Frontotemporal Dementias

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Finger discusses the unlabeled/investigational use of disease-modifying therapies in development, dopaminergic medications, neuroleptic medications, oxytocin, and selective serotonin reuptake inhibitors for the treatment of frontotemporal dementias.

ABSTRACT

Purpose of Review: This article reviews the common behavioral and cognitive features of frontotemporal dementia (FTD) and related disorders as well as the distinguishing clinical, genetic, and pathologic features of the most common subtypes.

Recent Findings: Advances in clinical phenotyping, genetics, and biomarkers have enabled improved predictions of the specific underlying molecular pathology associated with different presentations of FTD. Evaluation of large international cohorts has led to recent refinements in diagnostic criteria for several of the FTD subtypes.

Summary: The FTDs are a group of neurodegenerative disorders featuring progressive deterioration of behavior or language and associated pathology in the frontal or temporal lobes. Based on anatomic, genetic, and neuropathologic categorizations, the six clinical subtypes of FTD or related disorders are: (1) behavioral variant of FTD, (2) semantic variant primary progressive aphasia, (3) nonfluent agrammatic variant primary progressive aphasia, (4) corticobasal syndrome, (5) progressive supranuclear palsy, and (6) FTD associated with motor neuron disease. Recognition and accurate diagnoses of FTD subtypes will aid the neurologist in the management of patients with FTD.

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INTRODUCTION

Frontotemporal dementia (FTD) classically affects adults in their fifties to sixties, although cases have been reported in patients from 30 to more than 90 years of age. FTD is a progressive neurodegenerative disorder; thus, the patient's history typically reveals a gradual onset and progression of changes in behavior or language deficits for several years prior to presentation to a neurologist. The term FTD is typically used to refer to one of several clinical subtypes including behavioral variant of FTD (bvFTD), semantic variant primary progressive aphasia (PPA), nonfluent agrammatic variant PPA, and FTD associated with motor neuron disease (FTD-MND). FTD-related disorders include two tau-associated neurodegenerative diseases, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP), which can present with frontal lobe dysfunction. The clinical subtypes of FTD and related disorders are defined by the hallmark patterns of symptoms and signs observed. Variations in clinical presentation across the FTD subtypes are attributed to differences in the brain regions affected by FTD pathology. The term frontotemporal lobar degeneration (FTLD) is reserved for patients with clinical presentations of FTD and identification of an FTD-causing mutation or histopathologic evidence of FTD (on biopsy or postmortem).

EPIDEMIOLOGY OF FRONTOTEMPORAL DEMENTIA

FTD is generally considered to be the second most common cause of

early-onset neurodegenerative dementia (before age 65), second only to Alzheimer disease (AD).[1] The estimated prevalence of FTD is highest in the 45 to 64 year age group and ranges from 15 to 22 per 100,000 persons ages 45 to 64, with 10% of FTD occurring in patients less than 45 years of age and approximately 30% occurring in patients older than 65.[1] There is consensus that the prevalence is likely underestimated due to lack of recognition and diagnosis of the FTD syndromes by non-neurologists.[1,2] Of the FTD subtypes, bvFTD is the most common clinical presentation, accounting for more than 50% of patients with autopsy-confirmed FTLD.[3] FTD affects both genders in roughly equal distribution.

BEHAVIORAL VARIANT OF FRONTOTEMPORAL DEMENTIA

bvFTD is defined by the gradual onset and progression of changes in behavior, including disinhibition, loss of empathy, apathy, and may include hyperorality and perseverative or compulsive behaviors (**Table 5-1**).[4] Patients presenting with symptoms consistent with bvFTD but with normal brain imaging (ie, CT, MRI, positron emission tomography [PET]/single-photon emission computed tomography [SPECT]) are classified as possible bvFTD, while patients meeting symptom criteria who show focal atrophy, hypometabolism, or hypoperfusion in the frontal or temporal lobes are classified as having probable bvFTD.

Symptoms

Disinhibition may manifest in a variety of ways, including increased disclosure of personal information to strangers or acquaintances (eg, medical information, finances), increased sexual interest or comments, loss of manners (such as belching in public), new use of derogatory or racist language in reference to others (eg, calling someone fat or bald in public), and impulsivity (eg, inappropriate spending). Apathy is a common early feature and may present as a loss of interest in usual social and non-social activities. Patients may be noted to spend hours sitting on the couch staring at the television or wall. Some patients will develop simple or complex repetitive behaviors such as touching items in a room, counting figures on patterned wallpaper, or picking up scraps of paper in public places. Hyperorality typically involves increased consumption, particularly of sweets, and in the extreme, can include consumption of spoiled foods and inedible objects. Some patients will begin to use tobacco or alcohol for the first time or increase their use of such substances. Although not included in the core criteria, patients with FTD, particularly those with *C9ORF72* expanded repeat mutations, may also exhibit psychotic features early in the disease course, including visual or auditory hallucinations and bizarre or somatic delusions.[5]

Neurologic Examination

Evidence of the above behavioral changes may be observed during the course of the neurologic examination. Patients with bvFTD may show evidence of poor grooming and hygiene on presentation and loss of manners, such as belching during the examination. Either a flat affect may be observed, or conversely, a silly, childlike affect may be seen and manifested by a patient hugging the examiner or giggling after being instructed to stick out his or her tongue or during the testing of the reflexes. Patients with bvFTD may appear obviously restless, standing up and even attempting to leave the room midexamination. Patients with a flat affect may appear apathetic and lack spontaneous speech, giving only brief one- to two-word responses to questions despite preserved language abilities. Although

KEY POINTS

- Frontotemporal dementia classically affects adults in their fifties to sixties, although cases have been reported from 30 to more than 90 years of age.
- The prevalence of frontotemporal dementia is likely underestimated due to lack of recognition and diagnosis of the frontotemporal dementia syndromes by non-neurologists.
- Behavioral variant of frontotemporal dementia is defined by the gradual onset and progression of changes in behavior, including disinhibition, loss of empathy, apathy, and may include hyperorality and perseverative or compulsive behaviors.
- Patients with frontotemporal dementia may exhibit psychotic features early in the disease course, including visual or auditory hallucinations and bizarre or somatic delusions.

TABLE 5-1 International Consensus Criteria for Behavioral Variant of Frontotemporal Dementia[a]

I. Neurodegenerative Disease

The following symptom must be present to meet criteria for behavioral variant of frontotemporal dementia (bvFTD).

A. Shows progressive deterioration of behavior and/or cognition by observation or history (as provided by a knowledgeable informant)

II. Possible bvFTD

Three of the following behavioral/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early[b] behavioral disinhibition (one of the following symptoms [A.1–A.3] must be present)

A.1. Socially inappropriate behavior

A.2. Loss of manners or decorum

A.3. Impulsive, rash, or careless actions

B. Early[b] apathy or inertia (one of the following symptoms [B.1–B.2] must be present)

B.1. Apathy

B.2. Inertia

C. Early[b] loss of sympathy or empathy (one of the following symptoms [C.1–C.2] must be present)

C.1. Diminished response to other people's needs and feelings

C.2. Diminished social interest, interrelatedness, or personal warmth

D. Early[b] perseverative, stereotyped, or compulsive/ritualistic behavior (one of the following symptoms [D.1–D.3] must be present)

D.1. Simple repetitive movements

D.2. Complex, compulsive, or ritualistic behaviors

D.3. Stereotypy of speech

E. Hyperorality and dietary changes (one of the following symptoms [E.1–E.3] must be present)

E.1. Altered food preferences

E.2. Binge eating, increased consumption of alcohol or cigarettes

E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions (all of the following symptoms [F.1–F.3] must be present)

F.1. Deficits in executive tasks
F.2. Relative sparing of episodic memory
F.3. Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A–C) must be present to meet criteria.

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating Scale or Functional Activities Questionnaire scores)

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TABLE 5-1 International Consensus Criteria for Behavioral Variant of Frontotemporal Dementia[a] *Continued from page 466*

C. Imaging results consistent with bvFTD (one of the following [C.1–C.2] must be present)

C.1. Frontal and/or anterior temporal atrophy on MRI or CT

C.2. Frontal and/or anterior temporal hypoperfusion or hypometabolism on positron emission tomography (PET) or single-photon emission computed tomography (SPECT)

IV. bvFTD With Definite Frontotemporal Lobar Degeneration Pathology

Criterion A and either criterion B or C must be present to meet criteria.

A. Meets criteria for possible or probable bvFTD

B. Histopathologic evidence of frontotemporal lobar degeneration on biopsy or at postmortem

C. Presence of a known pathogenic mutation

V. 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 disease

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.

[a] Reprinted with permission from Rascovsky K, et al, Brain.[4] *brain.oxfordjournals.org/content/134/9/2456.short.* © The Author (2011). Published by Oxford University Press on behalf of the Guarantors of Brain.

[b] As a general guideline, *early* refers to symptom presentation within the first 3 years.

such abnormal behaviors typically increase over the course of the disease, at early stages patient's conduct may be generally appropriate for the limited time of the examination. Positive snout or grasp reflex may be present, although these frontal release signs are not sensitive or specific for FTD.[6] Cranial nerve, motor, sensory, and the remainder of reflex examinations are typically normal.

Neuropsychological Testing in Behavioral Variant of Frontotemporal Dementia

Standard neurocognitive testing in patients with bvFTD classically demonstrates deficits in executive function tasks, with relative sparing in memory and visuospatial domains. However, many patients with early-stage disease may still perform well on executive tasks, particularly those patients with right temporal predominant atrophy. It is now appreciated that some patients with bvFTD have significant episodic memory deficits.[7] While specific standardized tests of social cognition are in validation stages for bvFTD, patients with bvFTD generally show poor performance on tasks of facial expression recognition, particularly for negative emotions, as well as on theory of mind tasks, such as visual cartoons in which they must understand the mental state of others. Consideration of qualitative aspects of performance during neurocognitive testing including behaviors and error types may be more helpful than raw scores in detecting bvFTD. Specifically, during testing, patients with bvFTD

KEY POINTS

- Standard neurocognitive testing in behavioral variant of frontotemporal dementia classically demonstrates deficits in executive function tasks, with relative sparing in memory and visuospatial domains.
- Consideration of qualitative aspects of performance during neurocognitive testing, such as impulsive behaviors and error types, may be more helpful than raw scores in detecting behavioral variant of frontotemporal dementia.

may appear restless, apathetic, perseverative, confabulatory, and impulsive, failing to wait for the examiner to finish task instructions and including expletives in phonemic fluency tests.[8]

Neuroimaging Characteristics

Atrophy or hypometabolism of the right frontal or right temporal lobe is the hallmark neuroimaging finding in patients with bvFTD (**Case 5-1**). Bilateral frontal lobe involvement may also be seen, although when atrophy is observed in the dominant hemisphere, language symptoms are typically also present (see later discussion of semantic variant PPA and nonfluent agrammatic variant PPA). Patterns of atrophy in other brain regions vary according to mutation type. Patients with *C9ORF72* expanded repeats demonstrate atrophy predominantly in the frontal lobes, with some atrophy also observed in the anterior temporal lobes, parietal lobes, occipital lobes, and cerebellum and thalamus; in *MAPT* mutations, atrophy is greatest in the anteromedial temporal lobes; patients with bvFTD and *GRN* mutations show temporal, insular, and parietal lobe atrophy.[10,11] On fluorodeoxyglucose positron emission tomography (FDG-PET) imaging, hypometabolism in the right temporal or right or bilateral frontal lobes is suggestive of FTD (**Figure 5-2**[12]). Patterns of frontal or anterior temporal hypoperfusion with preserved parietal signal on SPECT can distinguish FTD from AD with a sensitivity and specificity of approximately 80%.[13] Similar patterns of hypometabolism on FDG-PET imaging show approximately 90% diagnostic accuracy when distinguishing FTD from AD.[14] PET amyloid imaging shows a similarly high accuracy of

Case 5-1

A 54-year-old man presented to the psychiatric emergency department for bizarre behavior, claiming he had won the lottery. The family reported that 6 years prior to presentation he became less organized managing his finances. The family discovered 3 years ago that bills, including the mortgage, were going unpaid, and he had accumulated significant credit card debt. His affect became flat, and his family reported that it was ''hard to get a reaction out of him.'' He began to cook in an impulsive way, turning the burners on maximum for everything. The patient had lost his job for inappropriate borrowing of money from clients 1 year prior to presentation. He began buying multiple lottery tickets each week, and despite financial difficulties, he purchased a luxury motorcycle. He began wearing the same clothing multiple days in a row and required encouragement to shower. He lost interest in his hobbies and spent increasing amounts of time ''staring'' at the television. Family history was negative for any neurodegenerative diseases, although his father died in his forties of a myocardial infarction, and his mother died in her early sixties of cancer. On examination, the patient was mildly unkempt, with a flat affect, and appeared apathetic. His speech was fluent with preserved naming, repetition, and comprehension. Cranial nerves were intact, including normal saccades. There was no evidence of bradykinesia. Sensory and motor examinations were normal. He had mild difficulty performing the Luria hand sequence (a three-step hand movement sequence of fist-side-flat) on the left compared to the right. Snout and grasp reflexes were absent (normal). On cognitive testing, he scored 26 out of 30 on the Mini-Mental State Examination (MMSE) and 14 out of 30 on the Montreal Cognitive Assessment (MoCA), losing points for attention, concentration, working memory items, and Trail Making B test sample. Semantic and phonemic fluency were both moderately impaired. MRI imaging demonstrated bifrontal and temporal atrophy (**Figure 5-1**). Subsequent genetic testing for *C9ORF72*, *GRN*, and *MAPT* did not reveal any pathogenic mutations. A diagnosis of probable behavioral variant of frontotemporal dementia (FTD) was made. He was advised to stop driving and was reported to the Department of Transportation. Family were referred to a social worker and an FTD caregiver support group. Citalopram 20 mg/d was started with modest improvement of the obsessive behaviors.

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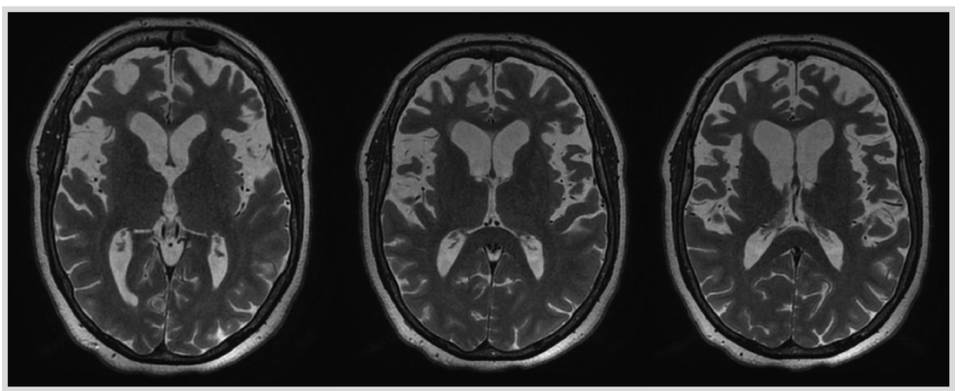

FIGURE 5-1 T2-weighted axial MRI shows bifrontal and temporal atrophy in the patient in **Case 5-1** with sporadic behavioral variant of frontotemporal dementia.

Comment. There is commonly a long delay between the onset of symptoms and time of presentation, given the subtle nature of the personality and behavior changes that are the hallmark of early FTD. Patients often accumulate significant debt prior to diagnosis. It is important for caregivers to put a power of attorney in place for care and finances to limit patients' access to spending money. In patients with frontal lobe deficits, inattention and impulsivity pose significant risks during driving and typically are indications for driving cessation. While there are no treatments specifically approved for use in patients with FTD, off-label use of selective serotonin reuptake inhibitors (SSRIs) may help with agitation, obsessive-compulsive behaviors, and hyperphagia.[9]

distinguishing FTD from AD, with patients with FTD typically showing low levels of amyloid binding on PET (amyloid negative), while patients with AD show elevated amyloid binding (amyloid positive).[12] Several PET tau ligands are currently under investigation in FTD but are not validated to date.

Diagnostic Challenges in Behavioral Variant of Frontotemporal Dementia

Making and confirming a diagnosis of bvFTD can be challenging as the personality or behavioral changes are insidious, and diagnosis in the early stages is highly reliant on caregiver reports of behavioral changes. Furthermore, the degree of frontal atrophy can overlap with that observed in normal controls.[15] The term *bvFTD phenocopy syndrome* has been used to characterize patients who present with a history obtained from a caregiver that meets symptom-based criteria for possible FTD but who lack focal atrophy on neuroimaging and who do not progress to demonstrate objective behavioral or cognitive deficits.[16] Patients with bvFTD phenocopy syndrome who fail to progress have increased rates of mood disorders, substance abuse, obsessive-compulsive personality traits, Asperger syndrome traits, or recent intense life events that likely contribute to the observed behaviors.[17] Thus, careful consideration of the patient's baseline personality, life events, and relationship factors that may influence behavior, and the caregiver's perspective on behaviors, is necessary.[18]

KEY POINTS

- Consideration of the patient's baseline personality, life events, and relationship factors that may influence behavior, and the caregiver's perspective on behaviors, is necessary for accurate diagnosis of behavioral variant frontotemporal dementia.
- The hallmark symptom of semantic variant primary progressive aphasia is the loss of word meaning.

SEMANTIC VARIANT PRIMARY PROGRESSIVE APHASIA

The hallmark symptom of semantic variant PPA, previously called semantic

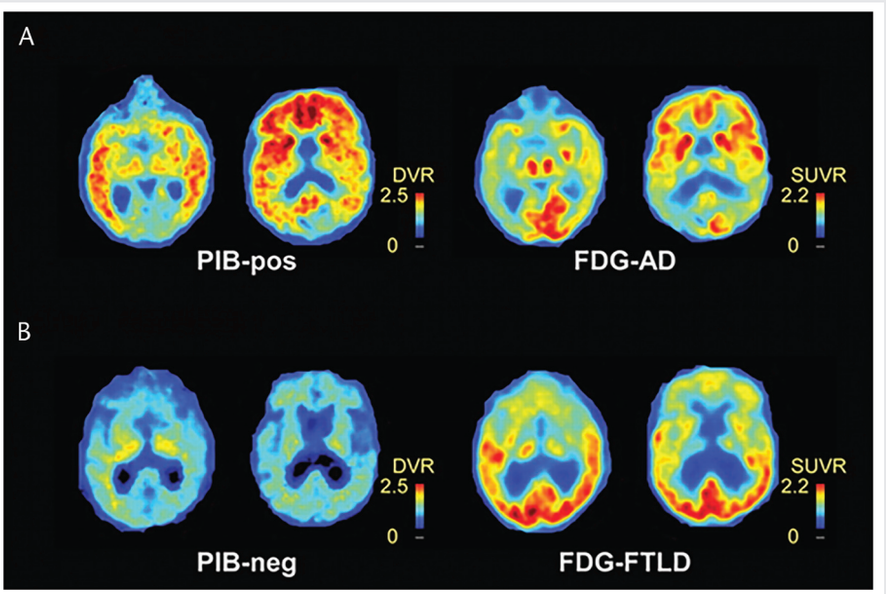

FIGURE 5-2 Example of amyloid (Pittsburgh compound B [PiB]) and fluorodeoxyglucose positron emission tomography (FDG-PET) scans demonstrating typical patterns of diffuse amyloid deposition and temporal and parietal hypometabolism in Alzheimer disease (*A*) in contrast to the absence of amyloid deposition and presence of frontal hypometabolism in a patient with frontotemporal dementia–motor neuron disease, confirmed on autopsy to have frontotemporal lobar degeneration (FTLD) with TDP-43 inclusions (*B*).

AD = Alzheimer disease; DVR = distribution volume ratio; neg = negative; pos = positive; SUVR = standardized uptake value ratio.

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dementia, is the loss of word meaning.[19] Due to atrophy in the dominant anterior temporal pole (**Case 5-2**), patients with semantic variant PPA demonstrate anomia and single-word comprehension deficits and may ask what words mean (ie, ''What is spaghetti?''). While fluency and grammar are generally maintained, speech becomes increasingly empty, with vague words or jargon phrases replacing specific nouns and verbs (**Table 5-2**[20]).

Case 5-2

A 69-year-old right-handed retired secretary was referred for a neurologic consultation for difficulties with ''memory'' and behavior. She had a long history of anxiety and depression that had been managed by medications until 2 years prior to presentation, when she was dismissed from her volunteer job for ''lacking control.'' Her family noted trouble with word comprehension, as the patient would ask, ''What is a screwdriver?'' and ''What is a buffet?'' Circumlocutions were noted in her descriptions, such as describing a pizza as a ''round thing.'' This was followed by lack of recognition of objects. For example, when her husband handed her an ice cream cone, she grabbed at the ice cream on top rather than from the cone. Recently, she had not recognized her niece and nephew or herself in photographs. The patient stopped initiating household chores, such as doing the dishes or laundry, and appeared confused when attempting such tasks. According to her husband, she was ''always walking, pacing, or standing.'' She became very self-centered and seemed to lack appreciation of others' needs. She became fixated on daily routines

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even if inconvenient to others. Her personal hygiene declined. Family history was notable for multiple family members on her mother's side with anxiety and depression. There was no known history of neurodegenerative dementia or amyotrophic lateral sclerosis in any family members.

On examination, while her speech rate was generally high, she used frequent fillers, such as ''thing'' or ''da da da.'' Her responses to direct questions were tangential. The remainder of her neurologic examination was normal, including the absence of frontal release signs. On further cognitive testing, she scored 8 out of 30 on the Mini-Mental State Examination (MMSE), typically not understanding the question being asked. Her clock drawing skills were reasonably preserved. Semantic fluency was severely impaired with only two animals named in 1 minute. In contrast, phonemic fluency was only mildly impaired with a total of 20 F-A-S Test words named over the 3 minutes (patient was given 1 minute to list words beginning with the letter *F*, followed by 1 minute to list words beginning with *A*, and then 1 minute to list words beginning with the letter *S*). Naming on the Western Aphasia Battery was impaired, with only 11 out of 20 items correct and some evidence of visual object agnosia, including nonrecognition of a pipe. Deficits in semantic association were also demonstrated on the Pyramid and Palm Trees Test. Trail Making B test was normal at the 50th percentile.

Review of a recently performed brain MRI demonstrated severe anterior left temporal lobe atrophy and moderate atrophy of the right temporal pole (**Figure 5-3**). A diagnosis of semantic variant primary progressive aphasia was made.

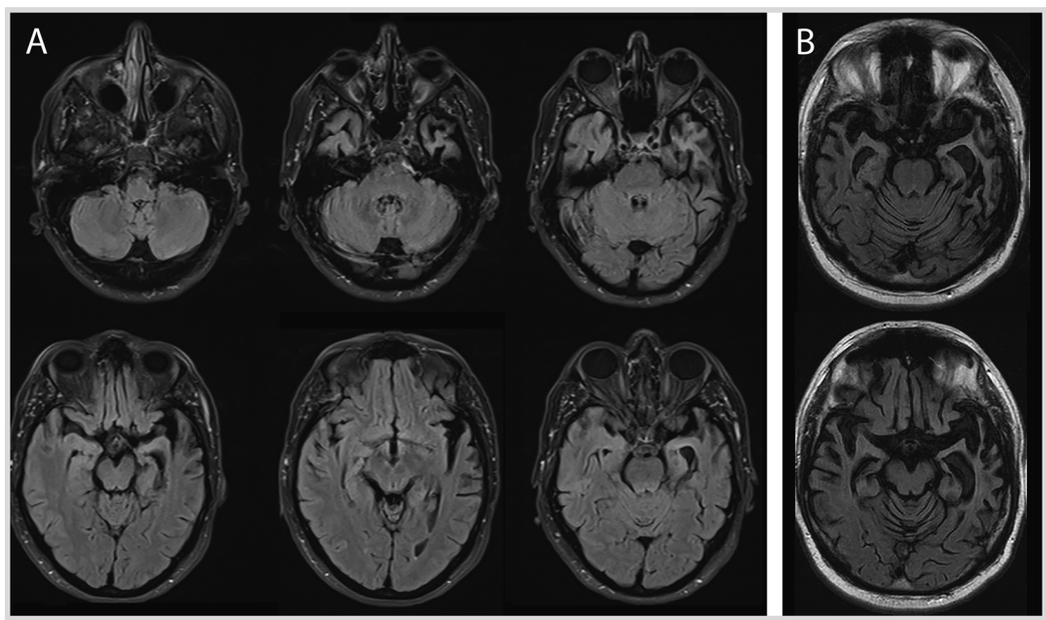

FIGURE 5-3 Imaging of the patient in **Case 5-2.** *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI demonstrating left temporal pole atrophy suggestive of semantic variant primary progressive aphasia. *B*, With disease progression, severe atrophy is observed in the left temporal pole as well as significant atrophy in the right temporal pole on axial FLAIR MRI.

Comment. This patient demonstrates a classic presentation of semantic variant primary progressive aphasia. Often, the family members may identify the chief complaint as memory deficits, but with careful assessment, it is clear that loss of word meaning and comprehension deficits underlie the observed changes. Behavioral features are usually present early on and progress with increasing atrophy of the right temporal lobe.

KEY POINT

- Atrophy of the dominant anterior temporal pole is the characteristic finding in semantic variant primary progressive aphasia.

TABLE 5-2 Diagnostic Criteria for Semantic Variant Primary Progressive Aphasia[a]

Both of the following core features must be present

1. Impaired object naming
2. Impaired single-word comprehension

Three of the following ancillary features must be present

1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared grammaticality and motor aspects of speech

[a] Modified with permission from Gorno-Tempini ML, et al, Neurology.[20] *www.neurology.org/content/76/11/1006.full*. © 2011 American Academy of Neurology.

Patients with semantic variant PPA may lose the normal give and take of conversation, talking incessantly and requiring interruption to conduct the examination. Patients with semantic variant PPA also demonstrate abnormal behaviors, largely overlapping with those described above for patients with bvFTD, likely due to involvement of the right anterior temporal lobe and connections to the orbitofrontal cortex.[21,22] Patients with right-sided temporal atrophy may present with behavioral features and relatively preserved language, but over time will also develop semantic deficits. As the disease progresses and begins to involve the posterior temporal regions and visual temporal association areas, patients may also develop visual agnosia and prosopagnosia.

Neuropsychological Testing in Semantic Variant Primary Progressive Aphasia

Patients with semantic variant PPA demonstrate deficits in single-word comprehension when asked to define single words (eg, "What is an accordion?"). Speech production during picture descriptions (ie, cookie jar theft picture) shows a normal or near-normal word production rate but frequent use of filler words (**Case 5-2**). Tests of semantic associations, such as the palms and pyramids task, show deficits for words, and over time, often for picture stimuli. (In the palms and pyramids task, patients are shown a stimulus [a picture or word] and must choose the related picture or word from two choices; eg, a vest is shown with choices of a bowtie [correct] and necklace [incorrect]). Patients with semantic variant PPA may show an interesting pattern of episodic memory deficits opposite to that observed in AD, with better recall of recent events and people and relative loss of more remote autobiographic memories.[23]

Neurologic Examination

Loquacious but empty, tangential, or repetitive speech is evident during the course of the interview and examination. Patients may repeat short catch phrases or jokes. The remainder of the neurologic examination, including frontal reflexes, is typically normal.

Neuroimaging

Atrophy of the dominant anterior temporal pole is the hallmark finding in semantic variant PPA (**Figure 5-3**).[24] While involvement is typically asymmetric at onset, over time the contralateral temporal lobe is also affected.

NONFLUENT AGRAMMATIC VARIANT PRIMARY PROGRESSIVE APHASIA

Nonfluent agrammatic variant PPA, also known as progressive nonfluent aphasia, features progressively nonfluent, agrammatic speech that is hesitant or halting (**Table 5-3**[20]). Grammatical errors are observed in spontaneous speech and frequently include omission of small, closed class words (eg, and, or, a, the), dropping of verb endings, and errors in subject/verb agreement (**Case 5-3**). Patients with nonfluent agrammatic PPA frequently also demonstrate apraxia of speech, defined as impaired motor speech planning, manifest by articulation deficits.[25] Although comprehension is generally preserved in early stages of disease, deficits comprehending grammatically complex sentences such as those featuring objective relative clauses are common (ie, ''The lion was killed by the tiger. Which animal is alive?''). Patients presenting with nonfluent agrammatic variant PPA may also demonstrate or develop behavioral changes of bvFTD or features of CBS or PSP. Longitudinal, autopsy-confirmed studies of patients presenting with nonfluent agrammatic variant PPA demonstrate several final clinical and pathologic diagnoses, most commonly bvFTD, PSP, or CBS.[26]

Neurologic Examination

Nonfluent speech with word-finding difficulties, circumlocutions, stuttering, and grammatical errors with relative preservation of comprehension is typically observed, although deficits may be mild at first. Subtle right-side motor deficits (slower fine motor movements, pronator drift) may be observed in some patients with more widespread pathology in the left (or dominant) frontal lobe.

Neuroimaging

Nonfluent agrammatic variant PPA is associated with atrophy of the dominant inferior frontal lobe (**Figure 5-4**).

PROGRESSIVE SUPRANUCLEAR PALSY

Although originally classified as a Parkinson-plus syndrome, PSP is now also included as an FTD-related disorder based on the presence of frontal lobe involvement and tau pathology. Prior to the onset of hallmark features including early postural instability and vertical gaze impairments, approximately 20% of patients with PSP first present with FTD symptoms, including behavioral changes or progressive language deficits (**Table 5-4**). The most common behavioral symptoms in patients with PSP include apathy,

KEY POINTS

- Hallmark features of nonfluent agrammatic variant primary progressive aphasia include nonfluent speech with word-finding difficulties, circumlocutions, stuttering, and grammatical errors with relative preservation of comprehension.
- Approximately 20% of patients with progressive supranuclear palsy first present with frontotemporal dementia symptoms including behavioral changes or progressive language deficits.

TABLE 5-3 Diagnostic Criteria for Nonfluent Agrammatic Variant Primary Progressive Aphasia[a]

One of the following core features must be present

1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)

Two of the following three ancillary features must be present

1. Impaired comprehension of syntactically complex (noncanonical) sentences
2. Spared single-word comprehension
3. Spared object knowledge

[a] Modified with permission from Gorno-Tempini ML, et al, Neurology.[20] *www.neurology.org/content/76/11/1006.full*. © 2011 American Academy of Neurology.

Case 5-3

A 66-year-old woman presented for a neurologic consultation because of difficulty speaking. She reported 2 to 3 years of gradually increasing deficits in ''getting the words out.'' She stated, ''I know what I want to say, but the words get stuck at the tip of my tongue.'' Her spouse noticed that at times she would get part of the sound of the word correct, and part wrong, such as calling a ''fork'' a ''fort.'' She had also developed a mild stutter. Her husband noticed she was often able to describe the meaning of the word, even when she could not say the word itself.

On examination, she demonstrated halting, hesitant speech although she could generally answer questions appropriately. She correctly named a chair and key, but could not name the glove, instead gesturing to her hand. She could not name cactus, but said ''it is a thing that grows…desert…ouch.'' During repetition she omitted small words and made paraphasic errors. She followed all verbal and written commands. When asked to write a sentence, she wrote, ''Today very sunny outside.'' When asked to describe the picnic scene from the Western Aphasia Battery, she demonstrated word-finding deficits, paraphasic errors, and hesitations (item she was pointing to in parentheses): ''The carpet, and man, and woman…on their black (blanket). Man's food…food there (sandals). The man…bag…bark (book). The man glass (glasses). Bag (basket). Boy has a kite…a gags…(dog). Girl…song…sand…make (rake), sarvs (shovels), cake…cast (castle). Man on dark (dock) and fish. Sailboat and two babli (people)…there. A house there. A car… garange (garage) there and flangs (flag). Tree.'' The remainder of her neurologic examination was unremarkable. Neuroimaging demonstrated atrophy in the left inferior frontal lobe (**Figure 5-4**).

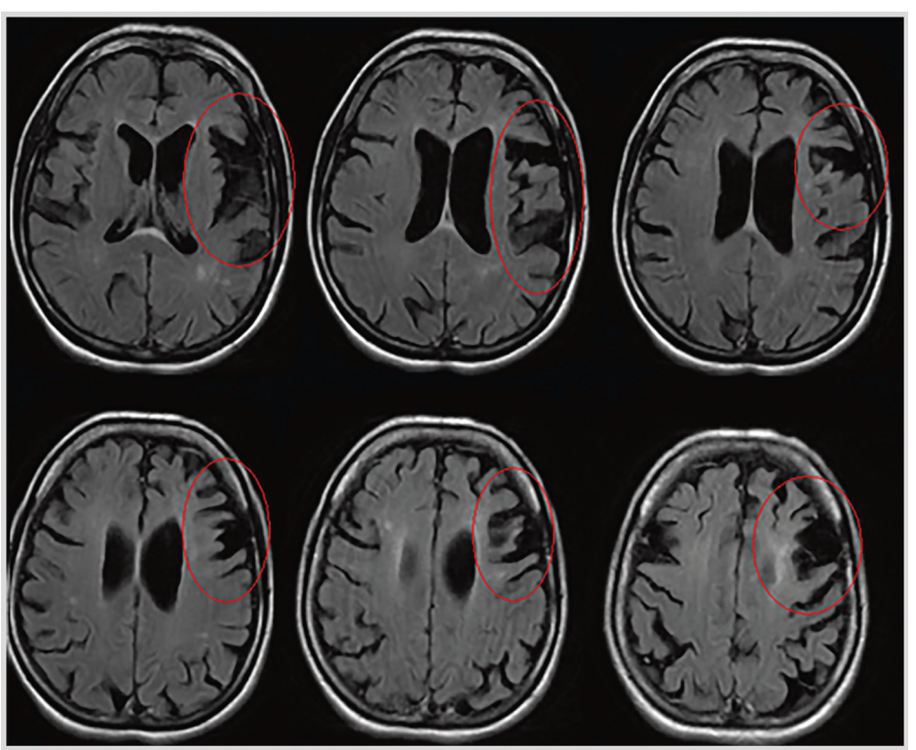

FIGURE 5-4 Imaging of the patient in **Case 5-3** who presented with nonfluent agrammatic variant primary progressive aphasia. Axial fluid-attenuated inversion recovery (FLAIR) MRI demonstrating left posterior frontal and frontoinsular atrophy (*circled in red*).

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Continued from page 474

One year later, the patient presented with further deficits in articulatory speech consistent with verbal apraxia. She also demonstrated worsening short-term verbal memory deficits and new difficulty with dressing (despite normal strength). On examination, mild rigidity and odd involuntary posturing of her right arm were noted, with ideomotor apraxia and deterioration of handwriting (**Figure 5-5**).

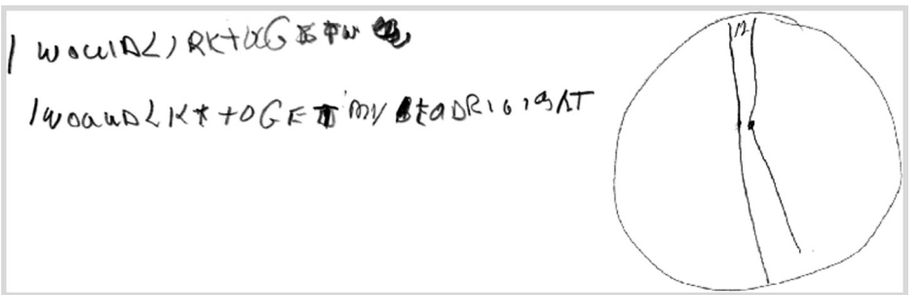

FIGURE 5-5 Handwriting sample and attempt at clock drawing of the patient in Case 5-3 with corticobasal syndrome including symptoms of the nonfluent agrammatic variant primary progressive aphasia. The handwriting sample demonstrates spelling and grammatical errors, as well as difficulty forming and spacing letters. Visual construction deficits are apparent on the clock drawing.

Comment. This patient initially presented with symptoms meeting criteria for nonfluent agrammatic variant primary progressive aphasia and indicative of dominant frontal lobe pathology. Over time, her symptoms progressed to include apraxia and alien limb phenomenon, consistent with evolution to corticobasal syndrome. In addition to progression to corticobasal syndrome, patients presenting with nonfluent agrammatic variant primary progressive aphasia may also develop symptoms consistent with behavioral variant of frontotemporal dementia or progressive supranuclear palsy.

disinhibition, anxiety, dysphoria, stereotypic or repetitive behaviors, and up to 30% of patients with PSP will meet criteria for bvFTD.[26,27] Patients with PSP may also present with primary apraxia of speech, combined apraxia of speech and progressive nonfluent aphasia, or develop these symptoms

TABLE 5-4 Clinical Presentations of Progressive Supranuclear Palsy

- Richardson syndrome (early falls, cognitive dysfunction, vertical gaze abnormalities, axial rigidity, postural instability, symmetric bradykinesia, little or no response to levodopa)
- Progressive supranuclear palsy–parkinsonism (early asymmetric bradykinesia, some response to levodopa)
- Corticobasal syndrome
- Pure akinesia with freezing of gait
- Primary progressive apraxia of speech
- Progressive nonfluent aphasia
- Behavioral variant of frontotemporal dementia
- Cerebellar ataxia

KEY POINTS

- Most commonly, patients with progressive supranuclear palsy demonstrate cognitive slowing and poorer performance on timed tests of executive function and verbal fluency.
- In patients presenting with primary apraxia of speech, progressive supranuclear palsy is the most common underlying pathology.
- Patients with corticobasal degeneration may first present with behavioral changes, executive function deficits, or language features consistent with early frontal lobe pathology.

during the disease course.[25] In patients presenting with primary apraxia of speech, atrophy or hypometabolism is found in the superior premotor cortex and supplementary motor area, and PSP is the most common underlying pathology.[28]

Neurologic Examination

In the most common subtype of PSP, Richardson syndrome, increased axial rigidity of the neck and trunk, slowed vertical saccades, dysarthria, apathy or depression, and general slowing of speech and thought are observed.[26] Gait is often narrow based in early stages of the disease despite a history of falls and imbalance. As the disease progresses, patients often develop ophthalmoplegia particularly of vertical gaze, akinetic rigid parkinsonism, dystonia, verbal apraxia, pseudobulbar palsy, and frontal release signs.

Neuropsychological Testing

Cognitive deficits are found in the majority of patients with PSP. Most commonly, patients with PSP demonstrate cognitive slowing and poorer performance on timed tests of executive function and verbal fluency.[27] Comprehension and memory are generally preserved.

Neuroimaging

Structural imaging in PSP may reveal midbrain atrophy referred to as the hummingbird sign on sagittal images (**Figure 5-6**[29]), as well as hypometabolism in frontal, caudate, midbrain, and thalamic regions on FDG-PET.[30]

CORTICOBASAL DEGENERATION

Corticobasal degeneration (CBD) is a progressive neurodegenerative disorder affecting the frontal and parietal cortices and basal ganglia associated with abnormal 4-repeat tau isoform pathology. The term *corticobasal syndrome* (CBS) is used to describe patients presenting with the clinical features associated with CBD but who lack histologic confirmation, as CBS presentations may be associated with a variety of underlying neuropathologies including AD, FTD, and CBD. CBD is typically sporadic, although occasionally CBS is the presenting phenotype for patients with *MAPT*, *GRN*, or *C9ORF72* mutations. Classic features of CBS include apraxia and alien limb phenomenon, frontal deficits, and extrapyramidal motor symptoms such as myoclonus or rigidity. Five phenotypic presentations of CBD have recently been proposed (**Table 5-5**).[31] As in PSP, patients with CBD may first present with behavioral changes, executive function deficits, or language features consistent with early frontal lobe pathology. Behavioral changes include those described for bvFTD. Language presentations of CBS are most commonly agrammatic nonfluent aphasia or apraxia of speech. Symptoms referable to the parietal

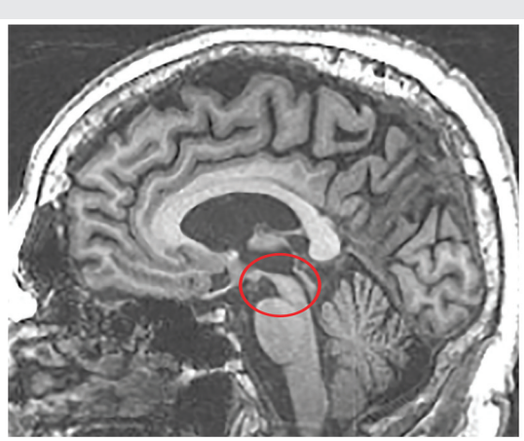

FIGURE 5-6 Midbrain atrophy in progressive supranuclear palsy. Midsagittal MRI in a patient with progressive supranuclear palsy demonstrating thinning of the rostral midbrain resulting in the hummingbird sign.

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TABLE 5-5 Proposed Clinical Phenotypes Associated With the Pathology of Corticobasal Degeneration[a]

Syndrome	Features
Probable corticobasal syndrome	Asymmetric presentation of two of the following symptoms
	Limb rigidity or akinesia
	Limb dystonia
	Limb myoclonus
	Plus two of the following symptoms
	Orobuccal or limb apraxia
	Cortical sensory deficit
	Alien limb phenomena (more than simple levitation)
Possible corticobasal syndrome	May be symmetric: one of the following symptoms
	Limb rigidity or akinesia
	Limb dystonia
	Limb myoclonus
	Plus one of the following symptoms
	Orobuccal or limb apraxia
	Cortical sensory deficit
	Alien limb phenomena (more than simple levitation)
Frontal behavioral-spatial syndrome	Two of the following symptoms
	Executive dysfunction
	Behavioral or personality changes
	Visuospatial deficits
Nonfluent agrammatic variant primary progressive aphasia	Effortful, agrammatic speech plus at least one of the following symptoms
	Impaired grammar/sentence comprehension with relatively preserved single-word comprehension
	Groping, distorted speech production (apraxia of speech)
Progressive supranuclear palsy syndrome	Three of the following symptoms
	Axial or symmetric limb rigidity or akinesia
	Postural instability or falls
	Urinary incontinence
	Behavioral changes
	Supranuclear vertical gaze palsy or decreased velocity of vertical saccades

[a] Reprinted with permission from Armstrong MJ et al, Neurology.[31] *www.neurology.org/content/80/5/496.full*. © 2013 American Academy of Neurology.

KEY POINT

- Frontotemporal dementia symptoms are found in approximately 30% of patients diagnosed with amyotrophic lateral sclerosis.

lobes, including apraxias and visuospatial deficits, may also be a presenting feature.[32] Motor abnormalities may be absent in as many as approximately 50% of patients at the time of presentation with cognitive deficits, although during the course of the disease the majority of patients will show motor features. Approximately 30% of patients with CBS will develop alien limb syndrome, in which one arm may levitate or assume involuntary postures or movements, and 25% will have cortical sensory deficits.[31]

Neurologic Examination

Patients presenting with frontal or aphasic subtypes of CBS may present with inappropriate behavioral features described above for bvFTD, or language deficits consistent with nonfluent agrammatic variant PPA, or apraxia of speech. Asymmetric limb rigidity and bradykinesia are the most common motor findings, present in approximately 50% of patients at the time of presentation.[31] Ideomotor apraxia is a frequent finding and may also be asymmetric. Other motor features can include tremor, postural instability and falls, axial rigidity, dystonia including blepharospasm, alien limb, and myoclonus. Cortical sensory deficits may include sensory extinction, agraphesthesia, and astereognosia.

Neuropsychological Testing

Performance patterns on cognitive testing may vary according to the subtype. Many patients with CBS will demonstrate deficits on tasks of executive function, writing, visuospatial, and construction tasks (**Figure 5-5**). Patients presenting with dominant frontal lobe involvement may show word-finding deficits, agrammatism, and spelling errors similar to patients with nonfluent agrammatic PPA.[32]

Neuroimaging

Structural brain imaging in patients with CBS may show asymmetric frontal and parietal lobe atrophy,[33] although imaging findings may overlap with those seen in other FTDs and AD. Thus, diagnosis at present is based on clinical criteria, with neuroimaging performed to rule out other structural causes of symptoms.

FRONTOTEMPORAL DEMENTIA–MOTOR NEURON DISEASE

Frontotemporal dementia symptoms are found in approximately 30% of patients diagnosed with amyotrophic lateral sclerosis (ALS). Patients with FTD-ALS may present with behavioral changes consistent with bvFTD or a milder dysexecutive profile including verbal fluency deficits.[34] Hallucinations and delusions are more common in patients with FTD-ALS, in particular in patients with *C9ORF72* expanded repeat mutations (see the following section on genetic risk factors), the most common genetic cause of familial FTD-ALS.[35,36]

PROGNOSIS

The average survival for patients diagnosed with FTD is approximately 7 to 10 years. Estimates differ somewhat according to FTD subtype, with survival in FTD-MND averaging just 2 to 3 years, approximately 6 to 8 years in PSP, approximately 9 to 10 years in bvFTD and nonfluent agrammatic variant PPA, and the longest median survival in patients with semantic variant PPA of approximately 12 years.[2] Common proximate causes of death in patients with FTD related to the disease include pneumonia or complications of falls.

RISK FACTORS

Although approximately 50% to 60% of FTD is considered to be sporadic in

etiology, genetic mutations account for the majority of risk factors identified for developing FTD.

Environmental

To date there have been few studies of environmental risk factors for FTD. Retrospective case-control studies have found an increased incidence of head injury in patients with a clinical diagnosis of FTD (odds ratios of 3 to 4).[37,38] While repetitive concussions have been linked to progressive neuropsychiatric symptoms, cognitive deficits, and pathologic tau deposition in the frontal and temporal lobes in chronic traumatic encephalopathy,[39] the relationship of isolated concussion or mild head injury in relation to chronic traumatic encephalopathy and other forms of FTD is not yet understood.

Genetic

Approximately 40% of FTD is associated with an autosomal dominant pattern of inheritance, with remaining cases considered sporadic.[40] A careful family history considering not only diagnosis, but also possible FTD symptoms in other family members is essential, as FTD was rarely diagnosed before the 1990s, and family members may have been misdiagnosed with AD, vascular dementia, or late-onset psychiatric disorders. bvFTD and nonfluent agrammatic variant PPA are the most common phenotypes in genetic FTD, although CBS presentations can also occur. Semantic variant PPA is almost always sporadic. PSP is not associated with the FTD mutations described below, although is linked to the H1 haplotype in the *MAPT* gene (see **Box 1 Glossary of Gene and Protein Abbreviations**). Mutations in approximately eight genes have been linked to FTD, accounting for approximately 50% of familial FTD, with mutations in *GRN*, *C9ORF72*, and *MAPT* accounting for the majority of cases of genetically confirmed FTD (**Table 5-6**[35,36,41–53]).[41] Several other genetic mutations are known to be rare causes of familial FTD, including mutations in the *CHMP2B* gene encoding charged multivesicular body protein 2B and mutations in the gene for valosin-containing protein (*VCP*), which is associated with the clinical triad of FTD, inclusion body myopathy, and Paget disease. Of interest, variants in the gene for transmembrane protein 106B (TMEM106B) have been identified to confer protection and delay onset of FTD in patients with *GRN* and *C9ORF72* mutations.[54] A genetic mutation may be found in approximately 6% of patients with no family history of FTD; thus, referral to a genetic counselor for consideration of genetic testing may be considered for all patients presenting with FTD.[55]

NEUROPATHOLOGY

Abnormal accumulations of tau or TDP-43 account for the majority of pathologically confirmed cases of FTD, with FUS inclusions most common in the remaining 10% (**Figure 5-7**[56]).[55] Abnormal aggregations of tau can be found in patients with sporadic bvFTD, CBS, nonfluent agrammatic variant PPA, and PSP as well as *MAPT*-associated familial FTD (**Figure 5-8**[57]). Tau inclusions are rare in patients with semantic variant PPA. Abnormal TDP-43

KEY POINTS

- Approximately 40% of frontotemporal dementia cases are associated with an autosomal dominant pattern of inheritance, with remaining cases considered sporadic.
- A genetic mutation may be found in approximately 6% of patients with no family history of frontotemporal dementia; thus, referral to a genetic counselor for consideration of genetic testing may be considered for all patients presenting with frontotemporal dementia.
- Abnormal accumulations of tau or TDP-43 account for the majority of pathologically confirmed cases of frontotemporal dementia, with FUS inclusions most common in the remaining 10%.

Box 1 Glossary of Gene and Protein Abbreviations

C9ORF72: Chromosome 9 open reading frame 72
CHMP2B: Charged multivesicular body protein 2B
FUS: Fused in Sarcoma RNA binding protein
GRN: Progranulin
MAPT: Microtubule-associated protein tau
TDP-43: Transactive response DNA binding protein 43 kDa
TMEM106B: Transmembrane protein 106B
VCP: Valosin containing protein

TABLE 5-6 Frontotemporal Dementia Gene Mutations[a]

Genes	Chromosome	Protein	Main Clinical Phenotypes
GRN	17q21.32	Progranulin	bvFTD > PPA, semantic variant PPA, CBS
C9ORF72	9p21.2	Unknown	bvFTD, ALS, FTLD-ALS
MAPT	17q21.32	Microtubule-associated tau protein	bvFTD > PSP, CBS
VCP	9p13.3	Valosin-containing protein	Multisystem proteinopathy/IBMPFD
TARDBP	1p36.21	TDP-43	ALS > FTLD-ALS, FTD
FUS/TLS	16p11.2	Fused in sarcoma protein	ALS > bvFTD, FTLD-ALS
SQSTM1	5q35	Sequestome 1/p62	Paget disease of bone, ALS, bvFTD
CSF1R	5q32	Colony-stimulating factor 1 receptor	bvFTD, CBS, strokelike
TREM2	6p21.1	Triggering receptor expressed on myeloid cells	PLOSL, bvFTD,
CHMP2B	3p11.2	Chromatin-modifying protein 2B	bvFTD, FTLD-ALS
UBQLN2	Xp11.21	Ubiquilin 2	ALS > FTLD-ALS
hnRNPA2B1	7p15	Heterogeneous nuclear ribonucleoprotein A2/B1	Multisystem proteinopathy/IBMPFD

ALS = amyotrophic lateral sclerosis; bvFTD = behavioral variant of frontotemporal dementia; CBS = corticobasal syndrome; FTD = frontotemporal dementia; FTLD = frontotemporal lobar degeneration; HDLS = hereditary diffuse leukoencephalopathy with spheroids; IBMPFD = inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia; PLOSL = polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy.

[a] Reprinted with permission from Le Ber I, Rev Neurol (Paris).[41] *www.em-consulte.com/article/840375/alertePM*. © 2013 Elsevier Masson SAS.

KEY POINT

- CSF biomarkers may help to distinguish between frontotemporal dementia and Alzheimer disease, but at present there are no validated biomarkers that can reliably distinguish patients with frontotemporal dementia from controls or other non-Alzheimer disease dementias.

inclusions account for the majority of the remaining tau-negative patients. TDP-43 pathology is found in patients with semantic variant PPA, FTD-MND, and bvFTD, as well as in genetic variants including *C9ORF72*, *GRN*, and *VCP* mutations. TDP-43 pathology is characterized by four patterns that show associations with FTD clinical phenotypes (**Figure 5-9**[57]). FUS pathology is associated with an earlier age of onset of FTD, prominent neuropsychiatric features, and a more rapid course.[55] It has been hypothesized that von Economo neurons, large bipolar neurons in layer V of the cortex, in the anterior cingulate region and frontoinsular junction may be the first site of disease pathology, as early loss of these neurons is found in patients with FTD compared to AD and controls.[58]

CEREBROSPINAL FLUID AND SERUM BIOMARKERS

At present, CSF biomarkers may help to distinguish between FTD and AD, but there are no validated biomarkers that can reliably distinguish patients with FTD from controls or other non-AD dementias. The presence of an AD pattern of biomarkers is considered an exclusion criterion for probable FTD.[4] CSF biomarkers demonstrating

Mode of Inheritance	Mutation Frequencies in Familial FTLD	Pathology	References
Autosomal dominant	5 to 22%	FTLD with TAR DNA binding protein-43 (TDP-43) proteinopathy (type A)	Cruts et al, 2006[42]
Autosomal dominant	FTLD: 7 to 29% FTLD-ALS: up to 66%	FTLD with TDP-43 proteinopathy (types A and B)	Renton et al, 2011[35]; DeJesus-Hernandez et al, 2011[36]
Autosomal dominant	5 to 15%	FTLD with tauopathy	Hutton et al, 1998[43]
Autosomal dominant	3%	FTLD with TDP-43 proteinopathy (type D)	Watts et al, 2004[44]
Autosomal dominant	2%	Undetermined	Benajiba et al, 2009[45]
Autosomal dominant	1%	Undetermined	Broustal et al, 2010[46]
Autosomal dominant	2%	FTLD with TDP-43 proteinopathy	Fecto et al, 2011[47]; Rubino et al, 2012[48]
Autosomal dominant	Undetermined	HDLS	Rademakers et al, 2011[49]
Autosomal recessive	<1%	Undetermined	Guerreiro et al, 2013[50]
Autosomal dominant	< 1%	FTLD with no inclusions	Skibinski et al, 2005[51]
X-linked dominant	<1%	Undetermined	Gellera et al, 2013[52]
Autosomal dominant	Undetermined	Undetermined	Kim et al, 2013[53]

reduced amyloid-β_{42} ($A\beta_{42}$) and increased tau/phosphorylated-tau can distinguish AD from FTD (sensitivity of approximately 80%, specificity of approximately 80%), in which tau levels are normal or low and $A\beta_{42}$ levels are higher than in AD.[59] To aid in FTD diagnosis and track disease progression, several candidate CSF biomarkers are currently under investigation, including neurofilament light chains, TDP-43, and progranulin. Low serum progranulin levels can predict *GRN* mutation status in carriers and patients; however, serum and CSF progranulin levels are only modestly correlated and may vary as a function of age, gender, and other genetic factors.[60]

DIAGNOSTIC WORKUP OF PATIENTS WITH SUSPECTED FRONTOTEMPORAL DEMENTIA

Assessment of patients with possible FTD requires a thorough history with the patient and caregiver or informant. As most patients with bvFTD and semantic variant PPA will have limited insight into their symptoms, it is essential to obtain a history of behavioral, cognitive, or functional decline from a reliable informant who has known the patient for some time in order to assess the extent to which

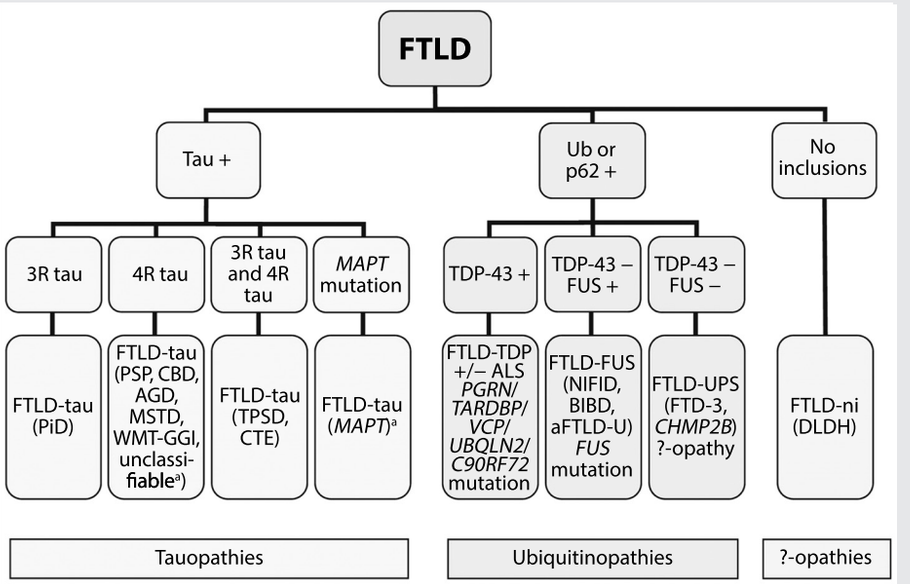

FIGURE 5-7 Neuropathologic classification of frontotemporal lobar degeneration.

aFTLD-U = atypical frontotemporal lobar degeneration; AGD = argyrophilic grain disease; ALS = amyotrophic lateral sclerosis; BIBD = basophilic inclusion body disease; CBD = corticobasal degeneration; CTE = chronic traumatic encephalopathy; DLDH = dementia lacking distinctive histology; FTLD = frontotemporal lobar degeneration; FTD-3 = frontotemporal dementia associated with chromosome 3; FTLD-FUS = frontotemporal lobar degeneration with fused in sarcoma proteinopathy; FTLD-ni = frontotemporal lobar degeneration with no inclusions; FTLD-tau = frontotemporal lobar degeneration with tauopathy; FTLD-TDP = frontotemporal lobar degeneration with TDP-43 proteinopathy; FTLD-UPS = frontotemporal lobar degeneration with involvement of the ubiquitin proteasome system; MSTD = multiple system tauopathy with dementia; NIFID = neuronal intermediate filament inclusion dementia; PiD = Pick disease; PSP = progressive supranuclear palsy; TPSD = tangle predominant senile dementia; Ub = ubiquitin; WMT-GGI = white matter tauopathy with globular glial inclusions; 3R = 3 microtubule-binding repeats; 4R = 4 microtubule-binding repeats; ?-opathy = subtype without a hallmark protein aggregate identified to date; + = inclusions present; - = inclusions absent.

[a] Unclassifiable and *MAPT* related: 3R, 4R, or both.

behavior represents a change from baseline personality traits and habits. Ascertainment of behavioral changes can be facilitated by standardized questionnaires such as the Frontal Behavioral Inventory[61] or the Frontotemporal Dementia Rating Scale (available at *www.ftdrg.org/ace-r-download/frontotemporal-dementia-rating-scale-frs-download/*).[62,63] A full neurologic examination should be performed, including assessment of vertical saccades, axial tone, the presence of parkinsonism, cortical sensory tests, apraxia testing, and frontal release signs. Brain imaging, preferably MRI, is essential to rule out structural and vascular abnormalities and to assess for patterns of focal atrophy. When structural imaging is inconclusive, FDG-PET or SPECT imaging may help to identify the presence of hypometabolism or hypoperfusion and whether the pattern observed is most consistent with FTD. Where available, Pittsburgh compound B (PiB)-PET

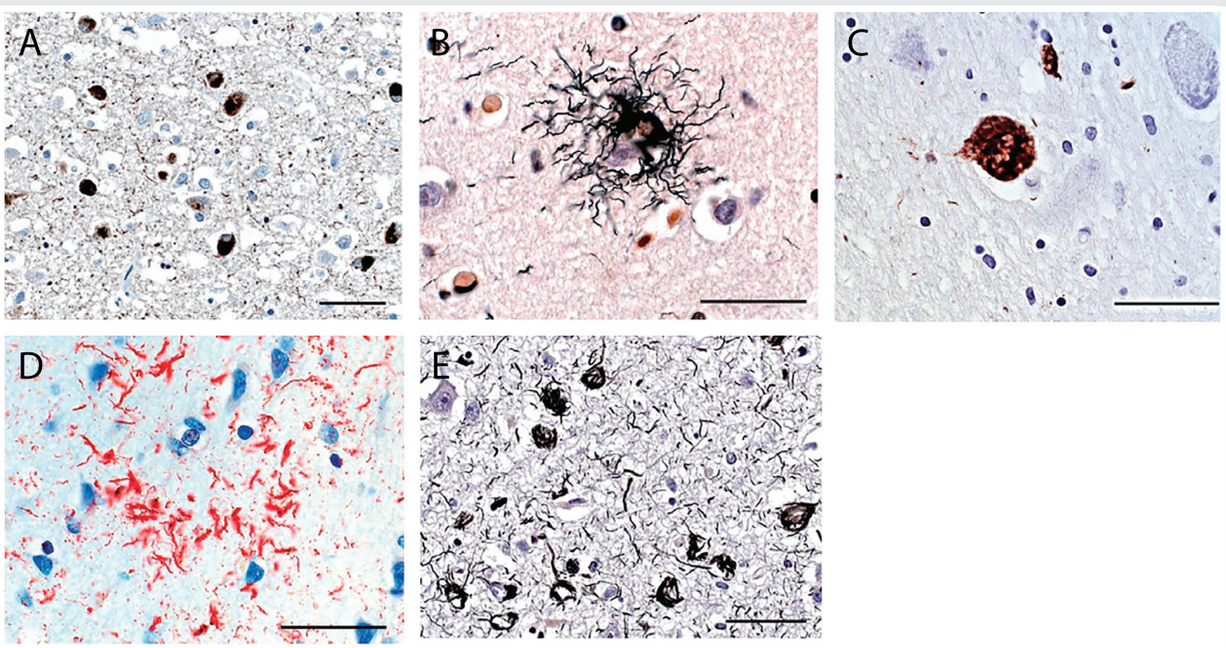

FIGURE 5-8 Pathologic features in frontotemporal lobar degeneration with tauopathy. *A*, Pick bodies in the temporal cortex of a patient with Pick disease; *B*, tufted astrocyte in a patient with progressive supranuclear palsy; *C*, a globose tangle in a case with progressive supranuclear palsy; *D*, astrocytic plaque as a hallmark lesion of corticobasal degeneration; E, neuronal and glial tau pathology in the frontal cortex of a patient with *MAPT* gene mutation. *Panels A, C*, and *D* are tau immunohistochemistry; *Panels B* and *E* are Gallyas-Braak silver stain. Scale bars: 50 mm.

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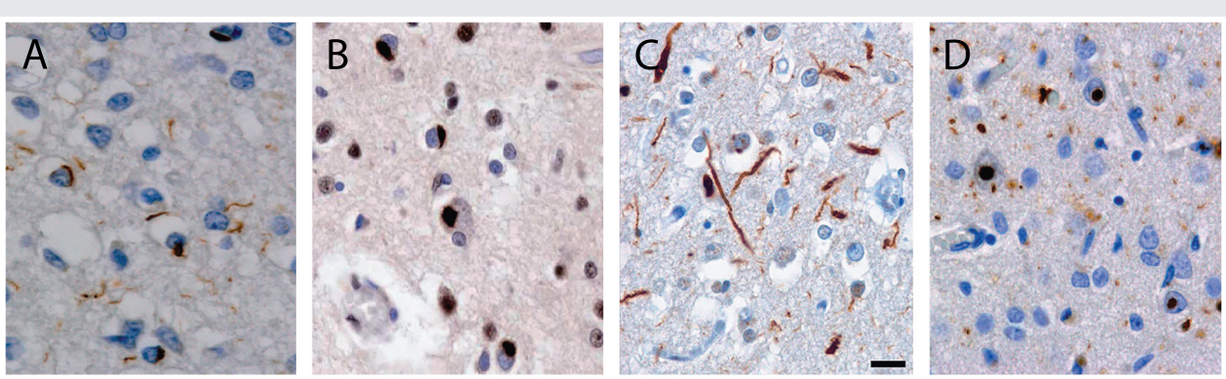

FIGURE 5-9 Types of TDP-43 pathology in frontotemporal lobar degeneration. *A*, Type A is characterized by compact neuronal cytoplasmic inclusions and short neurites and is most commonly associated with behavioral variant of frontotemporal dementia, progressive nonfluent aphasia, and *GRN* mutations. *B*, Type B is characterized by compact and granular cytoplasmic inclusions and is associated with frontotemporal dementia–motor neuron disease, behavioral variant of frontotemporal dementia, and *C9ORF72* expanded repeats. *C*, Type C is characterized by long neurites and is found in semantic variant primary progressive aphasia. *D*, Type D is characterized by numerous neuronal intranuclear inclusions and is found in patients with *VCP* mutations.

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imaging or CSF $A\beta_{1-42}$ and tau analysis may aid in distinguishing FTD from frontal or language presentations of AD. For patients interested in genetic testing, or those with a family history suggestive of FTD or ALS, referral to a genetic counselor for consideration of genetic testing is indicated. Knowledge of genetic status can confirm a diagnosis of familial FTD and may aid referral of patients and carriers to current and future clinical trials targeting specific FTD mutations.

PATIENT MANAGEMENT

There are currently no therapies specifically approved for FTD. Thus, education and supportive management of safety and behavioral issues for the patient and caregiver are essential in supporting patients with FTD.[64,65]

Supportive Management and Follow-up Assessments

A power of attorney for personal care and finances should be put into place for patients with FTD, as impaired judgment and impulsivity can result in significant financial difficulties. There are few studies of driving safety in patients with FTD. Those available suggest that the risk of accidents is increased even in patients with mild disease and is related to inattention, impulsivity, and poor emotion regulation. Careful and frequent reassessment of patient's behavioral symptoms and cognitive testing performance when considering driving privileges is necessary, potentially supported by on-road driving assessments. Caregivers and families should also be counseled regarding gun safety or other potentially hazardous activities or pastimes. Speech and swallowing assessments are indicated to optimize communication strategies and screen for dysphagia, which is common, particularly in patients with nonfluent agrammatic variant PPA and PSP. Physical therapy evaluations of gait when falls or balance problems are reported and occupational therapy assessments of home safety are also indicated. Caregivers should be referred to local FTD or dementia support groups for support and education of behavioral management strategies. The changes in behavior chart offers helpful strategies for problematic behaviors (*www.theaftd.org/wp-content/uploads/2011/09/Packet-Changes-in-behavior-chart.pdf*).[66]

Pharmacologic Treatment

Current treatment approaches are limited to symptomatic treatments that employ off-label uses of medications modulating neurotransmitter systems, usually to modify difficult behaviors.[9,67] Most commonly, selective serotonin reuptake inhibitors (SSRIs), such as citalopram, or trazodone are used to improve behavioral symptoms including disinhibition, agitation/irritability, or compulsive behaviors (**Table 5-7**[9,68–75]). Psychosis and aggression may require neuroleptic medications, although gold standard randomized clinical trials of these agents are not available in patients with FTD. If needed, initiation at a low dose and frequent reassessment of efficacy and need for continued use are required given black box warnings for this class of medications due to increased mortality. Although parkinsonism in patients with FTD is usually not dopamine responsive, as a fraction of patients may benefit, a trial of carbidopa/levodopa titrating up to 25 mg/250 mg 3 times daily for parkinsonism is generally indicated. Cholinesterase inhibitors may frequently increase agitation in patients with bvFTD and, thus, are not indicated.

TABLE 5-7 Treatment Approaches for Behavioral Symptoms in Frontotemporal Dementia[a]

bvFTD Symptom	Current Treatment Options	Evidence for Current Treatments	Possible Future Treatment Options
Apathy	None	NA	Dopaminergic medications
Behavioral disinhibition	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram	Open-label studies supporting use of SSRIs[68–70]	
	Trazodone	Double-blind, placebo-controlled study supporting the use of trazodone[71]	
	Atypical antipsychotics: risperidone, aripiprazole, olanzapine, quetiapine	Case reports supporting use of antipsychotics[70,72,73]	
Loss of empathy	None	NA	Oxytocin
Perseverative behavior	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram	Open-label studies supporting use of SSRIs[68,74,75]	
	Trazodone	Double-blind, placebo-controlled study supporting the use of trazodone[71]	
Hyperorality	SSRIs: fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram	Open-label studies supporting use of SSRIs[68,70,75]	
	Trazodone	Double-blind, placebo-controlled study supporting the use of trazodone[71]	
Executive dysfunction	None	NA	Dopaminergic medications
Neuroprotective	None	NA	Medications that prevent tau hyperphosphorylation and accumulation
			Medications that increase progranulin levels
			Medications that reduce *C9ORF72* expanded repeat dipeptide production

bvFTD = behavioral variant of frontotemporal dementia; NA = not available; SSRIs = selective serotonin reuptake inhibitors.
[a] Modified with permission from Manoochehri M, Huey ED, Curr Neurol Neurosci Rep.[9] *link.springer.com/article/10.1007/s11910-012-0302-7*. © 2012 Springer Science + Business Media, LLC.

For patients with CBS or nonfluent agrammatic variant PPA who have memory deficits, approximately 30% to 40% may have underlying AD pathology, and therefore a 2- to 3-month trial of a cholinesterase inhibitor is warranted. A double-blind, placebo-controlled randomized trial of memantine for cognitive and behavioral symptoms of FTD showed no

benefit.[76] Clinical trials of novel agents targeting specific genes, related proteins and pathways for tau, progranulin, and *C9ORF72* are anticipated in the near future.

CONCLUSION

The FTDs can be recognized based on careful parsing of clinical features and neuroimaging characteristics. Consideration of referral for genetic counseling and genetic testing is indicated for most patients given the high incidence of hereditary FTD. Although not yet widely available for clinical use, molecular-specific diagnostic tools (eg, tau PET imaging, TDP-43 and tau biomarkers) and treatments are under development, making accurate recognition and diagnosis of FTD and FTD subtype essential for appropriate counseling and management.

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