, nonpharmacologic management of symptoms, management of comorbid conditions which may exacerbate cognitive-behavioral impairment, psychosocial support, and education of the family and patient. A multidisciplinary team of specialists is instrumental in caring for patients and families suffering from FTD. Pharmacologic and nonpharmacologic management depends on the identification and grading of severity of specific symptoms (including cognitive, behavioral, and motor symptoms), followed by their prioritization and monitoring over time. Once this is done, judicious empiric use of medications can be tackled. At present, no medications are approved for the symptomatic treatment of FTD, but many medications have demonstrated utility in small studies or case series. For example,
selective serotonin reuptake inhibitors or other antidepressants can modulate disinhibition or compulsive behavior, stimulants or pro-dopaminergic agents can sometimes reduce apathy or attentional impairment, and anticonvulsants/mood stabilizers or antipsychotic compounds can ameliorate aggression or agitation. Side effects of these medications may in some cases outweigh benefits, and patients always need close monitoring. Cholinesterase inhibitors are generally not helpful in patients with FTD, and in some cases may exacerbate problem behaviors. Nonpharmacologic symptom management strategies generally require the expertise of an experienced specialist clinician or team. These include speech and language therapy for communication or swallowing issues, occupational therapy for problems with hand-eye coordination or planning that impacts instrumental or basic activities of daily living, physical therapy for gait disorders, and in some cases psychotherapy for the patient. A growing body of evidence supports the utility of speech-language therapy in PPA. A driving assessment is critical, as is the evaluation of financial or health care decision-making capacity. Social work assistance with facilitating disability compensation can be very helpful. Paid or volunteer companions or home health aides to help patients remain active yet safe can be valuable. Day programs or respite residential programs may play important roles at some point in the course of the illness. Advanced care planning discussions should be considered early in the course of the illness. Ultimately, because the myriad of resources that may be helpful to patients and family members can be difficult to identify, it is essential to dedicate time and effort toward specialized education for the patient/family through the clinician or multidisciplinary team or the Association for FTD (http://www.theaftd.org/) or Alzheimer’s Association (http://www.alz.org). Psychosocial support resources can also be valuable for nearly all families and for some patients. Evidence is accruing that caregiver interventions improve quality of life in caregivers of patients with FTD. The development of close links between the FTD specialty care team and the primary care physician is very important to assist in general management, including monitoring comorbid conditions and considering the role of standard prophylactic care in the context of FTD. Finally, it is critical late in the course of the illness to assist patients and families with end of life care, facilitating access to palliative care resources and ideally obtaining nursing home and hospice care at the appropriate time. There continues to be a desperate need for residential or nursing facilities that have the capacity and skill to care for patients with FTD. And although research at present focuses largely on understanding the disease and offers little if any novel putative treatment options for patients with FTD, participation in studies can provide some meaning in an otherwise entirely tragic situation. Ultimately, the quality of the partnership between care providers experienced with FTD and patients/families with these diseases is a critical factor that influences the experience of living with FTD.

Summary and Key Points

- Frontotemporal dementia (FTD) encompasses a spectrum of clinical dementia phenotypes including behavioral variant FTD, primary progressive aphasia (PPA), corticobasal degeneration, progressive supranuclear palsy, and FTD with motor neuron disease or FTD with amyotrophic lateral sclerosis.
- The clinical syndromes of FTD arise from a diverse set of pathological diseases known as frontotemporal lobar degeneration (FTLD), with two major types: FTLD tau and FTLD TDP-43, as well as several rare pathologies.
- Age of onset is usually between 45 and 65, although cases as young as 21 and as old as 85 have been reported.

Multiple Choice Questions

1. The following points are true regarding the pathophysiology of FTLD:
   a. FTLD involves the aggregation of proteins that have important cellular functions which are then disrupted
   b. FTLD involves tau or TDP-43 pathology and possibly interactions between them in some forms of the disease
   c. Amyloid pathology plays a key role in FTLD
   d. Genetic abnormalities in some cases are illuminating FTLD pathophysiologic mechanisms
   e. a, b, and d

2. The clinical presentation of FTD
   a. Often includes memory loss as an early feature
   b. Typically includes prominent behavioral or language symptoms
   c. Often includes a prominent early motor component
   d. Is usually obvious at first evaluation and easy to diagnose
   e. Can easily be confirmed with a blood test
3. The assessment of patients with FTD typically includes all of the following except:
   a. Detailed history
   b. Neurologic and psychiatric exam
   c. Brain MRI
   d. FDG PET
   e. Amyloid PET

4. Evidence supports the following treatment options for some patients with FTD:
   a. Antidepressant medications
   b. Speech-language therapy
   c. Cholinesterase inhibitors
   d. Caregiver support
   e. a, b, and d

**Multiple Choice Answers**

1. **Answer: e**
   As discussed in the pathophysiology section, amyloid does not play a role in FTLD. The other points are correct.

2. **Answer: b**
   Most patients with FTD present with behavioral or language symptoms. Although many patients have memory loss as part of their clinical phenotype, it is not usually the most prominent early feature. Motor symptoms or signs often occur as FTD progresses, but only a minority of cases exhibit motor impairment as an early feature (i.e., PSP, CBS, or FTD-MND). There are no blood tests for pathologic markers of FTLD at present.

3. **Answer: e**
   Although amyloid PET may play a role in ruling out AD in some cases of FTD, it is not part of the typical clinical evaluation at most centers in part because of availability. In many cases, the clinician will be highly confident in the diagnosis after a, b, and c.

4. **Answer: e**
   As discussed in the section on treatment, there is evidence for the use of each of these therapies in at least some patients with FTD or their caregivers. Cholinesterase inhibitors are not effective in treating FTD.

**References**


