Incorporating New Diagnostic Schemas, Genetics, and Proteinopathy into the Evaluation of Frontotemporal Degeneration

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ABSTRACT

Purpose of Review: Within the continuously growing body of knowledge in the field of dementia, frontotemporal degeneration stands out in importance as the second most common cause of early-onset dementia after Alzheimer disease. Neurologists, neuropsychologists, and speech pathologists are particularly involved in the diagnosis and recognition of etiologies for patients with deficits in frontal lobe function and language.

Recent Findings: The recent discovery of a novel mutant gene (C9ORF72) and the new nomenclature adopted for subclassification have significantly promoted our understanding of this disorder.

Summary: This article relates the most recent consensus criteria for diagnosis of the two forms of frontotemporal degeneration (ie, behavioral and primary progressive aphasia variants) to basic neurologic principles and remind clinicians of the neuropsychiatric and neuroradiologic components that clarify frontotemporal degeneration diagnoses and guide management.

FRONTOTEMPORAL DEGENERATION FACTS AND FIGURES

While the term “frontotemporal dementia” has been used to refer to the overall syndrome of neurodegenerative disorders involving mainly the frontal and temporal lobes, more recent diagnostic criteria have promoted a separation of the behavioral and language forms of the overall syndrome into the behavioral variant frontotemporal degeneration (bvFTD) and primary progressive aphasia (PPA) subtypes. The bvFTD subtype can carry the simpler acronym FTD, while each of the PPAs is referred to more specifically as a nonfluent/agrammatic, semantic, or logopenic variant of PPA. Although it is tempting to continue to refer to all of the disorders as FTD since many overlapping symptoms occur over the span of bvFTD and PPA courses of illness, this article will state “frontotemporal degeneration”...
without use of an acronym when referring to both bvFTD and PPA. Some writers use frontotemporal lobar degeneration (FTLD) to refer to the overall syndrome, but others, including the authors of this article, prefer to save the FTLD designation as a neuropathologic diagnosis. Clinicians should be aware that patients and their family advocates shun the term “dementia” and have expressed their preference for FTD to stand for frontotemporal degeneration (www.theaftd.org).

**Epidemiology**

Frontotemporal degeneration is the second most common form of early-onset dementia after Alzheimer disease (AD), with prevalence between 2.7 and 15.1 per 100,000 in adults younger than 65 years. The bvFTD subtype accounts for more than 50% of patients with frontotemporal degeneration and typically presents before the age of 65 years, with an average onset age of 58 years. The nonfluent/agrammatic variant of PPA is the second most prevalent subtype of frontotemporal degeneration, accounting for 25% of cases, but semantic PPA runs a close third, with only a slightly smaller percentage (20% to 25%).

**Etiologies According to Proteinopathy**

Autopsies confirming FTLD can report several types of proteinopathy evidenced by the presence of abnormal, ubiquitinatated protein inclusions in cytoplasm or nuclei of neuronal and glial cells. The majority of reports from neuropathology will conclude one of the following, in order of prevalence: (1) transactive response (TAR) DNA binding protein 43 (TDP-43), (2) hyperphosphorylated tau protein (not the same as in Alzheimer tangles), or (3) fused in sarcoma (FUS) protein. In the last decade, one of the biggest breakthroughs in dementia was the discovery that 80% to 95% of the patients with FTLD who were tau-negative harbored TDP-43 inclusions instead. Especially interesting is the preponderance of TDP-43 inclusions in the von Economo neurons concentrated in the anterior insula.

**Syndromic Symptomatology**

**Behavioral variant frontotemporal degeneration.** Neurologists are trained to recognize patients with frontal lobe dysfunction in the contexts of traumatic brain injury, stroke, or multiple sclerosis. The relationship in time to a head injury, sudden onset, or episodic character of frontal lobe dysfunction distinguishes these etiologies from the gradual onset and progression of a neurodegenerative dementia. When loss of sustained attention, self-monitoring, appropriate task-shifting, abstract thinking, and judgment appear in the context of dementia to a degree that surpasses memory loss or visuospatial impairment, the diagnostician brings bvFTD to the top of the differential diagnosis.

In a patient younger than 65 years at onset of marked behavioral changes or aphasia symptoms and gradual progression over time, a history from an informant is key to ascertaining a diagnosis of bvFTD. Because of the loss of insight and other behavioral and psychiatric symptoms of dementia (BPSD), it may be impossible to finalize a diagnosis of bvFTD without history from an informant who has known the patient well premorbidly.

The 1998 Neary criteria for clinical diagnosis of frontotemporal degeneration provided an important launchpad for researchers to produce convergent studies on the neuroimaging of these dementias and to conduct multicenter trials. The criteria did not allow flexibility to include patients who might be in an early stage of illness, and to address these difficulties in behavioral
neurology clinics, the International Behavioral Variant FTD Criteria Consortium recently developed new consensus criteria for bvFTD, based on multicenter autopsy-confirmed case histories. As shown in Figure 9-1, these criteria now allow for a subclass of possible bvFTD, which represents earlier stages of illness in which neuropsychological testing in high-functioning patients may not reveal executive deficits or in which neuroimaging does not yet support regional atrophy or regional dysfunction.

The core symptoms were specified to distinguish bvFTD from acute medical events or stable conditions such as long-standing psychiatric disease (see Case 9-1). For these diagnostic criteria, “early” refers to symptom presentation within the first 3 years.

For these criteria, a history of apathy may be elicited by asking about a marked change in the patient’s level of motivation, a new passivity, or a lack of spontaneity in the patient’s actions or conversation (see Case 9-2). Patients with early loss of sympathy or empathy have shown poor or absent responsiveness to family members’ needs and feelings, or they no longer relate well to others emotionally. The stereotypies and compulsive/ritualistic behaviors reported in bvFTD range from simple movements (such as clapping) to more complex actions (such as cleaning rituals and hoarding).

**Figure 9-1** The diagnostic process for behavioral variant frontotemporal dementia (bvFTD) according to Rascovsky and colleagues. Note the change from the 1998 Neary and colleagues criteria away from the use of supportive criteria for the equivalent of probable cases in order to diagnose early-stage possible bvFTD and the dropping of blood pressure lability and early incontinence from the list of features. As in accompanying text, clinicians can also consider the bvFTD diagnosis in patients who have onset after age 65, but are encouraged to keep Alzheimer disease high on the differential.
Case 9-1
A 77-year-old, right-handed woman with 13 years of education was referred for possible behavioral variant frontotemporal degeneration (bvFTD). Her husband warned the clinic that she had insisted on completing the history form herself and that he would not challenge her during the appointment. After the appointment, he hid in the basement of their home to submit a history by telephone.

She had a baseline personality of being “the life of the party” and sometimes telling inappropriate jokes to her grandchildren. Diagnoses of depression and anxiety lifted after treatment with citalopram 5 years ago. Since then, memory loss and further behavioral changes had been in place for 3 years. The patient’s husband was most concerned about physically violent behavior related to feelings of frustration: she sometimes slammed fragile items onto the kitchen counter, breaking them and injuring herself. She also sang continuously. She had lost her way in familiar places at times, but her husband felt that she was safe driving a car. She denied requiring assistance with activities of daily living, but her husband had to prompt her to dress appropriately and brush her teeth.

The only family history of neuropsychiatric illness was of paranoid delusions in her eldest sister during adolescence.

The patient’s husband had been quite isolated in caregiving and felt unable to share his concerns about her symptoms or his anxiety, exhaustion, and frustration with family or friends.

On mental status examination, the patient was awake, alert, attentive, articulate, pleasant, and efficient to test. She was even euphoric at times. She scored 28/30 on the Mini-Mental State Examination, missing one verbal recall item and not following all three commands. She scored only 70/114 on the short form of the behavioral neurology assessment (well into the dementia range of scores), which reflected mild difficulty with sustained attention, problems with memory and confrontation naming, and greatly reduced verbal fluency for both F words and animals. She did well on mathematical word problems.

Elemental neurologic examination showed no parkinsonism, a postural tremor in the right more than left hand, and no primitive reflexes. The patient’s gait had a normal base and arm swing; her tandem gait was normal despite her age and history of daily alcohol use until 2 years ago.

MRI of the patient’s brain (Figure 9-2) showed severe atrophy of the temporal lobes only. Single-photon emission computed tomographic (SPECT) scan of the brain reported right greater than

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**Figure 9-2** Brain MRI for Case 9-1. A, Midsagittal T1-weighted view shows no widening of the sulcus above the anterior cingulate (arrows), but B, more lateral sagittal view shows definite anterior temporal lobe atrophy. C, The right temporal horn is more enlarged than the left, and hippocampal atrophy is also more apparent on that side. The degree of atrophy may have made it difficult for nuclear medicine to distinguish mesial from lateral hypoperfusion signal in this patient.

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left hypoperfusion of the temporal lobes but lacked specificity regarding whether the deficit was located more mesially (supportive of Alzheimer disease [AD]) or laterally.

**Comment.** This patient does not meet clinical criteria for bvFTD, although her behavior has been alarming and she has some selective frontal lobe impairment clinically. Her history of having a colorful, outspoken personality makes the current symptoms less of a change in personality than is typically seen in bvFTD. Although the patient appears younger than her stated age, she did have onset after age 65, and at this age, along with memory loss and anomia, the most likely dementia etiology is AD, regardless of the details of the clinical history. However, a significant number of late-onset, autopsy-confirmed frontotemporal degeneration cases have been reported. Vascular dementia is also a possibility, given the patient’s advanced age, but she has been quite healthy and has no other stroke risk factors, and no mention of cerebrovascular disease was made on imaging reports. In this case, neuroimaging did not help make the diagnostic decision.

Management for this patient, even if she were to remain defiant to a diagnosis of dementia, includes addressing some important “collateral damage” issues, including the inappropriateness of her driving given both the severity of her dementia and her aggressive behavior, which could lead to disaster if it were to manifest while she were operating a vehicle. The other important issue in this case is caregiver support; the husband’s approach to the patient’s care is a serious concern. He refused to allow the clinician to call a family meeting to get his children involved, and he chose a very nonconfrontational approach (ie, “Don’t tell her she has dementia”), which has contributed to his isolation and exhaustation. He was advised to take advantage of resources such as outreach programs from the Alzheimer’s Association. The clinician anticipated that medication management would be difficult if the patient’s husband could not be contacted for progress reports by telephone.

In addition, because of her physically violent behaviors, quetiapine is recommended; however, given the black box warnings for atypical antipsychotics, careful explanation of the rationale behind using quetiapine for this patient’s specific symptoms should be specified, and informed consent to use this medication despite the potential risk of early mortality, stroke, or myocardial infarction should be obtained from the husband and documented.

Case 9-2

A 58-year-old, right-handed man with 17 years of education was referred for assessment of functional decline with marked progressive apathy. He had been seeing a psychiatrist since a major depressive episode at age 45. At that time, he was able to continue work as an engineer and his household instrumental activities of daily living (eg, home repairs) in his usual fastidious manner, but by age 55 he began to show declining activity levels. By the time of this referral, he had withdrawn from almost all of his former activities other than watching basketball on television. His current symptoms included marked apathy and hypersomnia (he slept 9 hours each night plus daytime naps for a total of 15 hours a day), but he did not report feelings of sadness, worthlessness, or hopelessness. Prior treatment with selective serotonin reuptake inhibitors had no effect. He had become much more passive than his original personality.

He had not been irritable and showed no signs of social disinhibition; he acted appropriately around other people except for excusing himself from social interactions. He had a new preference for sweets. The patient stated that he felt flat and did not know what to do with himself. Family history was significant for depression in the patient’s father and older sister (responsive to electroconvulsive therapy). Neither parent was known to have had dementia despite surviving into old age.

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Repetitive trips to the bathroom without need can be especially disruptive to the household. Hyperorality and dietary changes include altered craving for sweets, binge eating, increased consumption of alcohol or cigarettes (which may at first be perceived as new substance abuse), and oral exploration of nonfood objects.

A patient meeting only criteria for possible bvFTD may still be functioning with independence in the community, although once bvFTD is suspected as a diagnosis, implications of this progressive...
Dementia should be discussed with the patient with regard to driving privileges, liabilities at work, and long-term care planning. Patients with probable bvFTD exhibit significant functional decline, as described by their caregivers during the history; alternatively, the Clinical Dementia Rating Scale Modified for FTD\textsuperscript{14} or a functional questionnaire\textsuperscript{15} can be used to document or track loss of instrumental and basic activities of daily living.

In order to meet criteria for definite bvFTD, a patient must first meet the criteria of either possible or probable bvFTD and have either (1) histopathologic evidence of FTLD on biopsy or at postmortem or (2) presence of a known pathogenic mutation, such as progranulin or tau (see Genetic Testing, below). Progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) are two additional tauopathies that can cause clinical symptoms of bvFTD.

Some patients may be referred with personality change (eg, apathy and disinhibition) and other features of bvFTD as the chief complaint but will show signs of PSP on neuropsychiatric evaluation. The presentation may resemble bvFTD in early onset age (sixth decade). Otherwise-unexplained falls are the most common symptom of PSP and are required for the clinical diagnosis. In earlier stages, the differentiation between PSP and CBS may be difficult for clinicians, but the onset of falls early—as opposed to in advanced illness—can help to accurately indicate PSP over CBS.\textsuperscript{16} The other main feature is vertical gaze abnormality (ie, increased latency, decreased range of motion, or decreased saccadic speed). In the early stages of PSP, blink rate usually becomes profoundly sparse. Dysarthria, dysphagia, and parkinsonism unresponsive to levodopa therapy are other motor features. Cognitive disturbances include impaired abstract thought and decreased verbal fluency.\textsuperscript{17} The prevalence of PSP was reported as 1.00 to 1.39 per 100,000 of the general population in the United Kingdom and United States.\textsuperscript{18}

Corticobasal syndrome may also present with bvFTD symptoms, and patients develop limb apraxia shortly thereafter.\textsuperscript{19} The “textbook” case of CBS presents as a focal cortical deficit (eg, aphasia, frontal lobe syndrome, or cortical sensory loss) accompanying a progressive asymmetrical movement disorder (eg, limb apraxia, alien-limb phenomenon, bradykinesia, myoclonus, dystonia, or tremor). Cognitive dysfunction eventually reflects frontal\textsuperscript{20} and parietal lobe involvement, consistent with neuroimaging findings of frontoparietal and ipsilateral subcortical abnormalities that are contralateral to the asymptomatically affected limb(s). The onset age can range from the early twenties to the late eighties, with an average age of 50 years. There is little or no evidence to support use of levodopa therapy in CBS, despite parkinsonism.\textsuperscript{21} Corticobasal syndrome can alternatively cause nonfluent/agrammatic PPA.

Another rare tauopathy is argyrophilic grain disease (AGD), which accounts for approximately 5\% of neurodegenerative dementia cases, with an increasing prevalence in the elderly age group. Although the majority of patients with AGD will present with a clinical picture resembling mild cognitive impairment for many years, a small number of patients present with prominent abnormal behavior that may bring bvFTD to mind. If present, the aphasia resembles that seen in AD, transcortical sensory aphasia, as opposed to the three PPA variants described herein. AGD is not yet fully understood, and the diagnosis is usually made through biopsy or autopsy, as opposed to clinically.\textsuperscript{22}

Primary progressive aphasia subtypes. Figure 9-4 shows how a neurologist...
can use fluency, comprehension, and repetition to navigate the diagnostic criteria recently devised by Gorno-Tempini and colleagues.\(^2\) There are (1) nonfluent/agrammatic, (2) semantic, and (3) logopenic variants. An oversimplified rule of thumb is that the nonfluent/agrammatic variant is the least fluent of the three; the semantic variant has the worst comprehension deficit early in the illness; and repetition is a particular impairment for patients with logopenic variant PPA. However, patients frequently manifest signs that meet a few criteria for each of the variants but more criteria for one variant than the other two. Consultation with speech and language pathologists (especially in mildly affected cases) is invaluable, as some of the features of the primary progressive aphasias are difficult to identify without subspecialty training.

Unlike probable behavioral variant frontotemporal degeneration, activities of daily living are maintained well into illness, except those related to language (eg, using the telephone).

The description of logopenic progressive aphasia is new to the consideration of frontotemporal degeneration syndromes, and its inclusion remains somewhat controversial because of the Alzheimer disease pathology found in a fair number of logopenic variant cases.

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**KEY POINTS**

- Consultation with speech and language pathologists (especially in mildly affected cases) is invaluable, as some of the features of the primary progressive aphasias are difficult to identify without subspecialty training.
- Unlike probable behavioral variant frontotemporal degeneration, activities of daily living are maintained well into illness, except those related to language (eg, using the telephone).
- The description of logopenic progressive aphasia is new to the consideration of frontotemporal degeneration syndromes, and its inclusion remains somewhat controversial because of the Alzheimer disease pathology found in a fair number of logopenic variant cases.
articulation planning deficit that can sound like stuttering or word pronunciation distortions. The apraxia of speech may be difficult for neurologists to distinguish from the hypokinetic dysarthria due to Parkinson disease or PSP. The hypokinetic dysarthria of Parkinson disease has a hoarseness and hypophonia; in PSP, there is a nasal, rushed, and slurred aspect to speech production. Consultation from a speech and language pathologist is very helpful, unless the patient has progressed so far into PPA as to be nearly mute and has lost comprehension. While CBS can present with bvFTD features, it has been shown as the underlying cause of nonfluent/agrammatic variant PPA often enough to drive the impression that this variant of PPA will usually show tauopathy at autopsy (Case 9-3).

Semantic variant PPA (formerly known as semantic dementia) may be most easily distinguished by the loss of single-word meaning. Patients will ask the examiner to define commonly used nouns that are part of the neurologic examination—for example, “What is a chair?” after the invitation, “Be seated in that chair.” This aphas can greatly limit the neuropsychiatric evaluation.

### TABLE 9-1 Clinical, Imaging-Supported, and Definite Diagnoses of the Variants of Primary Progressive Aphasia

<table>
<thead>
<tr>
<th>Signs</th>
<th>Nonfluent/Agrammatic Variant</th>
<th>Semantic Variant</th>
<th>Logopenic Variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrammatism</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apraxia of speech</td>
<td>✓</td>
<td>✓</td>
<td>Slow rate of speech with pauses</td>
</tr>
<tr>
<td>Impaired comprehension of syntactically complex sentences</td>
<td>✓</td>
<td>✓</td>
<td>+/−</td>
</tr>
<tr>
<td>Impaired single-word comprehension</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired object knowledge</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired confrontation naming</td>
<td>✓</td>
<td>✓</td>
<td>+/−</td>
</tr>
<tr>
<td>Surface dyslexia or dysgraphia</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired repetition:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single words</td>
<td>✓</td>
<td>✓</td>
<td>+/−</td>
</tr>
<tr>
<td>Phrases/sentences</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Impaired prosody</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraphasia:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic</td>
<td>✓</td>
<td>✓</td>
<td>+/−</td>
</tr>
<tr>
<td>Phonemic</td>
<td>✓</td>
<td>✓</td>
<td>+/−</td>
</tr>
<tr>
<td>Regional imaging abnormality to support diagnosis</td>
<td>Predominant left posterior fronto-insular</td>
<td>Left anterior temporal lobe worse than right</td>
<td>Predominant left posterior perisylvian or parietal</td>
</tr>
<tr>
<td>Type of inclusions seen on neuropathology</td>
<td>Tau more common than TDP-43</td>
<td>TDP-43</td>
<td>Amyloid plaques and neurofibrillary tangles (most common)</td>
</tr>
</tbody>
</table>

**KEY POINT**

- Semantic variant primary progressive aphasia (formerly known as semantic dementia) may be most easily distinguished by the loss of single-word meaning.
Case 9-3
A 50-year-old, right-handed woman with 16 years of education was referred for possible primary progressive aphasia. She reported an approximately 18-month history of slowly progressive difficulties in expressing herself, which were insidious in onset.

She initially could not express herself in long, complex sentences, then with shorter sentences, and now she even struggled with large words. Fatigue exacerbated her difficulties. She had reduced her spontaneous speech, mostly out of embarrassment. She stuttered frequently. Although she had some difficulty articulating, her speech made sense and was understood by other people. Furthermore, she had no difficulty understanding what others were saying to her and specifically had not lost word meaning.

She reported no major changes to her personality. She showed excellent insight into her condition and exercised good judgment; she expressed feeling sad and depressed when thinking about her current difficulties, but this was not a constant mood, and there was no anhedonia. She also reported approximately 1 year of mild weakness and lack of coordination in her left hand.

On examination, the patient was awake, alert, cooperative, and anxious. Overall, her cognitive testing revealed some difficulties with attention and calculation, mild executive dysfunction, and prominent difficulties with expressed language. Despite that, she scored 30/30 on the Mini-Mental State Examination and 24/30 on the Montreal Cognitive Assessment (MoCA), losing one point for calling a camel a “giraffe,” two points for repetition, one point for verbal fluency, one point for abstraction, and one point for delayed verbal recall. On the short form of the behavioral neurology assessment, she scored 87/114, above the cut-point for dementia.

Reduction of phrase length and simplification of grammar were evident in the patient’s spontaneous speech and description of the “cookie theft” picture. She showed surface dyslexia with difficulty in pronouncing orthographically irregular words as tested by the North American Reading Test (eg, simile, lingerie). Her isolated buccal (“ma ma”), lingual (“la la”), and palatal (“koo koo”) sounds were normal, but there was an apraxia of her speech when pronouncing whole words, especially with multiple complex syllables (eg, artillery). Her comprehension was intact at the phrase-length level, but she had mild difficulty with comprehending complex syntactical relationships, especially with multiple prepositional phrases (eg, “This is the book given to the boy by the fireman from the same hometown as the boy’s father”). Her verbal fluency was decreased, particularly for F-word generation (nine words in 1 minute) as opposed to animal-name generation (16 in 1 minute), and her sentence repetition was markedly impaired, although single-word repetition was intact.

The patient performed below expectations for her educational level on tests of abstraction (eg, “How are a man and a tree alike?”) and proverb interpretations. She had difficulty with visuoconstruction and placing the hands in the correct position on a clock.

On the remainder of the neurologic examination, she had very mild bilateral rigidity, slightly elevated in the left arm more than the right, which was elicited with augmentation. Fine finger movements and other rapid alternating movements were reduced in amplitude and precision in the left hand and foot.

Assessments by a speech and language pathologist confirmed deficits in fluency and judgment of semantic associations for abstract words and concepts, phonemic and mixed-phonemic/semantic paraphasias, dyslexia, agrammatic speech output, and speech apraxia with lack of coordination of alternating lip movements. A subsequent formal neuropsychological assessment revealed impairments in verbal fluency, auditory working memory, and left finger-tap, with only selective executive dysfunction and mild impulsivity in responses.

MRI of the patient’s brain showed a stable, small, linear hyperintensity in the posterior limb of the right internal capsule; mild, generalized atrophy; and no diffusion weighting or susceptibility-weighted imaging abnormalities (Figure 9-5). Single-photon emission computed tomographic (SPECT) scan of her brain showed hypoperfusion in the right (but not left) frontal lobe.

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Comment. The most likely diagnosis is a neurodegenerative disease, and the patient’s aphasia resembles a nonfluent/agrammatic progressive variant. However, her rigidity in the left upper extremity and loss of left-hand agility raise suspicion for corticobasal syndrome as the underlying cause of the aphasia, or (less likely) an incipient motor neuron disease.

The finding of right frontal hypoperfusion may indicate that she is right-hemisphere dominant for language, and it may indicate the asymmetry of brain involvement seen in corticobasal syndrome (CBS), which would explain her left-sided motoric difficulties. Other patients have had right limb apraxia to go with nonfluent/agrammatic progressive aphasia caused by CBS.

Patients with speech changes due to Parkinson disease may report lack of fluency, but Parkinson-related speech changes (eg, hypokinetic dysarthria and hypophonia) leave grammar intact. Patients with speech changes due to progressive supranuclear palsy (PSP) also experience hypokinetic dysarthria instead of speech apraxia. Patients with CBS and PSP can both manifest vertical gaze palsy, but those with CBS tend not to have the falls that are required for the diagnosis of PSP.16

The patient responded to active speech and language pathology intervention, as well as 100 mg amantadine twice daily for approximately 1 year; she reported that the amantadine helped with her subjective sense of fluency.24 There was no objective gain observable with this medication, however. She transitioned into use of a communication device on her tablet computer to help communicate, but as her CBS symptoms became more severe, she lost the ability to tap accurately on the screen. Two years after diagnosis, the patient developed a decreased left arm swing. Dysphagia progressed slowly, requiring jejunal tube placement 3 years after receiving the diagnosis of CBS.
**TESTS**

**Neuroimaging**

Given the early age of onset of patients with frontotemporal degeneration, it is important to rule out neoplasm or other mass lesion. Brain MRI is preferred to CT in demonstrating the disproportionate frontal, insular, or anterior temporal lobe atrophy in bvFTD, although structural changes are not necessarily present in all cases or at very early stages of the disease.\(^5,13,25\) In the advanced case of frontotemporal degeneration, neuroimaging might show a preponderance of atrophy in frontal and temporal lobes, but more often patients show the same severe global atrophy as seen in advanced cases of the other neurodegenerative dementias. If moderate to severe white matter hyperintensities are found on MRI, clinicians may consider adult leukoencephalopathy with axonal spheroids as a diagnosis.\(^26\)

With advances in neuroimaging techniques, several tools have emerged that are fairly effective at sorting the patterns of atrophy among different subtypes from each other and from other disorders.\(^27\) However, semiautomated volumetrics are not available through routine clinical MRI facilities, nor are cortical thickness measurements.\(^28\) Attempts to identify the same patterns identified through these methods by visual inspection have failed to show either diagnostic accuracy or inter-rater reliability.\(^29\)

When structural imaging is inconclusive or the patient is still within the first few years of symptom onset, functional neuroimaging may help rule in the diagnosis (but cannot rule it out).\(^30\) Predominant frontal or fronto-temporal hypometabolism on 18F-fluorodeoxyglucose positron emission tomography (PET) or hypoperfusion on 99mTc-hexamethylpropyleneamine oxime (HMPAO) single-photon emission computed tomography (SPECT), as described in the new clinical diagnostic criteria, may precede noticeable atrophy on structural imaging.\(^25,30,31\) Left posterior frontoinsular or left posterior perisylvian or parietal regions may be abnormal in patients with a PPA syndrome.\(^30\)

Another type of functional imaging that is becoming available to clinicians is amyloid imaging. Imaging of typical early-onset cases with frontotemporal degeneration has not revealed any significant amyloid burden,\(^32\) leading some neurologists to foresee a role for Pittsburgh Compound B PET or florbetapir PET in differentiating between AD and frontotemporal degeneration, and this consideration may restrict clinicians’ decisions to expose patients to the radiation involved in PET imaging unless the results can be illuminating.

Patients’ family members may ask about repeat imaging. As with other decisions regarding resource utilization, it may be most appropriate to discuss with the family whether the results of a repeat scan would change the patient’s management. Certainly any unexpected or abrupt changes in symptomatology, new seizure onset, losses of consciousness, or falls with head trauma could warrant reimaging.

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**KEY POINTS**

- Given the early age of onset of patients with frontotemporal degeneration, it is important to rule out neoplasm or other mass lesion.
- When structural imaging is inconclusive or the patient is still within the first few years of symptom onset, functional neuroimaging may help rule in the diagnosis (but cannot rule it out).
- Any unexpected or abrupt changes in symptomatology, new seizure onset, losses of consciousness, or falls with head trauma could warrant reimaging.

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**Formal Neuropsychological Testing**

Depending on the educational level of the patient or on the stage of illness, it may be difficult to elicit the neuropsychological profile of bvFTD or the PPAs with standard bedside testing. Additions to the bedside mental status test that may help in evaluation of a frontotemporal degeneration...
degeneration should assess frontal lobe function. It may be more helpful for the examiner to monitor the quality of performance for sustained attention; response variability, set shifting, and mental flexibility; monitoring and utilization of feedback; and sequencing than to concentrate on total scores for the instruments administered. Clinicians may wish to administer the Frontal Assessment Battery along with the Mini-Mental State Examination or the Montreal Cognitive Assessment as a fairly time-efficient way to glimpse the frontal lobe functions listed above.

Early in the illness, the patient may be able to respond well enough to score within normal limits on tests such as the MMSE or the MoCA, but the quality of performance may betray the neuropsychological profile sought for the diagnosis of frontotemporal degeneration, especially in the case of bvFTD.

When bedside evaluation fails to shed light on the diagnosis, consultation with a neuropsychologist can be helpful. There are limitations to valid formal neuropsychological testing, however. They include a need for a modicum of cooperation from the patient and clear communication between the examiner and the patient. The patient’s behavioral disturbances cannot keep him or her from participating; language must be intact to at least show validity of the MMSE score; and a professional translator, not family member, may need to be arranged for the testing to be valid.

EMG
EMG is not routinely requested in an evaluation for frontotemporal degeneration unless there is suspicion of motor neuron disease (MND) from a combination of upper and lower motor neuron features on the elemental neurologic examination. Symptoms of bvFTD may precede, follow, or coincide with the onset of motor neuron symptoms. In one cohort of 40 patients with frontotemporal degeneration, five patients (12.5%) had EMG results confirming MND but not necessarily ALS. Of the five, three had bvFTD and two had nonfluent progressive aphasia by 1998 Neary criteria.

Conversely, when neuropsychological disturbances were evaluated in patients diagnosed primarily with sporadic ALS, 5% met criteria for bvFTD and 9% met criteria for a primary progressive aphasia by the 1998 Neary criteria. Patients meeting criteria for both frontotemporal degeneration and ALS have the shortest survival of all frontotemporal degeneration subtypes, with a mean survival of 2 to 3 years from the onset of first symptoms.

Speech and Language Pathology
Given the specifics of the new diagnostic criteria for PPA, speech and language pathology (SLP) consultation can assist greatly in the differentiation among variants of PPA; this evaluation can also help distinguish the aphasia seen in frontotemporal degeneration from the anomia and semantic deficits seen in AD.

Genetic Testing
Families who are alerted to the possibility of frontotemporal degeneration developing in future generations frequently ask the neurologist to order genetic testing. A referral to a genetics counselor should precede any collection of samples for genetic testing, unless the testing is done for research purposes and the results will not be disclosed to participants. The impact of genetic results (even if negative) is different for each member of the family, and the genetic counselor will explain the importance of identifying who should be privy to the results and educate the patient about how a negative result relates to the diagnosis. A negative result will not rule out frontotemporal degeneration.

KEY POINTS
- It may be more helpful for the examiner to monitor the quality of performance for sustained attention; response variability, set shifting, and mental flexibility; monitoring and utilization of feedback; and sequencing than to concentrate on total scores for the instruments administered. Clinicians may wish to administer the Frontal Assessment Battery along with the Mini-Mental State Examination or the Montreal Cognitive Assessment as a fairly time-efficient way to glimpse the frontal lobe functions listed above.
- Symptoms of behavioral variant frontotemporal degeneration may precede, follow, or coincide with the onset of motor neuron symptoms.
- A referral to a genetics counselor should precede any collection of samples for genetic testing, unless the testing is done for research purposes and the results will not be disclosed to participants.
degeneration; it may instead indicate that the patient carries an as-yet-untied mutation that has caused his or her illness. Not all patients with family histories of similar symptoms, Parkinson disease, ALS, or primary psychiatric disorder have positive genetic testing. Up to 40% of patients with autopsy-confirmed FTLD have a history that is suggestive of familial transmission, with roughly 10% of patients showing an autosomal dominant inheritance pattern. Positive family histories are most commonly elicited from patients with bvFTD and frontotemporal degeneration with ALS and infrequently from patients with semantic dementia.

Because it is rare for a patient with frontotemporal degeneration to have any of the known mutations without a positive family history, genetics clinics will generally consider the patient eligible for testing only if he or she had an early age of onset and at least one affected first-degree relative. Genetic testing should not be considered a tool for differentiating between frontotemporal degeneration and AD, since so many cases may carry either type of proteinopathy (eg, TDP-43 versus amyloid plaques and neurofibrillary tangles) without also carrying one of the few known mutations for these dementias. A significantly greater proportion of frontotemporal degeneration cases than AD cases have known genetic mutations. The three genes that may be sequenced at the lab for frontotemporal degeneration are the microtubule-associated protein tau (MAPT), progranulin (GRN), and C9ORF72. The first two genes account for 10% to 20% of familial cases and are both located on chromosome 17q21. The most common clinical phenotype associated with both MAPT and GRN mutations is bvFTD, although a more varied clinical spectrum has been associated with GRN mutations, including diagnoses such as PPA and CBS. A major recent discovery identified C9ORF72, which appears to be the most common genetic abnormality both in familial bvFTD (11.7% of cases) and ALS (23.5%). This new mutation is an expansion of a noncoding GGGGCC hexanucleotide repeat located in chromosome 9p. Where mutations in MAPT are associated with deposition of the hyperphosphorylated protein tau, both the GRN and C9ORF72 gene mutations are associated with deposition of TDP-43.

Other rare mutations explain less than 1% of familial FTLD. Mutations in the gene encoding valosin-containing protein on chromosome 9p13 can cause a syndrome associated with Paget disease and inclusion body myositis. Mutations in the charged multivesicular body protein 2B (CHMP2B) on chromosome 3p11 are linked, like GRN and C9ORF72, to MND and ALS.

CSF biomarkers
There is no CSF biomarker specific for the diagnosis of frontotemporal degeneration.

TREATMENT
There is no cure or disease-modifying therapy approved specifically for frontotemporal degeneration. Current management strategies rely on symptomatic pharmacologic treatment and nonpharmacologic approaches to improve quality of life for patients with frontotemporal degeneration and to mitigate the stress burden perceived by their caregivers.

Pharmacologic
Readers are referred to the 2010 review by Kaye and colleagues for rationales behind drug categories used for symptoms of frontotemporal degeneration and a summary of the levels of evidence to support those prescriptions.

KEY POINTS
- Not all patients with family histories of similar symptoms, Parkinson disease, ALS, or primary psychiatric disorder have positive genetic testing.
- Positive family histories are most commonly elicited from patients with behavioral variant frontotemporal degeneration and frontotemporal degeneration with ALS and infrequently from patients with semantic dementia.
- The most common clinical phenotype associated with both MAPT and GRN mutations is behavioral variant frontotemporal degeneration, although a more varied clinical spectrum has been associated with GRN mutations, including diagnoses such as primary progressive aphasia and corticobasal syndrome.
- A major recent discovery identified C9ORF72, which appears to be the most common genetic abnormality both in familial behavioral variant frontotemporal degeneration (11.7% of cases) and ALS (23.5%).
KEY POINTS

- The clinical trial yielding the highest level of evidence (through a randomized, double-blind, placebo-controlled crossover trial) in frontotemporal degeneration used trazodone at a dose of 100 mg orally three times a day.

- One challenge for the clinician is to determine whether the behavioral and psychiatric symptoms of dementia are a manifestation along the anxiety spectrum (including obsessive-compulsive features) or represent agitation.

- Acetylcholinesterase inhibitors developed to improve symptoms of Alzheimer disease do not seem to be effective in managing symptoms of frontotemporal degeneration, perhaps because the cholinergic neurons in the nucleus basalis of Meynert are relatively spared in frontotemporal degeneration.

- Regardless of the medication prescribed, it behooves the clinician to make sure that the caregiver understands the symptoms targeted by the medication so that there can be an ongoing dialogue about whether the medication is working or is still indicated.

Clinical trials have been mainly negative, and the few positive results are highlighted below. A more general review about neuroprotective agents has been written by Lauterbach and Mendez. Selective serotonin reuptake inhibitors (SSRIs) have shown some success in treating compulsions and carbohydrate cravings in patients with frontotemporal degeneration, although many of these studies were open-labeled and not controlled trials. The clinical trial yielding the highest level of evidence (through a randomized, double-blind, placebo-controlled crossover trial) in frontotemporal degeneration used trazodone at a dose of 100 mg orally three times a day for a mixed group of BPSD. Because obsessive-compulsive behaviors can be among the top challenges for caregivers, it is worth noting a recent case series of clomipramine responders. One challenge for the clinician is to determine whether the BPSD are a manifestation along the anxiety spectrum (including obsessive-compulsive features) or represent agitation. Medication recommendations for either of these can differ (anxiolytics versus sedatives), but empirical treatment recommendations for them can cut across dementia etiologies.

Patients who do not respond to SSRIs and who show aggressive or delusional behaviors may benefit from low doses of atypical antipsychotic drugs such as olanzapine, quetiapine, or risperidone. Typical and atypical antipsychotic drugs known to result in extrapyramidal side effects should be avoided, since those with advanced frontotemporal degeneration are likely to show parkinsonism. Maher and colleagues recently reported the numbers needed to harm to remove stimuli and avoid the associated behaviors, repetitive and purposeless behaviors such as pacing and bruxism can be more challenging to relieve. One of the most influential changes in behavioral management has been the shift away from medical

Nonpharmacologic

While a patient’s sexual disinhibition and hyperorality generally result in caregivers making changes to the environment to remove stimuli and avoid the associated behaviors, repetitive and purposeless behaviors such as pacing and bruxism can be more challenging to relieve. The numbers needed to harm may be useful in obtaining informed consent from lay substitute decision-makers to use these medications (as in Case 9-2). Acetylcholinesterase inhibitors developed to improve symptoms of AD do not seem to be effective in managing symptoms of frontotemporal degeneration, perhaps because the cholinergic neurons in the nucleus basalis of Meynert are relatively spared in frontotemporal degeneration. Furthermore, acetylcholinesterase inhibitors may cause agitation in patients with frontotemporal degeneration and are particularly dangerous for patients with frontotemporal degeneration with MND, since these medications may cause increased production of oral secretions.

Regardless of the medication prescribed, it behooves the clinician to make sure that the caregiver understands the symptoms targeted by the medication so that there can be an ongoing dialogue about whether the medication is working or is still indicated.

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models of treatment for BPSD toward the reconceptualization of BPSD as responsive behaviors. Gentle, persuasive approaches are being taught to long-term care facility staff, companions, and family members to address these behaviors without using chemical or physical restraints.\(^5\) When caregivers begin with the assumption that an unusual or dysfunctional behavior is the patient’s way of signaling an unmet need, they can open the door to creative thinking about how to address those behaviors (for an example of an online resource for caregivers, see [http://www.marep.uwaterloo.ca/products/managing.html](http://www.marep.uwaterloo.ca/products/managing.html)).

**CONSULTATIONS FOR MANAGEMENT**

**Speech and Language Pathology**

SLP interventions for patients with PPA are often appreciated by the patient and family, even if the temporary gains it offers are eventually overwhelmed by the illness. Swallow evaluations conducted by an SLP specialist later in the illness can help safeguard quality of life regarding nutrition, prevention of infectious disease, and end-of-life planning.

**Occupational, Physical, and Recreational Therapies**

Clinicians naturally perceive a role for occupational therapy in the context of limb apraxia in CBS and PSP, but tips on feasible activities to offset BPSD may also be gleaned from the experience.\(^5\) In addition to occupational therapy, physical therapists may be important allies for maintaining safe ambulation and mobility as a frontotemporal degeneration proceeds. Recreational therapists are helpful in community, day program, and hospital settings to identify some degree of meaningful activity that can help distract the patient from BPSD. The day program for frontotemporal degeneration at the authors’ institution was created through the hire of more recreational therapy staff, as opposed to more nursing.\(^5\)

**Supporting Family and Caregivers**

In the absence of a cure and the presence of a dementing illness that can go on for more than a decade, providing support to family members and caregivers is a crucial part of the ongoing care in frontotemporal degeneration. The equivalent of the Alzheimer’s Association for these families is the Association for Frontotemporal Degeneration ([www.theaftd.org](http://www.theaftd.org)). This organization provides education and support to caregivers, caregiver support group leaders, and health care professionals seeking more information about frontotemporal degeneration.

Because patients with early-onset dementia may have children with a wide range of ages who are active informal caregivers, there is a need for groups that support children and emphasize balance between growing up and caregiving.\(^5\) Online resources for children and their well parents are available through [www.theaftd.org](http://www.theaftd.org), [www.lifeandminds.ca/whendementiaisinthehouse](http://www.lifeandminds.ca/whendementiaisinthehouse), and [http://research.baycrest.org/chow-lab](http://research.baycrest.org/chow-lab).

Behavioral changes figure prominently in the disease, so the safety of the patient and those with whom he or she interacts must be a primary concern. Having a social worker familiar with the in-home, financial, and long-term planning needs of these families is a valuable resource for clinics managing these patients. As with all types of dementia, removing dangerous items from the home (eg, firearms), deactivating driving privileges, and limiting access to bank accounts must be facilitated by the health care team. Staff at caregiver support agencies often do not have the authority to write letters to officials or

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**KEY POINTS**

- One of the most influential changes in behavioral management has been the shift away from medical models of treatment for behavioral and psychiatric symptoms of dementia toward the reconceptualization of behavioral and psychiatric symptoms of dementia as responsive behaviors.
- Because patients with early-onset dementia may have children with a wide range of ages who are active informal caregivers, there is a need for groups that support children and emphasize balance between growing up and caregiving.
bank managers to explain the illness and the family’s special needs. The social worker or case manager can also prepare families for end-of-life decisions or organize family meetings to bring the clinician, a nurse, and important decision-makers for the patient together. It may be useful to hold such family meetings shortly after the diagnosis has been made, and again as the cadence of illness is shifting more clearly toward end-of-life decision-making. At the current level of knowledge, it is difficult to anticipate with accuracy any patient’s survival at the outset of frontotemporal degeneration, but reviewing where the patient is relative to landmarks of behavioral disturbance, loss of motivation and communication, and withdrawal from his or her former sphere of activities and interests can help families understand where they are in the course of illness and what the next 2 years may bring. Caregivers for all dementias are able to cope with their responsibilities longer and better with counseling (even if by phone) and opportunities for respite (whether by day program or a formal overnight respite facility).

FUTURE DIRECTIONS

Imaging researchers are exploring the diagnostic utility of diffusion tensor imaging and resting-state functional MRI as sequences that can be added onto a clinical structural MRI without adding so much scan time as to make the procedure intolerable to patients with BPSD. Abnormalities in the salience network, which subserves social decision-making and emotional responses and can be evaluated through resting-state functional MRI were first described by Zhou and colleagues and show promise not only in differentiating bvFTD from AD, but also in indicating how network coherence is lost over the course of the illness. One strategy for future therapeutic modalities would target proteinopathies. Thus far, clinical trials for tauopathy related to frontotemporal degeneration have focused on PSP, because it is a quicker model of dementia due to tauopathy. Results of these clinical trials should be available within the next few years. It is hoped anti-TDP-43 interventions will also become available. Patients interested in trial enrollment can be referred to www.clinicaltrials.gov for IRB-approved clinical trial details that are searchable by diagnosis and geographic location.

The authors also anticipate more evidence to support or refute the role of prions in the spread of neurodegenerative disorders, including frontotemporal degeneration. Wong and colleagues are hopeful that prions can be counteracted with antibody therapy, and this could be an exciting new modality of intervention for all types of dementia.

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