Chapter 9
Frontotemporal Dementia

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Clinical Pearls

- Although considered a "young-onset" dementia, FTD can occur at later ages, with approximately 25% of patients occurring after age 65.
- The early accurate diagnosis of bvFTD depends on a detailed history of significant behavioral changes representing a departure from the premorbid state. Neuropsychological assessment and imaging alone are not sufficient for a diagnosis.
- Motor changes can emerge as FTD progresses, but can also be present at the time of diagnosis. These take the form of Parkinsonism (PSP and CBD—usually associated with tau pathology) or motor neuron disease (MND or ALS—invariably associated with TDP-43 pathology).
- Isolated progressive language deficits must be present for at least 1 or 2 years for PPA to be diagnosed. These language deficits must remain the principle cause of disability as the disease progresses.
- FTD is a highly genetic syndrome, with up to 50% of patients showing a strong familial inheritance. Many genes have been identified, but MAPT, C9orf72, and GRN account for most familial cases.
- The underlying pathology in FTD is complex. Although any one case will generally be the consequence of a single pathology, FTD remains a syndrome that results from many possible processes, the two most common being tau and TDP-43.
- There are no specific treatments for FTD or PPA. Unless Alzheimer's disease pathology is highly suspected (as in lvPPA), there is no role for cholinesterase inhibitors or memantine, which may worsen the clinical symptoms. Serotonergic agents are the treatment of choice for behavioral changes. Non-pharmacologic management such as the "ABC" approach may be useful.

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Introduction—Nomenclature, Epidemiology, Genetics, and Pathology

Frontotemporal dementia (FTD) is a term used to express a collection of possible clinical presentations that develop as the consequence of one of a number of distinct pathologic processes. Frontotemporal Lobar Degeneration (FTLD) is a pathological term that refers to the fairly selective degeneration of the frontal and anterior temporal lobes and results in the clinical manifestations of FTD [1]. Although these clinical manifestations are fairly consistent, the underlying pathological processes can be varied.

Reflecting its focal onset, FTD presents classically as a progressive degenerative disorder involving the initially selective disintegration of either behavior (behavioral variant FTD or bv-FTD) or language (primary progressive aphasia—PPA). PPA generally evolves from one of three different patterns of speech dysfunction: semantic dementia (or semantic variant, sv-PPA), non-fluent or agrammatic variant (nfv-PPA) and the logopenic variant (lv-PPA). Behavioral variants account for nearly 60% of cases while PPA accounts for 40% [2]. There is also significant overlap with movement disorders (progressive supranuclear palsy and corticobasal degeneration—PSP and CBD) and motor neuron disease or amyotrophic lateral sclerosis (MND/ALS). Patients may initially present with a defined clinical syndrome, such as nfv-PPA, and then evolve to develop features of CBD, PSP, or even MND [3, 4]. Some have recommended the use of "overlap" terms such as PPA-CBD to better reflect this evolution [5].

Although often a "young-onset" dementia, accounting for nearly half of dementias occurring before age 65 [6], FTD also affects older patients. One quarter of patients with FTD present after age 65, often being misdiagnosed as AD [7]. Younger onset patients are often misdiagnosed with psychiatric disorders, including depression, obsessive compulsive disorder (OCD), bipolar disorder, and even schizophrenia [8]. The reported prevalence of FTD varies, but is estimated at 15–22/100,000 [7]. Average age of presentation is in the sixth decade. There may be a slight overrepresentation of male patients.

FTD is a highly heritable disease. As many as 50% of cases report a family history with approximately 15% showing a clear autosomal dominant pattern of inheritance [9], with most familial cases explained by one of three common mutations (Microtubule Associated Protein Tau—MAPT, progranulin—GRN, and Chromosome 9 open reading frame 72—C9orf72). Together, these three mutations account for up to 20% of all cases of FTD.

Unlike Alzheimer's disease, in which diagnostic pathological changes must include the combined presence of both amyloid-based plaques and tau-based neurofibrillary tangles, pathologic changes in FTLD can be varied. Two different abnormal inclusions each account for about 45% of cases. These are accumulations of either abnormal tau or TDP-43. The remaining 10% of cases include FUS based pathology (FUsed in Sarcoma) or other yet to be characterized changes. Pathologic MAPT mutations always lead to tau pathology, while mutations in GRN and C9orf72 result in TDP-43 related changes. Clinically, cases that progress to include movement disorders tend to be the consequence of tau changes, while the development of motor neuron disease is almost exclusively the result of TDP-43 pathology.

Although frequently used interchangeably, Pick's disease (PiD) is currently considered a subgroup of the FTLDs. It is pathologically defined by the presence of circumscribed frontotemporal atrophy and associated tau containing intraneuronal agyrophilic spherical aggregations called Pick bodies.

Clinical Manifestations, Radiologic Findings, and Diagnostic Criteria

Patients with FTD present with insidious changes involving either behavior (bvFTD) and/or language (PPA) and the core diagnostic criteria reflect this dichotomy [10, 11].

Behavioral Variant FTD (bvFTD)

The primary manifestations of bvFTD involve early progressive changes in socio-emotional behavior or comportment, and include (1) behavioral disinhibition, (2) apathy and inertia, (3) loss of sympathy or empathy, (4) perseverative, stereotyped or compulsive/ritualistic behaviors, and (5) hyperorality and dietary changes. (6) Cognitive changes may also be present and involve executive/generation deficits with relative preservation of memory and visual spatial abilities.

Apathy and inertia are possibly the earliest and most common manifestations and can present as subtle changes such as difficulties making decisions, increased passivity, and reduced interest in usual hobbies. Progression often leads to more significant and impactful changes such as reduced attention to (or care about) work and home responsibilities, and personal hygiene. Early loss of functional independence is not uncommon, despite relative preservation of cognition.

Disinhibition may be less common than apathy, but is often more disruptive. Socially inappropriate behaviors and loss of decorum or manners are embarrassing to family and include excessive familiarity, inappropriate touching or hugging of strangers, or loud rude unconsidered remarks (such as about people's weight or appearance). Disinhibition can also take the form of impulsivity and lead to rash or careless actions. Criminal behavior, including speeding, theft (i.e., shoplifting), public nudity or urination, and even assault, can occur.

Loss of empathy usually manifests as reduced personal warmth and affection towards love ones. There is often inability to properly appreciate or respond to others' needs or emotions. This may manifest as striking selfishness or lack of concern for a loved ones' illness or tragedy.

Compulsive, repetitive, or ritualistic behaviors can take on various forms. There can be repetitive stereotyped behaviors such as incessant humming, rocking, or tapping. Verbal stereotypies may include repetition of words or catch phrases. Obsessive cleaning and insistence on rigid orderliness can occur. Other complex behaviors may involve hoarding, repetitive trips to the bathroom, or rigid and ritualistic feeding habits (such as eating only certain foods at certain times).

Dietary changes may include excessive sometimes compulsive binge eating (even in the face of satiety), new food preferences (most often for carbohydrates) or rigid or ritualistic food fads. There may be disregard for the poor comestible nature of the food in question (eating discarded foods from the garbage). There may even be consumption of inedible objects such as buttons or coins. Weight gain is common and is a relatively unique feature of FTD.

Early cognitive changes are usually subtle and may not be detectable with routine bedside diagnostic testing. Neuropsychological testing may capture deficits in attention and executive functions: working memory, cognitive flexibility and control (set-shifting), generation (lexical fluency), and abstraction. Performance in other cognitive domains, in particular episodic memory and visual spatial functions is generally sparred, although there are documented exceptions. Experimental tasks that probe Theory of Mind or social cognition may turn out to be most sensitive to early changes, but their development has not yet reached widespread clinical use. Failure on any task may be more the consequence of rule-breaking or poor effort than from an actual cognitive deficit.

Additional manifestations of the disease not captured by the diagnostic criteria can include psychosis, mood disorder, or OCD. Coupled with the relative initial mildness and frequent delayed appearance of cognitive deficits, as well as the younger age of onset, these changes often lead to psychiatric misdiagnosis for as many as 50% of patients [12]. This results in diagnostic and effective treatment delays.

Another critical finding in patients with bvFTD is the early presence of profound anosodiaphoria (awareness of a deficit but absence of adequate concern about its importance or impact) or anosognosia (lack of awareness altogether).

Physical examination in bvFTD is usually normal. As the disease evolves, patients may begin to show signs of asymmetric or axial extrapyramidal involvement, apraxia, eye movement abnormalities, and early falls, heralding a clinical trajectory towards CBD or PSP, or upper and lower motorneuron disease (weakness, spasticity, and fasciculations), betraying the development of FTD-ALS. These disorders are discussed elsewhere in this book. Occasionally, ALS or CBD/PSP disorders can be the initial manifestations of an FTLD-based pathology, and behavioral or language changes appear later in the course of the disease.

Radiological Findings

Using the Rascovsky criteria, the presence of characteristic findings on brain imaging raise the diagnostic confidence of bvFTD from possible to probable (Figs. 9.1 and 9.2). These include early and isolated, often circumscribed frontal and/or anterior temporal atrophy on magnetic resonance imaging (MRI) or computerized tomography (CT), or hypoperfusion or hypometabolism in the same areas on single photon emission computed tomography (SPECT) or fluorodeoxyglucose positron emission tomography (FDG) PET scan. For bvFTD, right-sided predominance of abnormalities is more frequent. SPECT or PET finding may precede the development of MRI changes by a few years. Absence of atrophy on MRI does not exclude the diagnosis. Conversely, the presence of such atrophy should never lead to a diagnosis in the absence of the clinical syndrome.

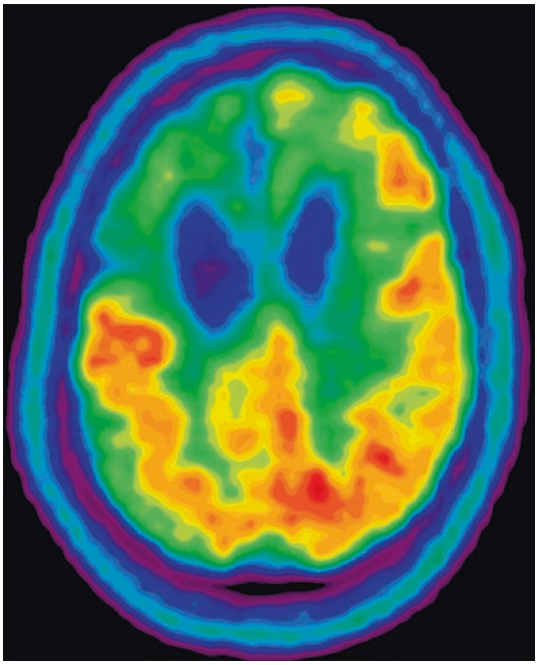

Fig. 9.1 FDG-PET (*axial view*). Note profound hypometabolism involving anterior right frontal mesial, polar, and convexity

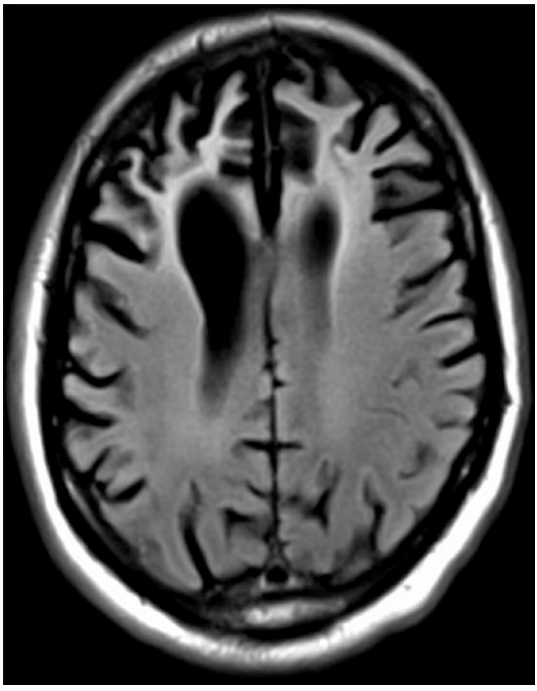

Fig. 9.2 FLAIR-MRI (*axial view*). Note knife-like cortical atrophy of frontal areas

New imaging techniques such as resting state functional MRI (fMRI) may reveal very early disintegration of key networks involving the anterior cingulate and frontoinsular cortices. Further development will be required before these can be applied clinically.

Each group of behavioral changes described above have been attributed to pathologic involvement of specific brain areas or disruption of networks involving: (1) anterior cingulate for apathy, (2) right orbitofrontal for disinhibition, (3) right frontoinsular and anterior temporal for loss of empathy, (4) lateral temporal and basal ganglia for compulsive behaviors, and (5) right orbitofrontal and insular cortices, and ventral striatum and hypothalamus for dietary or appetitive changes. The presence of specific behavioral changes and matching atrophy patterns on brain imaging (MRI or PET) help bolster diagnostic confidence.

Diagnosis of bvFTD

The diagnosis of *possible* bvFTD requires the clinician to elicit at least three of the six core behavioral (5) and cognitive (1) criteria described above (Table 9.1 and "Diagnostic flowchart for bvFTD"; Fig. 9.3). Because of the presence of early anosognosia, a detailed interview with a reliable caregiver or life partner is usually necessary. Although many of the relevant changes are sometimes spontaneously volunteered, directed questioning with examples as described above are often required. Neuropsychological testing may be required to capture the presence of early executive dysfunction. In moderately advanced cases, bedside cognitive testing (such as a Montreal Cognitive Assessment [MoCA]) may be adequate. Patients with early disease may not initially meet three criteria and reassessment in 6–12 months may be required. The diagnosis becomes *probable* when corresponding imaging abnormalities are found on MRI/CT or PET/SPECT *and* there is clear functional decline. The Rascovsky criteria have been found to be 85–95% sensitive and 82% specific for a diagnosis of possible bvFTD and 75–85% sensitive and 95% specific for probable bvFTD [10, 13]. Interrater reliability is also very high at 0.81 and 0.82 for possible and probable disease [14]. The presence of a pathologic mutation or confirmation (biopsy or post-mortem) of histopathologic changes raise the level diagnostic certainty to one of "*definite*".

The presence of any non-degenerative neurological, medical, or psychiatric disorder that better accounts for the behavioral changes should preclude a diagnosis of bvFTD. The presence of biomarkers that strongly support other neurodegenerative diseases (AD, Lewy body diseases, vascular disease) is allowed in "possible" bvFTD, but would exclude a "probable" diagnosis.

Primary Progressive Aphasia (PPA)

There are three variants of PPA: nonfluent/agrammatic (nfv), semantic (sv), and logopenic (lv) [11, 15]. While the histological changes underlying semantic and nonfluent variants are most often consistent with FTLD, the logopenic variant is

Table 9.1 Diagnostic criteria for FTD

Syndrome	Possible/clinical diagnosis	Probable/imaging supported diagnosis	Exclusionary criteria
bvFTD	At least three of the following: • Early behavioral disinhibition • Early apathy or inertia • Early lack of empathy or sympathy • Early perseverations, stereotypies or compulsions • Dietary habit changes or hyperorality • Executive-predominant deficits on neuropsychological testing with relative sparing of memory and visuospatial skills	All three of the following: • Meets possible criteria • Significant decline per informant, or CDR, or FAQ • Imaging consistent with bvFTD (frontal and/or anterotemporal)	• Deficits are better explained by alternative diagnosis (degenerative, nondegenerative, or psychiatric) • Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process (required for diagnosis of probable bvFTD)
nfvPPA	At least one of the following: • Agrammatism • Effortful, halting speech with inconsistent sound errors (AOS) At least two of the following: • Impaired comprehension of syntactically complex sentences • Spared single-word comprehension • Spared object knowledge	Both of the following: • Meets possible/clinical criteria • Imaging consistent with nfvPPA (left posterior frontoinsular)	• Deficits are better explained by alternative diagnosis (nondegenerative, or psychiatric) • Prominent initial memory, visuospatial, or behavioral deficits
svPPA	All of the following: • Impaired confrontation naming • Impaired single-word comprehension At least three of the following: • Impaired object knowledge • Surface dyslexia or dysgraphia • Spared repetition • Spared grammar and motor speech production	Both of the following: • Meets possible/clinical criteria • Imaging consistent with svPPA (anterior temporal)	
lvPPA	All of the following: • Impaired single-word retrieval in spontaneous speech and naming • Impaired repetition of sentences and phrases At least three of the following: • Phonologic errors in spontaneous speech and naming • Spared single-word comprehension and object knowledge • Spared motor speech • Absence of frank agrammatism	Both of the following: • Clinical diagnosis of logopenic variant PPA • Imaging consistent with lvPPA (predominant left posterior perisylvian or parietal)	

Based on [10, 11]

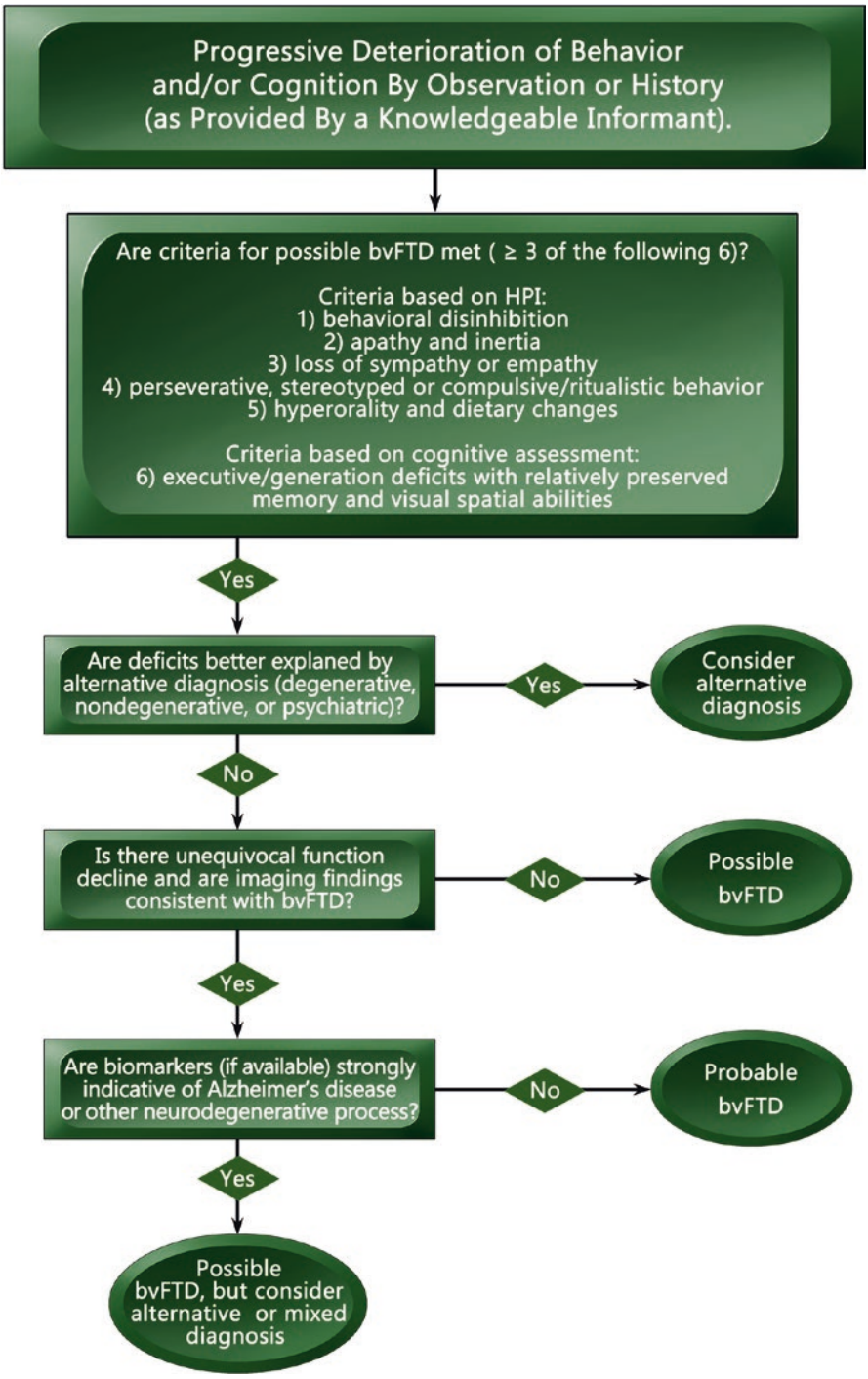

Fig. 9.3 Diagnostic flowchart for bvFTD

more frequently (although not exclusively) the consequence of Alzheimer's disease pathology. The 2011 Gorno-Tempini criteria allow for the classification of most progressive aphasias, but some patients may fail to meet criteria for any, or meet them for more than one, leading to terms such as "mixed" PPA (PPA-M) [16] or "not otherwise specified" (PPA-NOS) [5]. Closely related to nfv-PPA, primary progressive apraxia or speech (PPAoS) has been described and is characterized by impaired articulation and production as a consequence of a breakdown in motor programming, with a general sparing of language, at least initially [17].

Diagnosis of PPA is a two-step process. Before subtyping, patients must first meet basic PPA criteria as defined by Mesulam [11, 18, 19]: there must be (A) an insidious isolated decline in language, affecting at least one of speech production, object naming, syntax, or word comprehension, and (B) the aphasia must be the most prominent deficit for at least the initial 1–2 years and remain the principle cause of any impairment in activities of daily living (ADLs) (see "Diagnostic flow chart for PPA"; Fig. 9.4).

Further characterization of the aphasia can normally be accomplished by examining the main language domains, through simple observation and specific tasks. These domains include speech production (grammar, motor speech, sound errors, and word finding pauses), repetition (both short and longer sentences), single-word and syntax comprehension, confrontational naming, semantic knowledge, and reading/spelling [11]. See Table 9.1 for diagnostic criteria. See also "Approach to the clinical evaluation of a speech disorder" and to Table 9.2 for examples of tests and criteria specific findings. See the "Simplified flowchart for the diagnosis of PPA" for a streamlined approach based on the most critical diagnostic findings (Fig. 9.5).

As with bvFTD, there are levels of confidence in the diagnosis: clinical, "imaging-supported", and pathologic. Clinical diagnosis depends on the classification of the patient's deficits according to the clinical criteria explored below. Once clinical criteria are met, imaging-supported criteria are considered. Because there is generally a direct correspondence between language symptoms and the site of anatomic damage, there must be structural or functional imaging changes in a distribution consistent with the clinical syndrome. A particular genetic mutation or specific pathology defines the disorder as FTLD spectrum, AD, or some other known disease entity. Unfortunately, pathologic diagnoses do not further enhance characterization of the clinical syndrome as there is significant overlap between clinical presentations and possible underlying pathologies. Mixed pathologies are also not uncommon in older patients.

Nonfluent Variant PPA (nfvPPA)

NfvPPA is characterized by early difficulties in motor speech output and loss of syntax (Table 9.1). Speech is effortful (slow and labored), with frequent pauses and grammatical errors. Utterances are generally short and simple, with omission of function words and inflections. There may be articulatory deficits with inconsistent speech sound errors, including distortions, deletions, substitutions, insertions, or transpositions of speech sounds. Prosody is usually also affected. Patients are often aware of, and

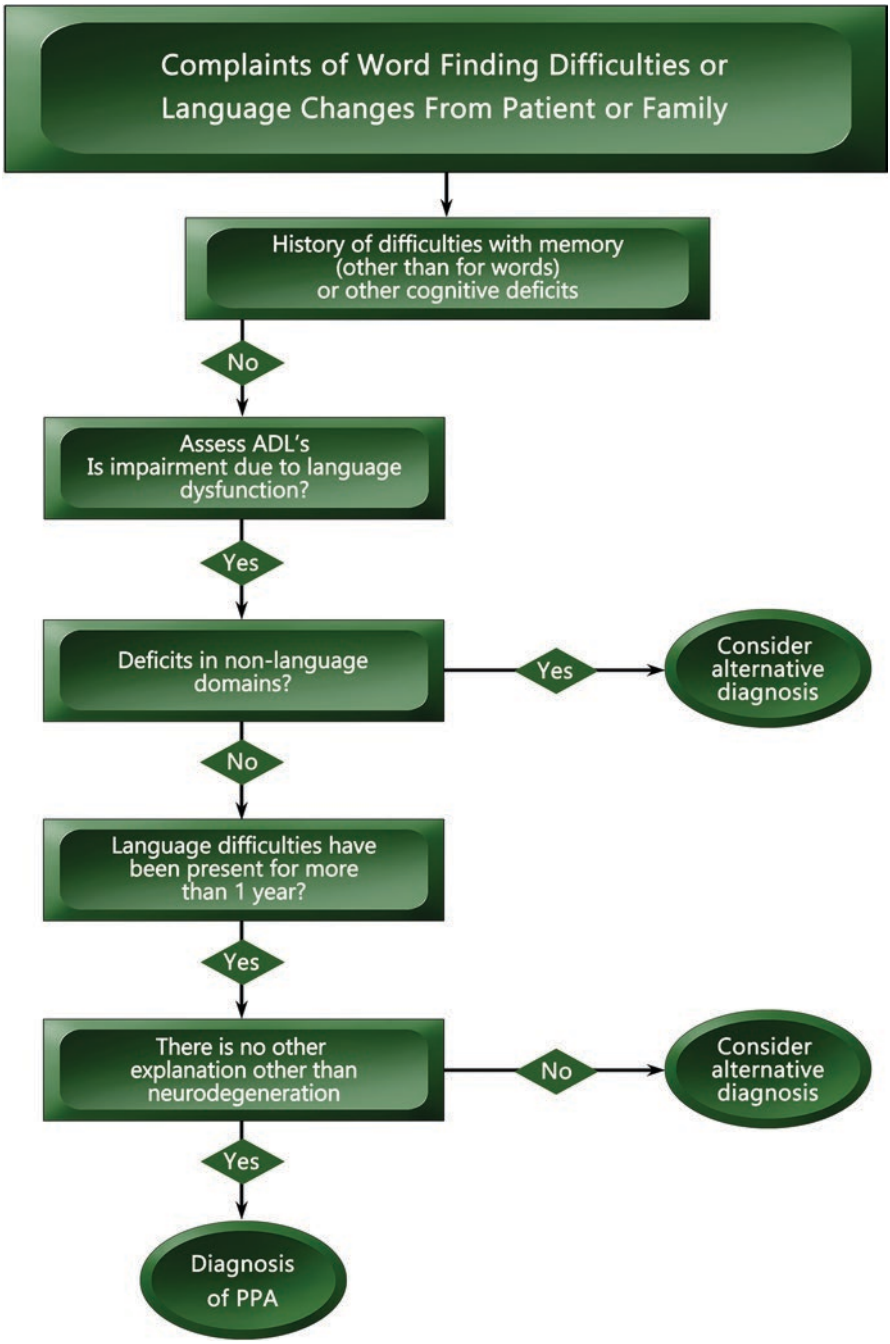

Fig. 9.4 Diagnostic flowchart for PPA

Table 9.2 PPA diagnostic criteria-specific tests and findings

Speech/ language function	Select example of tasks	Look for	Most impaired in
Speech production			
Grammar	Spontaneous speech Picture description task	Grammatical structure Mean length of utterance Speech rate Accuracy of content Melody & Prosody Error types in word selection Articulation	nfvPPA
Motor speech	Repetitions of multisyllabic words Diadochokinesis of speech articulators Spontaneous speech	Effortfulness & Hesitations Presence of apraxia of speech or dysarthria Speech sound errors Factors that affect articulation (e.g., word length in syllables)	nfvPPA
Confrontation naming	Single-word retrieval in response to pictures, sounds, foods, and odors	Error rate Delay in naming Factors that affect accuracy (e.g., familiar vs. unfamiliar items, nouns vs. verbs, semantic category) Error types (e.g., semantic vs. phonemic errors)	Severe in svPPA with semantic errors Moderate in lvPPA with phonemic errors
Repetition	Repetition of words, phrases, and sentences	Factors that affect accuracy (e.g. predictability of the phrase, sentence length, grammatical complexity) Error types (phonologic vs. articulatory)	lvPPA with phonological errors
Single-word comprehension	Word-to-picture matching Word-to-definition matching Synonym matching	Factors that affect comprehension (e.g., familiarity, frequency, grammatical word class)	svPPA
Sentence comprehension	Matching orally presented sentences to pictures Answering yes/no questions Following directions	Factors that affect comprehension (e.g., grammatical complexity; reversibility of the sentence, e.g., The boy was kicked by the girl vs. The ball was kicked by the girl)	nfvPPA when effect of grammatical complexity lvPPA when length and frequency effect
Semantic knowledge	Picture-picture matching Odd-one-out Semantic associations Gesture-object matching Sound-picture matching	Factors that affect object knowledge (e.g., familiarity, semantic category)	svPPA

(continued)

Table 9.2 (continued)

Speech/ language function	Select example of tasks	Look for	Most impaired in
Reading/ spelling	Regular and irregular word lists	Factors that affect reading/ spelling accuracy (e.g., regularity, frequency, word class) Error types (e.g., regularization, phonologically plausible errors; articulatory distortions)	svPPA with "regularization" errors lvPPA with phonologic errors

Based on [11]

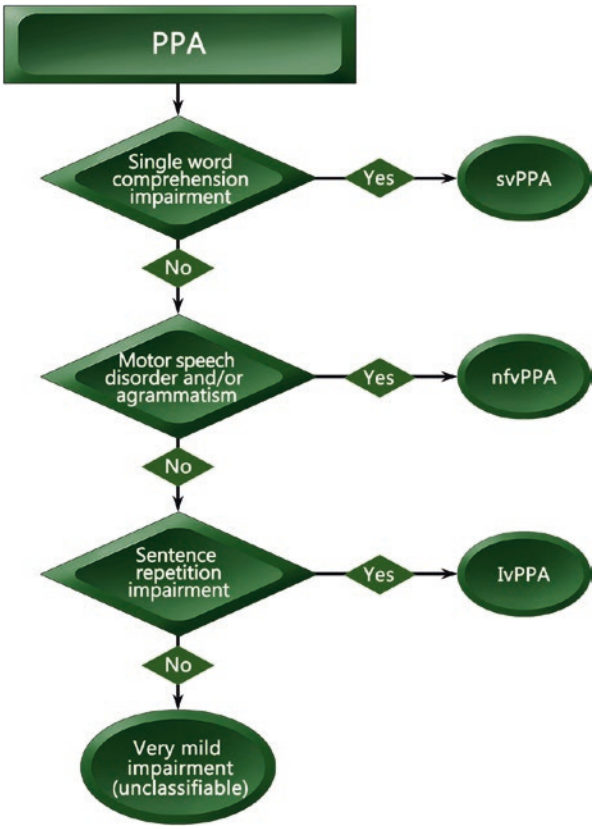

Fig. 9.5 Simplified flowchart for diagnosis of PPA variants

frustrated by, these deficits. Spared are single-word comprehension and object knowledge. There may be deficits in comprehension of grammatically complex sentences.

In some patients, very mild apraxia or slowing of fine finger movements may be present. These findings are harbingers as progression predominantly involves the development of motor changes consistent with CBD or PSP.

MRI shows focal atrophy and FDG-PET reveals focal hypometabolism involving left posterior frontal and insular regions (Figs. 9.6 and 9.7). The most frequent histopathology is tau, with less frequent cases involving TDP-43. Well characterized nfvPPA is almost never the consequence of AD pathology.

Semantic Variant PPA (svPPA)

Previously labeled *Semantic Dementia*, this clinical syndrome is characterized by the presence of *anomia* and *single-word comprehension deficits* (Table 9.1). These represent core features and both must be present for the diagnosis. Anomia is not uncommon in many neurodegenerative conditions, but it tends to be severe in

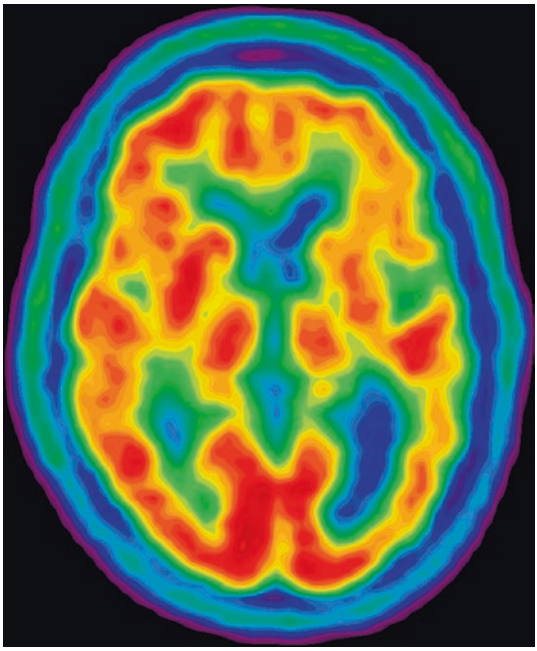

Fig. 9.6 FDG-PET (*axial view*). Note subtle hypometabolism involving left anterior perisylvian (frontal opercular) areas

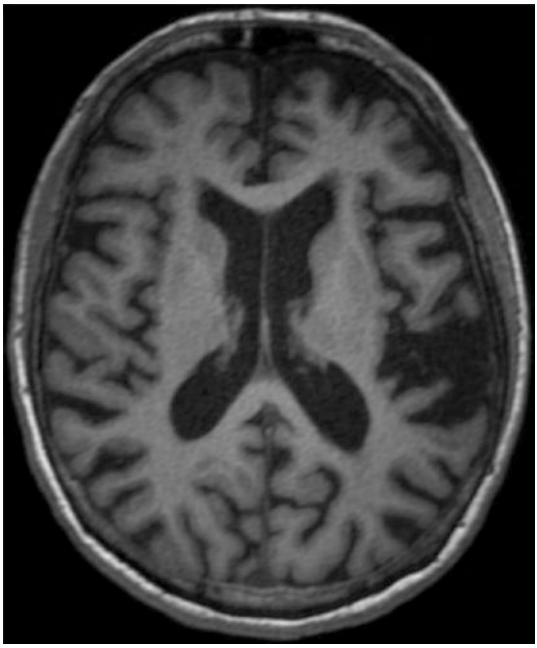

Fig. 9.7 T1-MRI (*axial view*). Note extensive atrophy of anterior perisylvian areas on the left relative to the right

svPPA, in which additional information about the object in question ("object knowledge", a form of semantic knowledge) may also be missing. A pen, for instance, is held in the dominant hand in a particular way and is used for writing. This kind of information may be completely lost, especially for less common (low-frequency) words—contrast for instance the less common word "zebra" with the more common or familiar "cat".

Single-word comprehension deficits arise when the patient cannot recognize, describe, or define an object or idea. It is also the consequence of loss of object knowledge. When asked to draw a clock, patients with moderately severe svPPA may simply say: "Clock? What's a clock?". They will be unable to name a clock when shown a picture or a cartoon of one, know that clocks are used to tell time, or recognize "*tic-toc*" as the sound that a clock may produce. As suggested by the eventual inability to recognize the sound "*tic-toc*", deficits in object recognition and knowledge can be multimodal. Recognition failure will ultimately transcend all sensory modalities such that the tactile experience of a rose petal or thorn, or the scent of its flower, will not be of any additional benefit in identifying a rose bush.

Early deficits in naming and word comprehension usually involve low-frequency words, but with progression, the meaning and semantic knowledge of more com-

mon words will also be lost. Selective involvement of certain object categories (tools, animals, people, or concrete vs. abstract) may be present early, but all are involved, eventually.

Another consequence of loss of object or word knowledge is the inability to recognize words with irregular spelling or pronunciation (*e.g.* "yacht", "colonel", and "cellist"). This results in so-called *surface dyslexia* and *dysgraphia*, where the patient will "regularize" such words when read or written: the word colonel would be read as "kol-o-nel" and written in some form to sound like "kur-nl".

Typically, even in advanced disease, repetition and motor speech remain intact. Adequate grammar, albeit with a shrinking vocabulary pool, is generally retained.

Even in the earliest stages, PET and MRI show focal hypometabolism or atrophy in the lateral and ventral aspects of the temporal poles, usually more prominent on the left (Figs. 9.8 and 9.9). Although uncommon, preferential involvement of the right temporal lobe can occur and results in a more behavioral syndrome (the so-called right-temporal variant FTD [20]).

The pathological findings in svPPA are more frequently TDP-43 related, although there are case reports of abnormal tau deposition [21]. Genetics are rarely involved.

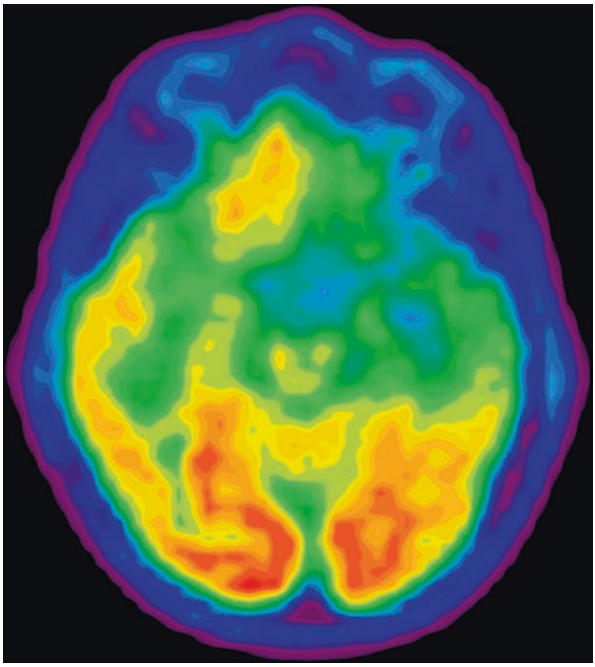

Fig. 9.8 FDG-PET (*axial view*). Note profound hypometabolism of the left anterior temporal lobe

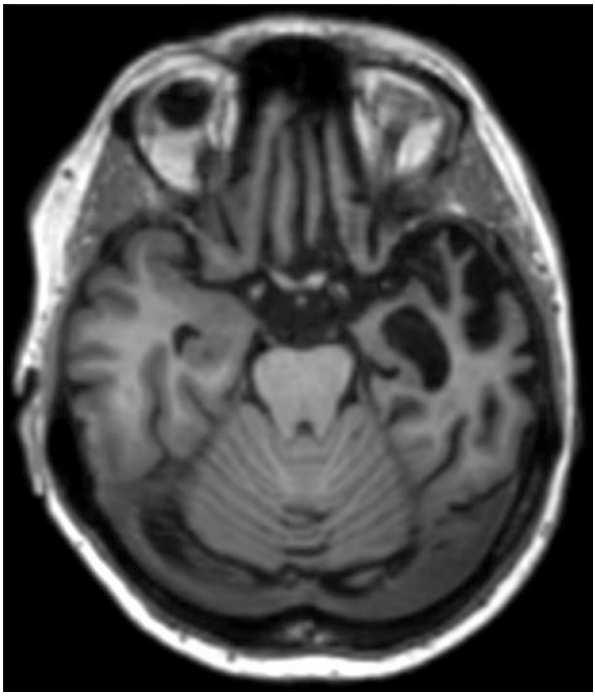

Fig. 9.9 T1-MRI (*axial view*). Note profound cortical atrophy of the left anterior temporal lobe with involvement of the hippocampus

Logopenic Variant PPA (lvPPA)

Logopenic variant PPA is the most recently described language variant [22]. The most salient features are *word retrieval* and *length-dependent sentence repetition* deficits (Table 9.1). Word retrieval or word finding deficits are most obvious during spontaneous speech or conversation. Speech is slowed, with frequent word finding pauses, but without agrammatism. Prosody is generally conserved, although the word-finding pauses disrupts the natural flow and can be frustrating to both the speaker and listener. Naming difficulties (anomia) may be present, but object knowledge is preserved so that the patient may describe objects in other more roundabout ways (circumlocution). Single word comprehension is also intact.

The disorder is thought to arise from damage to structures supporting phonologic short term memory (left temporoparietal areas). This type of memory is critical in word and sentence repetition. With disease progression, there is a gradual length-dependent sentence repetition deficit. The patient is able to repeat single words and

short sentences, but fails to repeat longer sentences, regardless of their grammatical complexity. A similarly length-dependent deficit will emerge affecting sentence comprehension.

Additional features include phonologic paraphasias (e.g., "greel" for "green") during spontaneous speech and confrontational naming. Words are misspoken because of phonetic substitutions, but there is no distortion of the word sounds, as seen in nfvPPA.

PET and MRI imaging abnormalities involve the left temporoparietal junction (Figs. 9.10 and 9.11). When lvPPA is well characterized, the underlying pathology is most often Alzheimer's disease, although there are published exceptions, with FTD-type pathology.

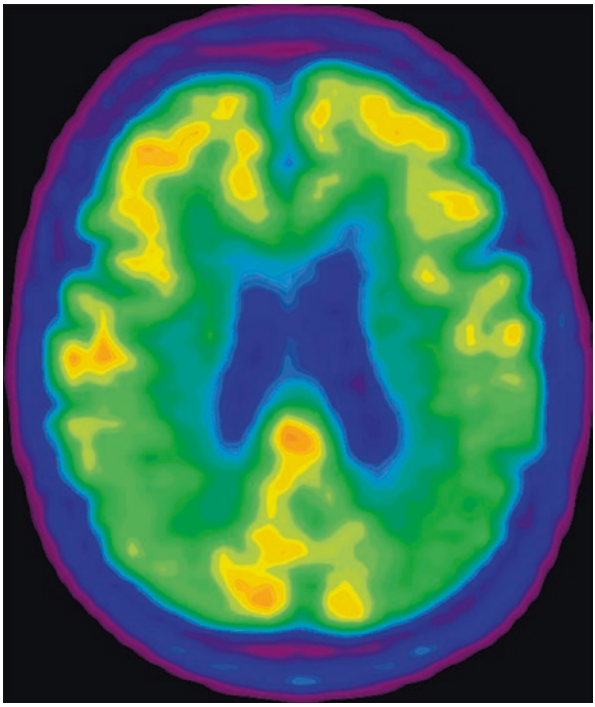

Fig. 9.10 FDG-PET (*axial view*). Note presence of bilateral parieto-temporal hypometabolism characteristic of AD, worse on the left

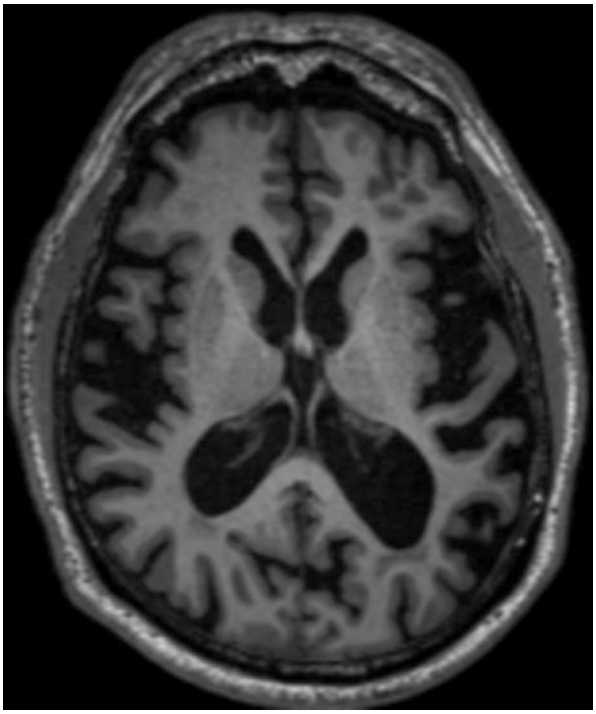

Fig. 9.11 T1-MRI (*axial view*). Note selective posterior perisylvian atrophy, much worse on the left

Differential Diagnosis

As for all conditions leading to gradual changes in mental status, reversible causes should be excluded. These involve endocrine, metabolic, and neoplastic or paraneoplastic conditions, central nervous system (CNS) infections, and dietary deficiencies.

The differential diagnosis for FTD will vary according to age. In younger patients it is often misdiagnosed as atypical depression, bipolar disorder, or late onset schizophrenia. Early-onset Alzheimer's disease can sometimes be difficult to differentiate clinically. Analysis of cerebrospinal fluid (CSF) for A-beta and tau proteins, demonstration of hippocampal atrophy on volumetric MRI, temporoparietal and posterior cingulate hypometabolism (rather than frontotemporal) on FDG PET, or the presence of amyloid on amyloid PET help accurately diagnose Alzheimer's disease. Late-onset major psychiatric disease should always raise suspicion for the presence of bvFTD.

In older patients, atypical depression, Alzheimer's disease, and Vascular Cognitive Impairment (VCI) are more frequent. Careful attention to the core criteria and a search for clinically consistent focal hypometabolism on PET and atrophy

MRI, as well as absence of significant or strategic vascular disease, will generally lead to an accurate diagnosis.

Because of its slow evolution, progressive aphasia is rarely confused with aphasias due to stroke or space occupying lesions. Alzheimer's disease represents the most common alternative diagnosis and is the most common pathological finding in lvPPA. CSF analysis for A-beta and tau, volumetric MRI and FDG or amyloid PET are helpful in this regard. CSF is typically normal in FTD; in Alzheimer's disease, the signature findings are elevated tau protein and reduced A-beta protein levels. If the clinical syndrome can be well characterized into one of the three PPA variants, the differential diagnosis becomes moot.

Treatment

As is the case for Alzheimer's disease, there are currently no approved or established treatments that address the underlying pathology or disease progression of FTD. Current approaches focus on addressing individual symptoms and promoting increased brain health and resilience (see healthybrains.org). Support and education of both patients and caregivers is critical. Education can be enhanced through referral to support groups and social work. The Association for Frontotemporal Degeneration (AFTD) and the Alzheimer's Association offer useful resources (www.theaftd.org & http://www.alz.org/dementia/fronto-temporal-dementia-ftd-symptoms.asp). Unfortunately, there still exit significant barriers to helping patients with FTD and their families access adequate care and resources [23].

Because judgment is often impaired early, usually resulting in poor job performance and impacting family finances, involvement of social work at the outset can help guide patients and caregivers though discussions of power of attorney. Additionally, patients with FTD and PPA may eligible for "compassionate allowance" from the Social Security Administration and be fast-tracked for access to Social Security disability benefits (http://www.alz.org/living_with_alzheimers_social_security_disability.asp#compassionate).

Driving and gun safety should always be addressed as early as possible. Occupational therapists and state Division of Motor Vehicles may be used for more formal assessments of driving capacity.

Non-pharmacological management of behavioral and psychological symptoms in dementia (BPSD) should be part of a patient-centered, systematic, and evidence-based approach [24, 25]. An "ABC" (antecedent—behavior—consequence) approach [26] to understanding problem behaviors and adopting preemptive plans should be encouraged. The AFTD offers concrete examples of most problematic behaviors and specific interventions that have been helpful in preventing or mitigating their impact (https://www.theaftd.org/wp-content/uploads/2011/09/Packet-Changes-in-behavior-chart.pdf).

All current symptomatic pharmacologic treatments remain off-label. Serotonergic agents such as trazodone, sertraline, or escitalopram can be helpful in controlling

disinhibition, agitation, irritability, and obsessive/compulsive behavioral changes. Serotonergic agents are particularly helpful in PPA, especially when there is preserved deficit awareness that can lead to anxiety and depression.

Antipsychotics may be helpful if there is aggression or frank psychosis but have limited usefulness otherwise. Because of the higher risk of parkinsonism, atypical neuroleptics such as quetiapine, risperidone, olanzapine, aripiprazole, and possibly pimavanserin (recently approved for the treatment of psychosis in Parkinson's disease) are preferred.

Agents approved for the treatment of Alzheimer's disease have been de facto adopted in treating FTD [27], but data supporting such usage is lacking. In fact, cholinesterase inhibitors have been associated with increased agitation in bvFTD [28]. A possible role remains in the treatment of PPA, particularly for lvPPA or if Alzheimer's disease remains in the differential. Treatment with memantine has been found to be of no benefit to patients with FTD [29].

There may be a role for dextromethorphan/quinidine in the treatment of agitation. It is approved for the treatment of pseudobulbar affect and has recently been demonstrated to be helpful in the control of agitation in Alzheimer's disease [30].

ICD-10 Codes

- G30 Alzheimer disease
  - G30.0 Alzheimer disease with early onset
  - G30.1 Alzheimer disease with late onset
  - G30.8 Other Alzheimer disease
  - G30.9 Alzheimer disease, unspecified
- G31 Other degenerative disease of nervous system, not elsewhere classified
  - G31.0 Frontotemporal dementia

    G31.01 Pick disease
    G31.09 Other frontotemporal dementia

There are no specific billable codes for PPA. All three variants can be coded under G31.09, although lvPPA might better be coded under G30.0 or G30.1.

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