REVIEW ARTICLE

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Behavioral Variant Frontotemporal Dementia

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ABSTRACT

PURPOSE OF REVIEW: This article describes the clinical, anatomic, genetic, and pathologic features of behavioral variant frontotemporal dementia (bvFTD) and discusses strategies to improve diagnostic accuracy, emphasizing common pitfalls to avoid. Key aspects of management and the future of diagnosis and care for the disorder are highlighted.

RECENT FINDINGS: BvFTD is a clinical syndrome, not a disease. Patients with the syndrome share core symptoms that reflect degeneration within the most consistently affected brain regions, but accompanying features vary and reflect the precise topography of regional degeneration. The clinician must distinguish a bvFTD syndrome from psychiatric illness and other neurodegenerative syndromes that feature a prominent behavioral component. Antemortem prediction of pathologic diagnosis remains imperfect but improves with careful attention to the clinical details. Management should emphasize prevention of caregiver distress, behavioral and environmental strategies, symptom-based psychopharmacology, and genetic counseling.

SUMMARY: BvFTD is an important and challenging dementia syndrome. Although disease-modifying treatments are lacking, clinicians can have a profound impact on a family coping with this disorder. Treatment trials are under way for some genetic forms of bvFTD. For sporadic disease, pathologic heterogeneity remains a major challenge, and ongoing research seeks to improve antemortem molecular diagnosis to facilitate therapeutic discovery.

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RELATIONSHIP DISCLOSURE:
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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Seeley discusses the unlabeled/investigational use of medications for the treatment of behavioral variant frontotemporal dementia, none of which are approved by the US Food and Drug Administration.

INTRODUCTION

The behavioral variant of frontotemporal dementia (bvFTD) is a devastating neurodegenerative syndrome that most often arises in midlife, with a mean age at onset around 58 years but a range from the twenties to the nineties.[1] Prevalence peaks in the early sixties at about 13 per 100,000.[2] The disorder belongs to a larger heterogeneous class of clinical syndromes, the frontotemporal dementias, which are united by their links to underlying frontotemporal lobar degeneration (FTLD) pathology. BvFTD, in which social and emotional functions slowly decline, is the most common frontotemporal dementia (FTD) syndrome, accounting for roughly 50% of all FTD patients.[1]

As a species, humans vary widely in their social-emotional aptitudes. Behaviors that represent a drastic change for one person may represent the baseline personality quirks, routine indiscretions, or stress responses of another. BvFTD symptoms also overlap with those seen in psychiatric diseases, creating further challenges for clinicians seeking to make an early bvFTD diagnosis. By the time a patient is cognitively impaired, care must be taken to distinguish bvFTD from other neurodegenerative disorders, most often an Alzheimer-type dementia, in which prominent frontal/neuropsychiatric features can arise. Attention to the clinical details, family history, neurologic signs, neuropsychology, and brain imaging can help neurologists navigate the diagnostic landscape for patients with a prominent behavioral change in mid to late life.

Upon reaching a bvFTD syndromic diagnosis, the clinician must formulate a pathologic differential diagnosis. The list of potential causes includes all the many distinct FTLD histopathologic subtypes as well as Alzheimer disease (AD) and, rarely, other neurodegenerative diseases. Although only autopsy can identify the specific cause, narrowing the list during a patient's life can inform prognosis, render some costly diagnostic tests unnecessary, influence genetic testing and counseling, and guide psychopharmacologic treatment and referral to clinical trials. Indeed, the advent of molecule-specific therapies will require that the specific cause of a patient's bvFTD is identified during life and early enough in the course to make intervention desirable.

KEY POINTS

- **Behavioral variant frontotemporal dementia (bvFTD) is an important disorder than can be difficult to recognize, in part because of the wide normative variation in social-emotional functions and the long list of disorders that affect those functions.**
- **BvFTD is a syndrome, not a disease, and clinicians who diagnose bvFTD should generate a differential diagnosis.**
- **BvFTD presents with slowly progressive decline in social and emotional functions.**
- **BvFTD core diagnostic features reflect degeneration of networked structures, typically including the anterior insula, anterior cingulate and adjacent medial prefrontal cortices, amygdala, striatum, and thalamus.**

CLINICAL AND ANATOMIC FEATURES

The early manifestations of bvFTD are subtle, insidious, rarely reported by the patient, and often mistaken for a "midlife crisis" or depression or other psychiatric illness.[3] Recurrent job loss and unanticipated marital discord are common. These outcomes stem from bvFTD's central features: (1) loss of motivation toward previously valued interests and activities (ie, apathy) and (2) a loss of social grace, resulting from deficits in response inhibition (ie, disinhibition) and compassion (sympathy, empathy, and prosociality). Pervasive errors of omission and commission result. Patients may abandon family duties; approach strangers (including children) with unwanted questions or other interpersonal boundary violations; or tactlessly comment on others' weight, attractiveness, or position in a social hierarchy. A spouse's major life events (eg, cancer diagnosis, death in the family, job loss) may be ignored or trivialized. Other common features include repetitive and compulsive or even ritualistic behaviors, a predilection for sweets, and relentless overeating. These behavioral features are the most critical to diagnosis and form the heart of prevailing bvFTD clinical diagnostic criteria (TABLE 4-1).[4] Research on brain-behavior relationships in bvFTD has clarified important aspects of human social and emotional function, ranging from emotion reactivity and regulation to autonomic, nociceptive, reward, and error processing. For further reading, reviews focusing on this rich literature are available.[5–8]

What neurodegenerative anatomic lesion gives rise to the core bvFTD features? The earliest[9] and most consistent[10] atrophy in bvFTD, regardless of the underlying cause,[11] involves the anterior cingulate cortex (pregenual and subgenual), anterior insula (ventral [ie, frontoinsular] and dorsal), striatum, amygdala, hypothalamus, and thalamus. These interconnected brain regions form a salience network in humans that represents the homeostatic relevance (ie, salience) of ambient

internal and external stimuli so that appropriate visceral-emotional-autonomic, behavioral, and cognitive responses can be deployed (FIGURE 4-1).[12] For success in social contexts, these diverse brain resources must be mobilized in a dynamic, time-sensitive manner that is tuned in response to rapidly evolving conditions. Perhaps not surprisingly, then, the system can break down in multiple distinct ways yet still manifest as bvFTD. As in all of neurology, how the system breaks depends on where it breaks, and where it breaks can help determine or predict the specific underlying disease process.

TABLE 4-1

Research Criteria for Behavioral Variant Frontotemporal Dementia[a]

Possible Behavioral Variant Frontotemporal Dementia (bvFTD)

Three of the following as persistent or recurrent features:

- **A** Early behavioral disinhibition
- **B** Early apathy or inertia
- **C** Early loss of sympathy or empathy
- **D** Early perseverative, stereotyped, or compulsive/ritualistic behavior
- **E** Hyperorality and dietary changes
- **F** Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions

Probable bvFTD

All of the following:

- **A** Meets criteria for possible bvFTD
- **B** Exhibits significant functional decline (by caregiver report, Clinical Dementia Rating, or Functional Activities Questionnaire)
- **C** Imaging results consistent with bvFTD:
  - **C1** Frontal and/or anterior temporal atrophy on MRI or CT
  - **C2** Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

bvFTD With Definite Frontotemporal Lobar Degeneration (FTLD) Pathology

All of the following:

- **A** Meets Criterion A for probable bvFTD
- **B** Histopathologic evidence of FTLD on biopsy or postmortem
- **C** Presence of a pathogenic mutation known to cause FTLD

Exclusionary Criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD but must be negative for probable bvFTD:

- **A** Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders
- **B** Behavioral disturbance is better accounted for by a psychiatric diagnosis
- **C** Biomarkers strongly indicative of Alzheimer disease or other neurodegenerative process

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

[a] Modified with permission from Rascovsky K, et al, Brain.[4] © 2011 The Authors.

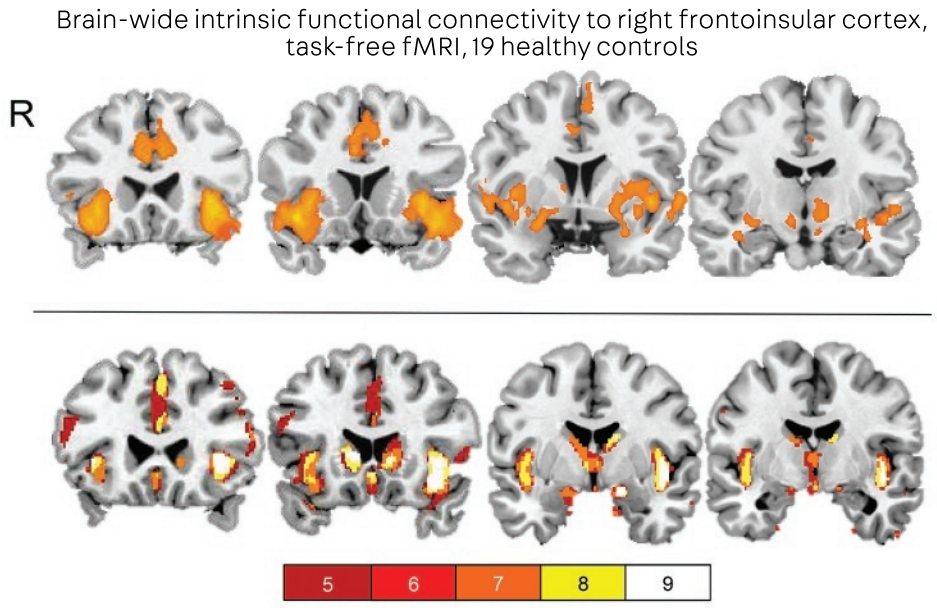

FIGURE 4-1

Network-patterned regional degeneration in behavioral variant frontotemporal dementia (bvFTD). BvFTD results from several distinct neuropathologic causes. In the University of California San Francisco Neurodegenerative Disease Brain Bank, the nine most common are frontotemporal lobar degeneration with transactive response DNA-binding protein 43 (TDP-43)–immunoreactive inclusions (FTLD-TDP) Types A through C and unclassifiable, Pick disease, corticobasal degeneration, progressive supranuclear palsy, atypical FTLD with ubiquitin-immunoreactive inclusions (aFTLD-U), and Alzheimer disease. Overlap analysis across these diverse diseases using voxel-based morphometry revealed core structures atrophied in all nine (*white shading, bottom row*),[11] which recapitulate the major nodes of the salience network, defined using task-free functional MRI (fMRI) (*top row*).[12]

Top row reprinted from Seeley WW, et al, Neuroscientist.[5] © 2012 SAGE Publications.

KEY POINTS

- **Features that develop less frequently in patients with bvFTD reflect variable involvement of additional brain regions.**
- **Patients with bvFTD often develop prominent motor deficits of various types later in the course of the syndrome.**

Beyond the core behavioral features, patients variably develop additional symptoms and deficits that relate to degeneration in specific brain structures: (1) distractibility, disorganization, mental rigidity, and other forms of executive dysfunction (dorsolateral prefrontal cortex); (2) semantic loss, especially for emotions and faces (right more than left anterior temporal lobe); (3) aphasia, often manifesting as an abulic, adynamic aphasia (left anterior midcingulate and presupplementary motor area); (4) memory loss (entorhinal-hippocampal complex); and (5) motor impairment that may include parkinsonism (substantia nigra, striatum), oculomotor control problems (frontal eye fields, dorsal midbrain), or motor neuron disease (upper and lower motor neurons). Uncommonly, but more often in inherited bvFTD, patients will develop some combination of alexia, agraphia, acalculia, anomia, and visuospatial dysfunction resulting from lateral posterior parietal involvement. Attention to these additional features can be one key to making an accurate antemortem prediction of the underlying neuropathology (TABLE 4-2).

GENETICS AND PATHOLOGY

BvFTD may result from any of the known FTLD-causing genetic mutations and any of the myriad FTLD histopathologic subtypes as well as AD and (very rarely)

TABLE 4-2 **Behavioral Variant Frontotemporal Dementia Symptom Characteristics**

Symptom/Feature	Anatomy	Frequency	Pathology Predicted
Apathy[a]	Medial frontal, anterior cingulate cortex	High (~80%)	All
Disinhibition[a]	Ventral anterior insula, orbitofrontal	High (~80%)	All
Repetitive/compulsive behavior[a]	Ventral striato-pallidum	High (~80%)	All
Change in eating behavior[a]	Anterior insula, ventral striatum, hypothalamus	High (~80%)	All
Loss of sympathy/ empathy[a]	Anterior temporal, ventral anterior insula	Moderate (~50%)	All
Frontal-predominant neuropsychological deficits[a]	Dorsolateral prefrontal	Occasional (~30%)	All
Motor neuron disease	Upper and lower motor neurons	Occasional (~30%)	TDP-B, TDP, unclassifiable
Oculomotor control problems	Dorsal midbrain, frontal eye fields	Occasional (~25%)	Progressive supranuclear palsy, corticobasal degeneration
Semantic loss for people, emotions, words	Anterior temporal	Occasional (~20%)	TDP-C>>Pick disease
Prominent episodic amnesia	Entorhinal-hippocampal	Low (<10%)	TDP-A or TDP-B with hippocampal sclerosis
Nonfluent or adynamic aphasia	Left frontal operculum, pre-supplementary motor area/anterior cingulate cortex	Low (<10%)	Corticobasal degeneration, progressive supranuclear palsy, Pick disease. or TDP-A/B
Alexia, agraphia, acalculia, visuospatial dysfunction	Lateral parietal	Low (<10%)	TDP-A (*GRN* or *C9orf72*), TDP-B (*C9orf72*)
Onset before age 40	NA	Low (<10%)	aFTLD-U (FTLD-FUS) or inherited FTLD

aFTLD-U = atypical FTLD with ubiquitin-immunoreactive inclusions; FTLD = frontotemporal lobar degeneration; FTLD-FUS = frontotemporal lobar degeneration with fused in sarcoma-immunoreactive inclusions; NA = not applicable; TDP = frontotemporal lobar degeneration with transactive response DNA-binding protein 43 (TDP-43)-immunoreactive inclusions; TDP-A = frontotemporal lobar degeneration with TDP-43-immunoreactive inclusions Type A; TDP-B = frontotemporal lobar degeneration with TDP-43-immunoreactive inclusions Type B; TDP-C = frontotemporal lobar degeneration with TDP-43-immunoreactive inclusions Type C.

[a] Core criteria for behavioral variant frontotemporal dementia.[4]

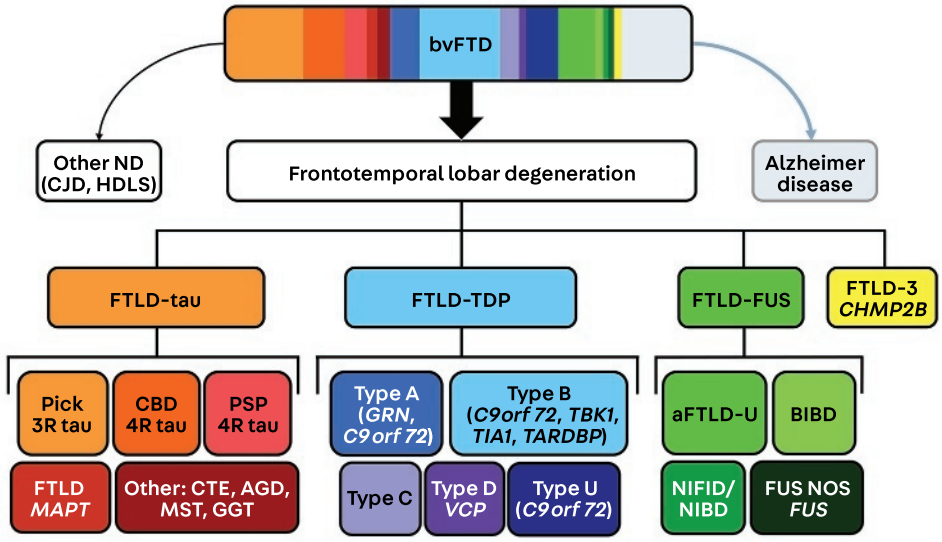

FIGURE 4-2

Genetic and pathologic spectrum of behavioral variant frontotemporal dementia (bvFTD). Most patients with bvFTD show underlying frontotemporal lobar degeneration (FTLD) pathology at autopsy. Color-coded bars within the bvFTD box depict the approximate proportion of patients whose syndrome results from each of the neuro pathologic entities shown. Embedded genetic causes of each pathologic diagnosis are shown in parentheses insofar as the relevant diagnosis can also be seen in sporadic bvFTD. Conversely, for the genes not in parentheses, the pathologic disease only results from a pathogenic variant in that gene.

3R = 3-repeat; 4R = 4-repeat; aFTLD-U = atypical frontotemporal lobar degeneration with ubiquitin-immunoreactive inclusions; AGD = argyrophilic grain disease; BIBD = basophilic inclusion body disease; CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; CTE = chronic traumatic encephalopathy; FTLD = frontotemporal lobar degeneration; FTLD-FUS = frontotemporal lobar degeneration with fused in sarcoma–immunoreactive inclusions; FTLD-tau = frontotemporal lobar degeneration with tau-immunoreactive inclusions; FTLD-TDP = frontotemporal lobar degeneration with transactive response DNA-binding protein 43 (TDP-43)–immunoreactive inclusions; FUS = fused in sarcoma; GGT = globular glial tauopathy; HDLS = hereditary diffuse leukoencephalopathy with axonal spheroids; MST = multisystem tauopathy; ND = neurodegenerative; NIBD = neurofilament inclusion body disease; NIFID = neuronal intermediate filament inclusion disease; NOS = not otherwise specified; PSP = progressive supranuclear palsy.

KEY POINT

- **BvFTD is the result of a known pathogenic variant in 15% to 20% of patients.**

other neurodegenerative disorders (FIGURE 4-2). For this reason, when first gaining the impression that a patient may have a bvFTD syndrome, it is best to keep all diagnostic possibilities in mind to guide further data collection. About 15% to 20% of bvFTD results from a mutation in a known disease-causing genetic variant,[2,13] and each of the major genes (*MAPT*, *GRN*, and *C9orf72*) is associated with a slightly different bvFTD flavor.

With *MAPT* mutations, symptom onset typically occurs in midlife and tends to be consistent within a given family. Presentation and tempo vary according to the particular *MAPT* mutation. Most patients have a ventral pattern of degeneration first affecting the amygdala, hippocampus, entorhinal cortex, and temporal pole but progressing to involve the anterior insula, orbitofrontal cortex, and ventral striatum.[14] Clinical features reflect the anatomy, with prominent memory or semantic deficits accompanying the behavioral change.

In patients with *GRN* mutations, age of onset is highly variable, even within families, and occasionally mutation carriers may even escape the illness if they die of other causes before age 75.[15] The anatomic pattern is more lateralized (to the right or left) and often spreads beyond the core bvFTD regions to involve posterior areas,

including posterior cingulate, precuneus, and lateral parietal neocortex,[16] although it remains unclear how often this posterior component is due to comorbid AD.[17]

Hexanucleotide repeat expansions in *C9orf72* are the most common genetic cause of bvFTD.[18] Mutations have been identified even in patients without a family history due to variable penetrance and possibly lengthening of the repeat expansion (ie, anticipation) from one generation to the next in some families. Here, the anatomic pattern involves core bvFTD structures but may be mild overall[19] or accentuated in the medial (especially pulvinar) thalamus[20–22]; less consistent cerebellar atrophy has also been reported.[22] Prominent psychiatric features (eg, delusions, hallucinations, even fuguelike nonepileptic spells) may be seen in the symptomatic[23] and presymptomatic phases,[24] but the cause of these symptoms remains unclear.[24] Motor neuron disease may emerge with, before, or after the bvFTD syndrome, or not at all, in patients with *C9orf72* expansions.

Despite these general statements about the genetic forms of bvFTD, considerable variation exists within each genetic subgroup. Less common genetic causes of bvFTD include pathogenic variants in *TBK1*, *TIA1*, *TARDBP*, *FUS*, *CHMP2B*, and *VCP*.

The list of genetic causes of bvFTD is long, but the list of pathologic substrates is longer (FIGURE 4-2). FTLD pathology is divided into three major molecular classes based on the protein composition of the neuronal and glial inclusions, which may contain tau (FTLD-tau, about 40% of cases), transactive response DNA-binding protein 43 (TDP-43) (FTLD-TDP, about 50% of cases), or fused in sarcoma (FTLD-FUS, about 10% of cases). Each major molecular class includes a few major and several minor histopathologic subtypes, defined based on the morphology and distribution of the neuronal and glial inclusions. In sporadic bvFTD, the most common pathologic substrates are Pick disease, FTLD-TDP (Type B more common than Type A), and corticobasal degeneration.[11] When bvFTD is due to a mutation, predicting pathology is more straightforward. *MAPT* mutations result in a mutation-specific tauopathy. *GRN* mutations are universally accompanied by FTLD-TDP, Type A. *C9orf72* expansions are also linked to FTLD-TDP, but the subtype is more variable; Type B is most frequent, but some patients show Type A or a pattern too sparse, blended, or atypical to classify. Clinical features that can help predict pathology in bvFTD are shown in TABLE 4-2.

DIAGNOSIS

BvFTD is best diagnosed by using a systematic, stepwise approach (FIGURE 4-3) to prevent treatable or reversible conditions from being overlooked. A bvFTD diagnosis communicates a serious prognosis for the patient and potential genetic risk to family members, such that it is best to achieve high confidence before rendering the diagnosis.

Step 1: Identify and Refine the Syndrome

As with most neurologic disorders, obtaining the clinical history is the most essential step toward making a correct bvFTD syndromic diagnosis. Verifying a gradual and progressive behavior change helps reduce the odds of overlooking a non-neurodegenerative bvFTD mimic (refer to Step 2). If the patient comes to the visit unaccompanied reporting executive dysfunction or even social errors, the correct syndromic diagnosis is rarely bvFTD.

To refine the anatomy of the syndrome, careful chronicling can suggest whether the bvFTD syndrome began with (1) disinhibition, overeating, compulsivity, and loss of disgust, reflecting a more ventral subtype involving

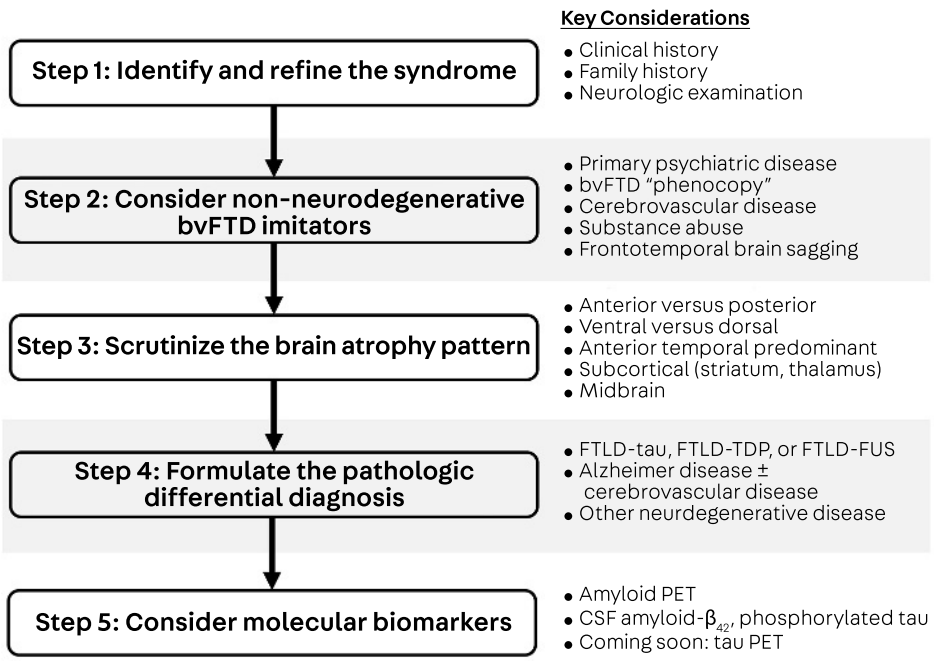

FIGURE 4-3

A stepwise approach to behavioral variant frontotemporal dementia (bvFTD) diagnosis.

FTLD-FUS = frontotemporal lobar degeneration with fused in sarcoma–immunoreactive inclusions; FTLD-tau = frontotemporal lobar degeneration with tau-immunoreactive inclusions; FTLD-TDP = frontotemporal lobar degeneration with transactive response DNA-binding protein 43 (TDP-43)–immunoreactive inclusions; CSF = cerebrospinal fluid; PET = positron emission tomography.

KEY POINTS

- **Expansions in *C9orf72* are the most common genetic cause of bvFTD and are commonly accompanied by motor neuron disease.**
- **BvFTD results from a diverse array of neuropathologic entities, most of which are classified as frontotemporal lobar degeneration.**
- **Accurate bvFTD diagnosis requires a methodical stepwise approach that relies heavily on the clinical history.**

ventral anterior insula, pregenual and subgenual anterior cingulate, ventral striatum, amygdala, and orbitofrontal areas (CASE 4-1); (2) apathy, impulsivity, and executive dysfunction, reflecting a more dorsal subtype involving dorsal anterior insula, anterior midcingulate, and dorsolateral/opercular prefrontal structures (CASE 4-2); or (3) loss of sympathy/empathy and agnosia for person-specific semantic knowledge, reflecting focal anterior temporal lobe degeneration. Recognizing these anatomic variations and others can be useful in formulating the neuropathologic differential diagnosis (refer to Step 4).

Family history taking should seek out not only bvFTD but also motor neuron disease, myopathy, bone disease (including Paget disease or bone cysts), and any form of dementia or psychiatric illness, keeping in mind that bvFTD misdiagnosis was even more common in preceding generations.

Useful neurologic signs include those that indicate emerging motor neuron disease (eg, muscle atrophy, fasciculations, focal weakness, or spasticity) or elements of a corticobasal syndrome (asymmetric bradykinesia-rigidity-dystonia) or progressive supranuclear palsy-Richardson syndrome (slowed saccades or vertical gaze restriction, axial rigidity, and gait instability).

Neuropsychological evaluation will usually show an executive-predominant pattern but may be normal or reveal unexpected episodic memory impairment. If a patient lacks the classic behavioral profile, detection of severe amnesia should raise concern about the possibility of underlying AD. In the presence of a classic bvFTD syndrome, however, severe amnesia may be a clue to FTLD-associated hippocampal sclerosis pathology (refer to the section on common myths and pitfalls).

CASE 4-1

A 51-year-old woman presented for evaluation of 4 years of behavioral symptoms that were affecting her work performance and home life. She was a business executive and had been passed over for promotions at work because her boardroom conduct had become less polished. She arrived exactly 5 minutes before each meeting and openly criticized others for being even seconds late. She interjected political views not related to the topic at hand. She told higher-ranking coworkers to "pipe down" and belittled the clothing or body habitus of support staff members. She became preoccupied with sugary coffee drinks, consuming two to three large beverages per day, and began collecting antique statuettes. Her husband discovered spending in excess of $15,000 on these and other collectibles, which she had been stockpiling in the family basement. She refused to drive her daughters to their basketball games, explaining that "their teams stink anyway" and presented her husband with a partly used cigar (found on the street) for Father's Day. She had no family history of dementia or related illness.

Neurologic examination revealed a healthy-appearing woman with a distant, yet sometimes jocular, affect who often spoke over the examiner or stood up to inspect framed credentials. Neuropsychological testing was normal, including tests of executive function. MRI showed right-predominant anterior insula, anterior cingulate, rostromedial prefrontal, and temporopolar atrophy (FIGURE 4-4).

The patient was diagnosed with behavioral variant frontotemporal dementia (bvFTD) and treated with escitalopram, which attenuated her overeating and collecting behaviors. She died after 12 years of symptoms, and autopsy revealed Pick disease, a subtype of frontotemporal lobar degeneration with tau-immunoreactive inclusions (FTLD-tau) (FIGURE 4-4).

COMMENT

This case provides a canonical presentation of bvFTD due to one of its most frequent neuropathologic causes. The disinhibited, socially inappropriate, and insensitive presentation reflects the patient's more ventral atrophy pattern involving the ventral anterior insula, orbitofrontal cortex, subgenual anterior cingulate cortex, ventral striatum, and anterior temporal lobe. Other FTLD subtypes that commonly present with a ventral pattern include FTLD with transactive response DNA-binding protein 43 (TDP-43)–immunoreactive inclusions (FTLD-TDP), Type B or unclassifiable (with or without a *C9orf72* expansion), atypical FTLD with ubiquitin-immunoreactive inclusions (aFTLD-U, a subtype of FTLD with fused in sarcoma–immunoreactive inclusions [FTLD-FUS]), and FTLD-tau due to a *MAPT* pathogenic variant.

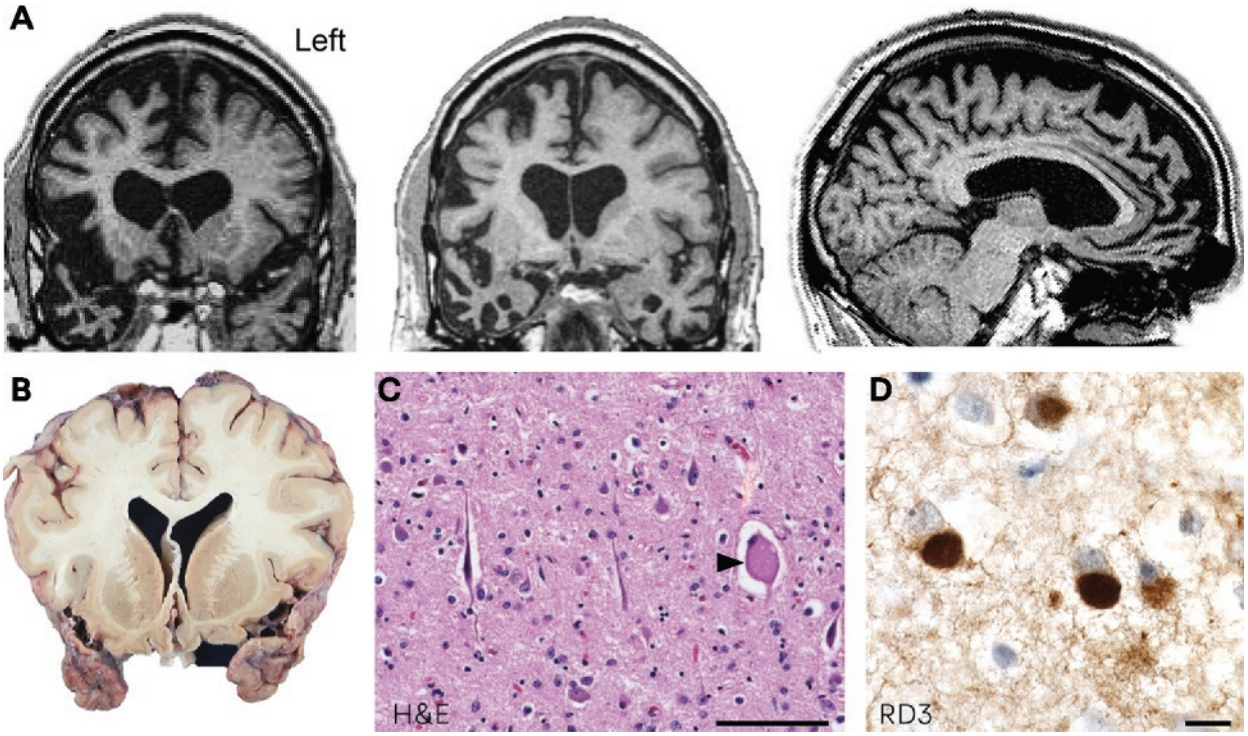

FIGURE 4-4

Imaging and pathology of the patient in CASE 4-1. *A*, Coronal and sagittal MRIs show a typical behavioral variant frontotemporal dementia pattern with right worse than left atrophy involving the anterior insula, anterior cingulate, anterior temporal lobes, amygdala, and ventral striatum. *B*, Gross inspection of the brain at autopsy revealed the same pattern. Note the remarkable sparing of more dorsal frontal and striatal structures. Microscopic pathology shows ballooned neurons (*arrowhead*) in layer 5 (*C*, shown in anterior cingulate cortex) and Pick bodies, which are round, circumscribed neuronal cytoplasmic inclusions that stain positively for 3-repeat tau (*D*). Scale bars represent 100 microns in *C* and 10 microns in *D*.

H&E = hematoxylin and eosin; RD3 = 3-repeat tau.

Step 2: Consider Non-neurodegenerative Behavioral Variant Frontotemporal Dementia Imitators

When a patient presents to a dementia specialist with a referring diagnosis of bvFTD, the underlying cause is usually neurodegenerative. In primary care or general neurology practice, however, non-neurodegenerative causes should receive serious consideration and be evaluated before a specialist referral. Metabolic, nutritional, endocrine, infectious, autoimmune, neoplastic, and toxicologic causes should be entertained in every patient with a dementia syndrome and screened for whenever suspicion is nonzero. The most common non-neurodegenerative causes of a bvFTD-like syndrome are discussed further here.

PRIMARY PSYCHIATRIC DISEASE. A reported long-standing history of psychiatric illness requiring psychopharmacologic treatment should prompt an in-depth

CASE 4-2

A 62-year-old man presented for evaluation of a 3-year history of new behavioral symptoms. He had become less hard-driving in his work as an attorney, accepting fewer cases and taking longer to close them. Although he had always been a diligent gardener, he left the yard unattended despite his wife's encouragement. He became less systematic when attempting to repair broken household fixtures or plan even short trips. His emotional range diminished; he remained agreeable, almost malleable, and warm toward his wife, but his conversations with her lacked depth. Spontaneous speech slowly diminished but was otherwise intact. He often repeated questions or asked for clarification about recent events.

On examination, motor function was spared. His Mini-Mental State Examination (MMSE) score was 21/30. Neuropsychological testing revealed executive deficits, especially in processing speed, generativity, and response switching, as well as poor delayed verbal recall and spared visuospatial function. MRI revealed severe left-predominant medial and dorsolateral frontal atrophy with conspicuous sparing of the anterior temporal lobe and posterior brain regions but marked left hippocampal atrophy (FIGURE 4-5). He died 8 years after symptom onset, and autopsy revealed frontotemporal lobar degeneration with transactive response DNA-binding protein 43 (TDP-43)–immunoreactive inclusions (FTLD-TDP), Type A, with hippocampal sclerosis (FIGURE 4-5).

COMMENT

This case highlights a more dorsal "apathetic-dysexecutive" presentation of behavioral variant frontotemporal dementia (bvFTD) and serves as a reminder that disinhibition and loss of caring, although common in behavioral variant frontotemporal dementia, are not universal features. A more dorsal presentation is often due to FTLD-TDP, Type A, or corticobasal degeneration, although other FTLD subtypes and Alzheimer disease merit consideration. In this case, the profound verbal memory deficit and hippocampal atrophy suggested hippocampal sclerosis, which is more commonly seen in FTLD-TDP.

psychiatric history and give the clinician great pause before diagnosing bvFTD. Careful scrutiny of the presenting symptoms is key; apathy must be distinguished from anhedonia, disinhibition from mania, compulsive behaviors from anxious obsessive-compulsiveness, and loss of empathy from lifelong autism spectrum or personality disorder.[25] Primary psychiatric disease may change or worsen in midlife in response to new stressors or comorbid medical or neurologic illness. In such cases, careful adjustment of the psychopharmacologic regimen, preferably led by the treating psychiatrist, may reveal a nonprogressive trajectory.[26] On the other hand, unheralded midlife psychosis, compulsivity, and manialike episodes are uncommon and should arouse suspicion for bvFTD or other neurologic disorders. The interpretation of psychiatric symptoms should also factor into the family history, as patients with inherited FTD may have a higher rate of psychiatric diagnosis

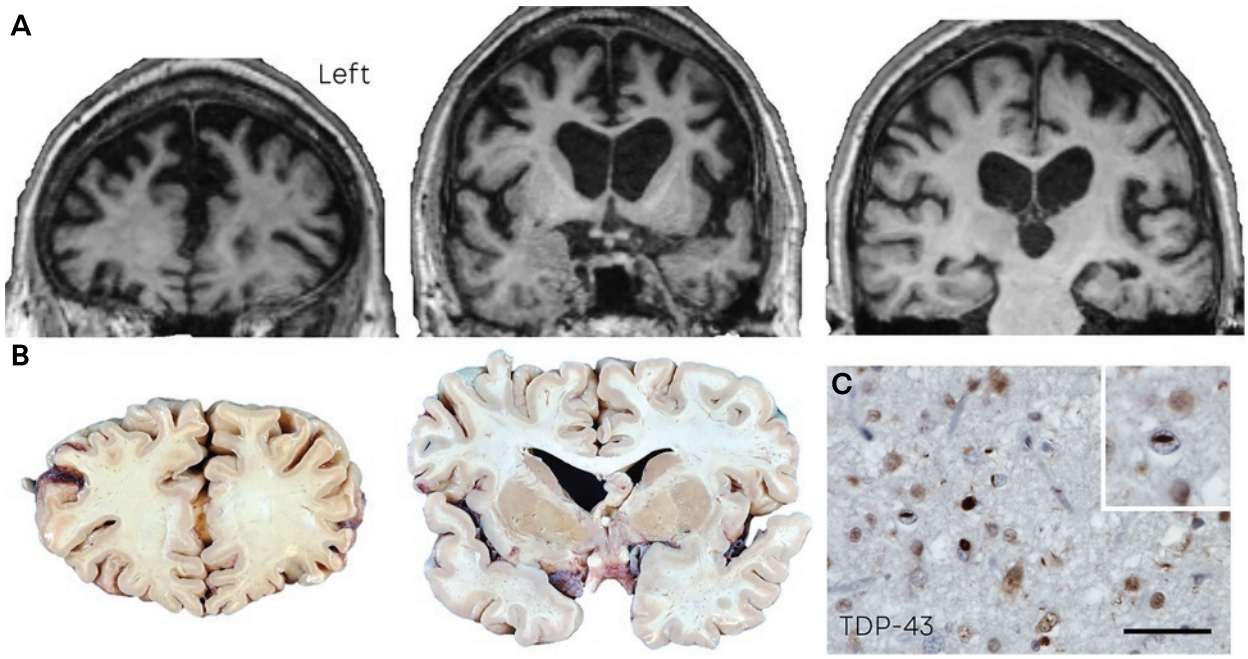

FIGURE 4-5

Imaging and pathology of the patient in CASE 4-2. *A*, Coronal MRIs show a more dorsal left worse than right atrophy pattern involving the superior frontal gyri, anterior and midcingulate cortex, dorsal striatum, and hippocampus. *B*, Gross inspection of the brain at autopsy revealed a similar pattern with conspicuous sparing of anterior temporal lobes. *C*, Microscopic pathology shows frontotemporal lobar degeneration with transactive response DNA-binding protein 43 (TDP-43)–immunoreactive inclusions, Type A, with numerous TDP-43–immunoreactive short, thin neuropil threads; small round or crescentic neuronal cytoplasmic inclusions, and occasional neuronal intranuclear inclusions (*inset*). Scale bar in *C* represents 50 microns.

during the presymptomatic phase. Whether this phenomenology represents prodromal neurodegeneration, abnormal brain development, bona fide psychiatric illness, or a mix of these factors remains uncertain, but asymptomatic carriers of bvFTD-causing mutations (especially *C9orf72*) often show subtle volume reduction in bvFTD-related brain regions compared to controls and their noncarrier siblings.[24,27]

BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA PHENOCOPY. In the mid-2000s, Hodges and colleagues[28] called attention to a "bvFTD phenocopy" syndrome. Patients with this syndrome met prevailing formal research criteria for bvFTD[29] but lacked clinical progression over long follow-up intervals. Brain imaging showed no, or mild nonspecific, changes, and tests of executive and other cognitive functions were often normal or mildly abnormal but stable. Today, we understand this group to include at least two major subgroups. First, and most relevant to this section, is a group of patients who indeed manifest social behaviors falling at, or even well below, the lower limits of normal. The onset and progression of these behaviors, however, is unclear, often because the patient lacks a reliable informant or has a new spouse or partner. The dynamic of recognizing poor social skills in a partner after marriage can, in some instances, lead spouses to seek a medical explanation when, in fact, the unwanted behaviors represent lifelong eccentricities, a personality disorder, or an undiagnosed high-functioning autism spectrum disorder. Gathering input from additional family members, friends, or coworkers can help clarify the temporal features. The second phenocopy subtype is a very slowly progressive bvFTD in which there is often prominent psychiatric symptomatology, minimal or focal thalamic atrophy, and a *C9orf72* expansion.[30]

CEREBROVASCULAR DISEASE. Patients with slowly accrued multifocal subfrontal infarcts may develop a seemingly gradual behavior-predominant dementia. Cognitive slowing is often prominent, and executive dysfunction outpaces social behavioral change. Strategic insular, striatal, or medial thalamic infarction may also produce a bvFTD-like syndrome, but the onset is abrupt or may seem subacute if there are barriers to detection.

SUBSTANCE ABUSE. Downward-spiraling work performance and evasive, suspicious, emotionally distant behavior toward loved ones can reflect an occult substance abuse disorder, often abuse of alcohol or opioid analgesic medications. Indicated studies include toxicology and brain MRI to rule out neurologic sequelae.

FRONTOTEMPORAL BRAIN SAGGING SYNDROME. Perhaps the least common disorder that imitates bvFTD is also the best mimic. Rare patients with intracranial hypotension develop clinical features that strongly overlap with bvFTD,[31] even when postural headache is minimal or absent (CASE 4-3). Brain MRI reveals sagging of brain contents into the foramen magnum, presumably creating tension on long tract pathways connecting frontal-insular-temporal cortical areas with subcortical and brainstem structures. These features are often associated with diffuse meningeal gadolinium enhancement. Although rare, this cause of the bvFTD syndrome is critical to detect since it can be partly or totally reversed with an intervention to patch the site of CSF leakage.

Step 3: Scrutinize the Brain Atrophy Pattern

MRI features were added to the revised research criteria for bvFTD with two intentions in mind: (1) avoid the non-neurodegenerative causes outlined above and (2) reduce the likelihood of a non-FTLD neurodegenerative disease. Patients can meet "possible bvFTD" criteria based on clinical features alone, but "probable bvFTD" requires a supportive MRI scan. What does "supportive" look like? When reviewing a brain MRI in a patient with possible bvFTD, the clinician must answer several key questions. Does evidence suggest cerebrovascular disease or other nondegenerative focal lesion sufficient to account for the clinical syndrome? If not, does the presence of cortical thinning, sulcal widening, subcortical atrophy, and ventricular enlargement suggest a neurodegenerative disorder? Is the cortical atrophy pattern anterior, posterior, or both? An anterior-predominant pattern is sufficient to reach a probable bvFTD diagnosis because it usually suggests underlying FTLD pathology. This anterior pattern almost always includes the anterior insula and anterior cingulate cortices,[11] but which additional structures are affected: frontal, temporal, parietal, limbic, subcortical, or brainstem? Answers to these questions can assist in formulation of the pathologic differential diagnosis (TABLE 4-2 and Step 4 below).

Step 4: Formulate the Pathologic Differential Diagnosis

Once the clinician rules out non-neurodegenerative causes of a bvFTD-like syndrome, it is time to generate a prioritized list of the most likely neuropathologic diagnoses. As shown in TABLE 4-2, several clinical features strongly increase the likelihood of one pathologic diagnosis over others. Of these features, only the genetic associations (and not all of those) have proven themselves invariant. During early clinical stages, anchoring clinical features such as motor neuron disease or a supranuclear gaze palsy are typically absent, and prioritizing the differential diagnosis relies on looser clinicoanatomic subtype–based associations. For example, severe asymmetric (usually nondominant) temporal lobe atrophy predicts underlying FTLD-TDP, Type C or, less often, Pick disease. Dramatic "knife-edge" frontal and insular atrophy predicts Pick disease (CASE 4-1) or, less often, FTLD-TDP, Type A. Midbrain atrophy can herald the emergence of progressive supranuclear palsy syndromic features, and focal thalamic atrophy can suggest *C9orf72* expansion even when the family history is unremarkable. A ventral frontal pattern accompanied by paper-thin anterior caudate nuclei suggests FTLD-FUS (aFTLD-U subtype), especially in a patient with a symptom onset before 50 years of age. Patients with prominent dorsal frontoparietal atrophy, with or without prominent memory loss, should raise concern for underlying AD (CASE 4-4).

Step 5: Consider Molecular Biomarkers to Rule Out Alzheimer Disease

Distinguishing bvFTD due to FTLD from a behavioral syndrome due to pathologic AD can be challenging in clinically atypical patients but has important management implications. Although still imperfect, clinically available biomarkers can sensitively detect AD-related molecular changes. A normal CSF amyloid-$\beta_{1\text{-}42}$ to phosphorylated tau ratio or negative amyloid imaging with, for example, florbetapir positron emission tomography (PET), greatly reduces the likelihood that AD is the cause of any FTD-like syndrome. These tests are most useful in young patients, however, because incidental CSF and amyloid PET biomarker abnormalities become more common with age, such that 25% to 40%

KEY POINTS

- **Both neurodegenerative and non-neurodegenerative causes should be considered in all patients with bvFTD.**
- **Structural MRI and, increasingly, molecular biomarkers play a key role in predicting pathology in patients with a bvFTD syndrome.**

of asymptomatic individuals test positively after 70 years of age.[32] Therefore, in this age group, a positive test cannot confirm that a patient's bvFTD is due to AD. In patients aged 45 to 60, however, the risk of false positives is much lower, and a positive biomarker usually means that the bvFTD-like syndrome is due to AD. Health insurance rarely covers these tests, so it is important to have a frank discussion with caregivers regarding costs and benefits.

COMMON BEHAVIORAL VARIANT FRONTOTEMPORAL DEMENTIA MYTHS AND PITFALLS

Despite growing awareness of bvFTD among primary care physicians and general neurologists, misdiagnosis remains common. Some diagnostic errors can be traced back to the following common misconceptions.

The Memory Loss Is Too Severe; It Must Be Alzheimer Disease

This myth arises from the fact that amnesia is not a defining feature of bvFTD, but even patients who meet probable bvFTD criteria may show severe memory

CASE 4-3

A 50-year-old man presented with a 1-year history of behavioral symptoms. He had been an upstanding and even-tempered grocery store manager but had begun to speak rudely to his wife, berating her for minor mistakes. He threw her neatly organized paperwork on the floor and laughed when she responded tearfully. He touched her publicly in ways that made her uncomfortable and told off-color jokes to his daughter's teenage friends. He spent significant savings on pornography, which he watched in front of others, including children. He was forced to retire because of repeated complaints from his employees to store ownership. He ate gummy bears compulsively yet had lost 13.6 kg (30 lb) over 2 years. He exhibited repetitive motor behaviors such as foot tapping and head scratching and made repeated trips to the bathroom. He forgot recent conversations and had occasional nonpostural headaches. His medical history was notable for a significant childhood head trauma.

On examination, he violated interpersonal boundaries, exhibited utilization behavior, and spoke out of turn in a hypophonic voice. He had square-wave jerks and a postural tremor predominantly affecting his trunk and right hand. His Mini-Mental State Examination (MMSE) score was 26/30. He showed prominent deficits in verbal memory and generativity but otherwise normal language and visuospatial function.

Brain MRI revealed a normal pattern of cortical thickness but distortion of brainstem structures, forward displacement of the third ventricle, a prominent pituitary, enlarged venous sinuses, the appearance of cerebellar tonsillar herniation, and diffuse pachymeningeal enhancement, all consistent with intracranial hypotension (FIGURE 4-6). An MRI myelogram of the whole spine showed a rim of extradural contrast in the upper thoracic canal (T2 through T6, above the level of the lumbar puncture). Targeted blood patching resulted in only short-lived benefits. After the fourth blood patch, his behavior improved significantly and remained stable for 2 years.

loss due to hippocampal sclerosis, in which CA1 and subicular pyramidal neurons are almost completely destroyed. FTLD-related hippocampal sclerosis is usually seen in the context of underlying FTLD-TDP and is distinct from hippocampal sclerosis of aging,[33] a TDP-43–related disease typically seen in patients older than 80 years of age. For more information on hippocampal sclerosis, refer to the article "Hippocampal Sclerosis, Argyrophilic Grain Disease, and Primary Age-Related Tauopathy" by Gregory A. Jicha, MD, PhD, and Peter T. Nelson, MD, PhD,[34] in this issue of *Continuum*. In older patients with bvFTD due to underlying FTLD, comorbid AD neuropathologic changes and other common age-related conditions may also mislead clinicians away from the FTLD diagnosis.[35]

The MRI Is Normal; It Cannot Be Behavioral Variant Frontotemporal Dementia

As preceding sections imply, a normal MRI should not lead clinicians to limit their differential diagnosis to non-neurodegenerative etiologies. In patients with *C9orf72* expansions, sporadic FTLD-TDP (Type B or unclassifiable), or even

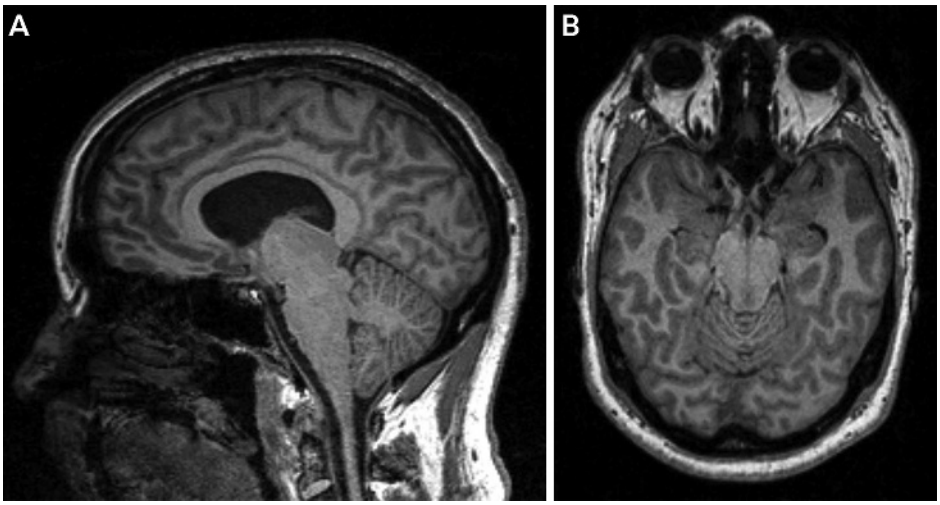

FIGURE 4-6

Imaging of the patient in CASE 4-3. *A*, Sagittal T1-weighted MRI shows sagging of brainstem and diencephalon toward the foramen magnum, with crowding of cerebellar tonsils. *B*, Axial T1-weighted MRI highlights crowding of the midbrain. Postcontrast T1-weighted images (*not shown*) revealed diffuse pachymeningeal enhancement.

COMMENT

Treatable causes of dementia are essential to rule out, and this case illustrates a behavioral variant frontotemporal dementia–like syndrome for which an MRI scan can make the diagnosis. Although treatment is invasive and not always effective, the small existing literature suggests that persistent treatment may be critical to long-term symptom relief, at least in some patients.[31]

CASE 4-4

A 55-year-old man presented for evaluation of a 3-year history of behavioral and cognitive symptoms. He was an accountant but could no longer retain his clients. Tax forms were filed late, and he mixed up appointments because of double bookings and missed emails. Papers piled up on his desk, including stacks of unopened envelopes. He became despondent, prone to angry outbursts, and clingy, following his wife around the house and watching her speak on the telephone. He approached strangers, often telling distasteful jokes or bursting into song in midsentence. Other times, he would retreat from social gatherings to watch television. He ate whenever food was present and often took food from family members' plates. Both of his parents had developed an amnestic dementia in their late seventies.

On examination, his affect was flat, and he fidgeted impulsively. Imitative, stimulus-bound behaviors took the form of motor mirroring and echolalia. Spoken language was tangential with circumlocution. He could not calculate 25 + 33 without paper. Praxis was normal. When asked about a recent major world event, he could not name the key participants but recognized their names among multiple-choice arrays. He had mild hypomimia, but the remainder of the general neurologic examination was normal. Neuropsychological testing revealed a Mini-Mental State Examination (MMSE) score of 22/30; he lost points for orientation, spelling *world* backward, and three-item delayed recall (0/3). He was unable to complete a modified trail-making task and made 26 stimulus-bound errors on the Stroop color-naming test. Verbal and category fluency were impaired. Verbal learning was poor, and free recall was absent after 10 minutes, unaided by recognition prompts. Visuoconstructive and visuoperceptive tests were normal. MRI showed mild to moderate dorsolateral frontal greater than lateral parietal atrophy (FIGURE 4-7).

The clinical syndrome was characterized as dysexecutive-amnestic with elements of behavioral variant frontotemporal dementia (bvFTD) but with suspicion for underlying Alzheimer disease (AD). Amyloid imaging with florbetapir positron emission tomography (PET) showed widespread tracer uptake. Clinical genetic testing revealed two copies of the *APOE* ε4 allele. Over time, amnesia and posterior cortical deficits blossomed. Treatment with donepezil made him somewhat less distractible but had no influence on disruptive, agitated behaviors, which made him difficult to manage at a residential care facility. Treatment with antipsychotic drugs made him calmer but apathetic and parkinsonian. He died after 10 years of symptoms, and autopsy showed advanced AD (FIGURE 4-6).

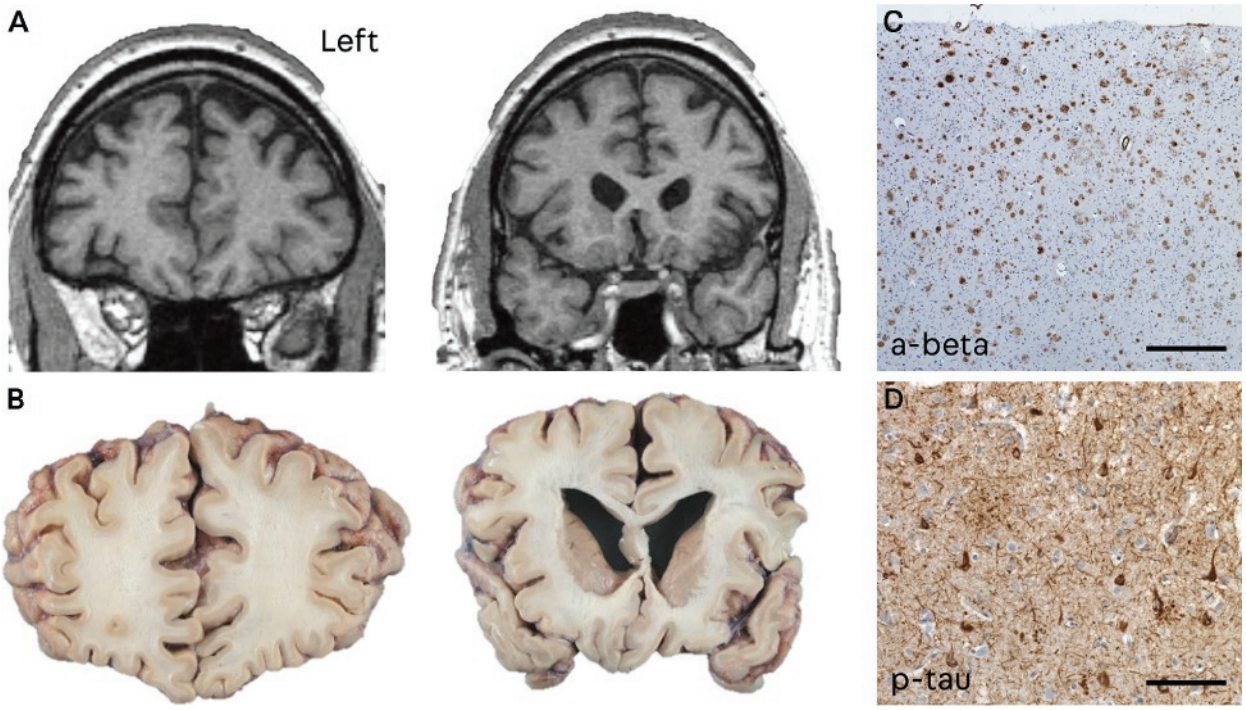

FIGURE 4-7

Imaging and pathology of the patient in CASE 4-4. Coronal MRIs (*A*) show a dorsal frontal atrophy pattern as well as mild posterior cingulate and lateral parietal atrophy (*not shown*). Gross inspection of the brain at autopsy (*B*) showed similar, although more severe, findings. Microscopic pathology showed abundant diffuse and neuritic amyloid plaques and mild cerebral amyloid angiopathy (*C*, as shown in middle frontal gyrus) accompanied by severe tau-immunoreactive neurofibrillary tangle and neuropil thread pathology (*D*, as shown using CP-13 antibody, inferior frontal gyrus). Scale bars represent 500 microns in *C* and 100 microns in *D*.

a-beta = amyloid-β; p-tau = phosphorylated tau.

COMMENT

This case illustrates a presentation of early-onset AD that may be mistaken for bvFTD. Although the patient had early behavioral symptoms, many of them, including irritability, agitation, and low mood, are more typical of Alzheimer-type dementia than bvFTD. Molecular imaging was particularly helpful because of the patient's young age.

early progressive supranuclear palsy pathology, the brain MRI may be so bland as to be startling. Careful review may reveal a focal pattern of medial thalamic or midbrain atrophy that may or may not blossom into a more widespread cingulate-insular pattern in the years to come. Some patients with *C9orf72* expansions have a long-term stable trajectory of slowly or minimally progressive behavior change, even after presenting to a dementia clinic. In others without a mutation, the anchoring clue may be the emergence of subtle motor neuron disease or eye signs, such as square-wave jerks or slowed saccades, that suggest an incipient supranuclear ophthalmoparesis.

Executive Frontal Functions Are the Worst Cognitive Deficit; It Must Be Behavioral Variant Frontotemporal Dementia

Executive functions are often the worst cognitive deficit in bvFTD, but they are rarely the worst deficit overall, being overshadowed by social-emotional dysfunction in most patients. Middle-aged patients with an executive-predominant deficit profile and a dorsolateral frontal atrophy pattern are commonly seen in dementia centers, often with a referring diagnosis of bvFTD. In most, the correct clinical diagnosis will be early-onset Alzheimer-type dementia (CASE 4-4). Meticulous assessment will reveal that executive dysfunction is (or will soon be) part of a larger pattern that includes other neocortical cognitive domains such as language (particularly lexical retrieval), visuospatial function, calculations, and praxis. Emotional changes may be prominent but tend toward anxiety, irritability, and even impulsivity, while social warmth, decorum, and connectedness with loved ones are broadly preserved. Occasionally a patient with underlying AD will present with a more typical bvFTD syndrome. Often in such patients the caregiver will confess that the patient has always been "the life of the party," having a loose, disinhibited personal style that has been, one imagines, amplified by the emergence of a disease that would have otherwise presented differently. Some patients with AD may also show more prominent frontal-behavioral features due to comorbid vascular subfrontal leukoencephalopathy stemming from arteriolosclerosis or cerebral amyloid angiopathy.

MANAGEMENT

The years leading up to a patient's bvFTD diagnosis are often the most stressful period in the lifetime of a spouse and other family members. Marital strife, financial chaos or even ruin, and estrangement from friends and family are common and may create resentment toward the patient that persists even after a neurologic diagnosis has been made. Caregiver emotional responses to a bvFTD diagnosis are often mixed. The diagnosis creates enormous grief because of the prognosis: progression to death within 5 to 7 years.[36] On the other hand, caregivers are often relieved—eventually—to know that a disease accounts for the patient's behaviors and that those behaviors are not just a new and permanent normal. Death typically results from motor impairment (parkinsonism, motor neuron disease, or both) leading to aspiration pneumonia, so caregivers should be advised to look out for emerging motor features. The patient's emotional response to the diagnosis is characteristically bland or concrete.

Caring for patients and families with bvFTD is challenging but rewarding. At a dementia specialty clinic, model care involves a multidisciplinary team that includes a physician (most often a neurologist, psychiatrist, or geriatrician), nurse, neuropsychologist, social worker, genetic counselor, and a seasoned pharmacist.

For the community practice neurologist, adding even one or two of these disciplines (but as many as feasible) to the care team can greatly enhance care quality.

Caregiver Support/Behavioral Management

With bvFTD, the major treatment imperative is to provide spouses and other caregivers with information, emotional support, strategies for behavioral management, and access to community resources. Without these tools, caregiver burnout is almost inevitable and can have major adverse consequences, including poor health outcomes, for both caregiver and patient.[37] Lay language informational materials are available via books and websites (refer to the Useful Websites section). Support groups can be helpful, especially if focused on non-Alzheimer dementias. Day-to-day caregiver-patient interactions should focus on redirecting attention away from unwanted preoccupations and activities in a nonconfrontational manner.[38] Harmless compulsions within the home environment (weed-pulling, recycling, sorting, ordering) need not be discouraged and can even provide caregiver relief. Unwelcome compulsive behaviors can be replaced by innocuous alternatives such as a squeeze ball (to replace touching strangers) or a lollipop (to diminish repetitive, stereotyped vocalizations).[38] Challenging the patient's newly ordered priorities or false beliefs is generally unproductive. Patient access to financial resources should be controlled and monitored or removed based on the context. Problematic public behaviors can often be defused by providing those involved with a business card–sized explanation that the patient has a brain disorder that affects behavior. Dietary or monetary rewards for desired behaviors (showering, grooming) can be effective in some patients.[38] Adult day programs that offer a structured environment for several consecutive hours can provide valuable caregiver respite if the staff is trained to manage behavioral symptoms in dementia. Caregivers should be encouraged to exercise and engage in other forms of stress management, prioritize their own sleep, and maintain social contacts and personal interests or hobbies as much as possible. Early consideration of end-of-life care and advance directives is warranted, although by the time patients are diagnosed with bvFTD, they rarely retain the capacity to make or even guide these decisions.

Psychopharmacologic Treatment

No disease-modifying therapies are available for patients with bvFTD. Therefore, drug treatment should focus on the most disruptive or targetable behaviors and be rooted in the neurochemical deficits observed in bvFTD. Overeating and, to a lesser extent, compulsivity may respond to selective serotonin reuptake inhibitors (SSRIs)[39]; citalopram or escitalopram are often used because of their low side effect profiles. Patients with an apathy-predominant form of bvFTD may show subtly increased energy/engagement in response to venlafaxine given its activating (ie, noradrenergic) properties. Social disinhibition is notoriously difficult to treat with drugs. When patients become agitated and confront other nursing home residents in a way that threatens resident or staff safety (or the patient's status at the facility), atypical antipsychotic drugs such as quetiapine or risperidone can be used in low incremental doses but with extreme caution given the risk of cardiac complications, including sudden death. Less commonly, patients with bvFTD develop frank psychosis, which may also respond to these medications.

KEY POINTS

- Occasionally, patients with bvFTD have severe early memory loss or a normal MRI.
- Executive dysfunction is common in bvFTD but also in other disorders and should not be used as an indicator of bvFTD unless accompanied by signature social-emotional features.
- Model care for bvFTD involves contributions from a multidisciplinary team that supports both patient and caregiver.
- BvFTD caregivers are at high risk for burnout.
- Nonpharmacologic approaches are often the best way to manage troublesome behavioral symptoms in bvFTD.
- Pharmacologic management of bvFTD should target specific symptoms, such as overeating, compulsivity, severe agitation, or psychosis.
- Selective serotonin reuptake inhibitors are first-line therapy for overeating and compulsivity symptoms in bvFTD.

Distinguishing bvFTD due to FTLD from a frontal/behavioral variant of AD has important implications for psychopharmacology. Whereas patients with underlying AD may show modest cognitive or even behavioral benefit from acetylcholinesterase inhibitors, patients with bvFTD due to FTLD have shown no benefit[40] and may even become agitated or irritable in response to these drugs.[41,42] Memantine showed no benefit in a randomized controlled trial for FTD (including bvFTD and semantic variant primary progressive aphasia)[43] but may decrease caregiver distress in patients with underlying AD, including those with a behavioral/executive presentation. It should be noted, however, that the previous memantine trial for FTD was not powered to assess the bvFTD subgroup, and no clinical trial has specifically recruited behavioral/executive forms of AD.

FAMILY CONSIDERATIONS AND GENETIC COUNSELING

Because bvFTD represents a monogenic, autosomal dominant inherited disease in 15% to 20% of patients,[13] families are often uneasy about and eager to discuss heritability implications. Clinical testing is available for the major known genetic causes and can help guide next steps in family counseling. Negative results from existing clinical tests provide only partial reassurance, especially if a worrisome family history is present, since there may be additional FTD-related genes awaiting discovery. If a genetic cause is identified in the patient (ie, proband), genetic testing of at-risk asymptomatic family members should be considered only for adults and only with appropriate genetic counseling in place. Such counseling can help at-risk individuals think through the psychological and family-planning consequences of knowing their own genetic status. If an at-risk individual tests positive for a known FTD pathogenic variant but wishes to start a family, preimplantation diagnosis followed by in vitro fertilization has become an option, although it remains uncommonly used in the United States for this indication.

FRONTIERS

Advancing clinical and basic science efforts promise to improve care for patients with bvFTD. A few among many horizons related to diagnosis and treatment are outlined here.

Diagnosis

Even once all patients with underlying AD within a bvFTD cohort can be identified, a need will remain for better prediction of the underlying FTLD pathologic diagnosis. FTLD is a rich and diverse category, and treatment trials will seek to target the specific molecular mechanisms related to tau, TDP-43, and FUS. Research-based PET imaging for the tau protein shows great promise for detecting the neurofibrillary pathology of AD,[44] but, to date, these approaches have proven neither sensitive nor specific enough for use in FTLD-tau diagnosis.[45,46] Further work is needed to identify new tau PET ligands and to develop approaches for imaging TDP-43 aggregates. Nonetheless, the sensitivity of existing tau PET ligands to Alzheimer-type neurofibrillary tau pathology may prove useful in older patients by clarifying whether a positive amyloid PET means that the patient's bvFTD syndrome is likely due to AD.

Treatment

Great optimism and excitement is emerging within the FTD patient, caregiver, and researcher communities about the potential for new therapies.[47] Several

approaches are in or nearing the clinical trials phase. For FTLD-tau, candidate strategies include stabilization or immunologic clearance of pathologic tau and therapeutic reduction of total tau, among others. For FTLD-TDP, the major treatment targets relate to the genetic forms caused by pathogenic variants in *GRN* or *C9orf72*. For *GRN*-FTD, researchers are pursuing ways to normalize circulating progranulin protein levels, which are reduced due to haploinsufficiency; obviate lysosomal dysfunction; and dampen neuroinflammation. For *C9orf72*-FTD, one major approach proposed is to use antisense oligonucleotides to diminish toxicity resulting from repeat RNA transcripts and the dipeptide repeat protein products of repeat-associated unconventional translation.[48]

KEY POINT

- **Acetylcholinesterase inhibitors have shown no benefit in bvFTD and may worsen behavioral symptoms.**

CONCLUSION

The human social brain, so wondrous in its capacities, remains a delicate frontier that slowly erodes in patients with bvFTD. Clinicians can play a major role in accurately diagnosing and treating bvFTD and caring for the patient and family. Ongoing research promises to clarify molecular mechanisms, raising hope for improved patient-centered diagnosis and disease-modifying treatment.

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USEFUL WEBSITES

ALZHEIMER'S ASSOCIATION
The Alzheimer's Association website describes the types of frontotemporal dementia (including behavioral variant frontotemporal dementia and primary progressive aphasia) and the key differences between frontotemporal dementia and Alzheimer disease and provides telephone numbers for support for patients and caregivers.
alz.org/alzheimers-dementia/what-is-dementia/types-of-dementia/frontotemporal-dementia

THE ASSOCIATION FOR FRONTOTEMPORAL DEGENERATION
The Association for Frontotemporal Degeneration website explains the difference between frontotemporal degeneration and Alzheimer disease and provides resources for living with frontotemporal degeneration and information on research and clinical trials.
theaftd.org/what-is-ftd/disease-overview/

CLINICALTRIALS.GOV
ClinicalTrials.gov lists clinical trials of medications for frontotemporal dementia and their status.
clinicaltrials.gov/ct2/results?cond=Frontotemporal+Dementia&term=&cntry=&state=&city=&dist=?

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE FRONTOTEMPORAL DEMENTIA INFORMATION PAGE
The National Institute of Neurological Disorders and Stroke frontotemporal dementia information page provides a definition of the disease and links to clinical trials, patient organizations, and publications.
ninds.nih.gov/Disorders/All-Disorders/Frontotemporal-Dementia-Information-Page

UNIVERSITY OF CALIFORNIA SAN FRANCISCO MEMORY AND AGING CENTER
The UCSF Memory and Aging Center website provides information on the forms of frontotemporal dementia; medications used to treat it; resources for patients, caregivers, and providers; and research trials.
memory.ucsf.edu/frontotemporal-dementia

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