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Frontotemporal dementia: diagnosis, deficits and management

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Summary

Frontotemporal dementia (FTD) is a progressive neurologic syndrome with diverse clinical presentations and attendant underlying pathologies. Psychiatric prodrome, neuropsychiatric symptoms and language difficulties are common in FTD, but the diversity of presentation raises unique diagnostic challenges that can significantly impact patient care and counsel for caregivers regarding clinical status and prognosis. While neuropsychiatric symptom measures are helpful, more sensitive assessments delineating the specific behavioral and linguistic deficits accompanying FTD are needed. Comprehensive clinical assessment in combination with evaluation of language, socio-emotional functioning, cognition and neuroimaging aid in accurate and early diagnosis and treatment planning. In what follows, we review each of the FTD syndromes, highlight current research investigating the cognitive, behavioral and socio-emotional deficits observed with this disease, address common diagnostic challenges and summarize best practices associated with management of FTD.

Keywords

differential diagnosis; frontotemporal dementia; neuropsychology; primary progressive aphasia; socio-emotional functioning

Frontotemporal dementia (FTD) is the third most common dementia for individuals 65 years and older, and is the second most common form for individuals 65 years and younger [1–3]. FTD defines a heterogeneous group of clinical syndromes marked by the progressive, focal neurodegeneration of the frontal and anterior temporal lobes [4]. First described by Arnold Pick in 1892, FTD affects brain regions implicated in motivation, reward processing, personality, social cognition, attention, executive functioning and language. Currently, FTD incorporates three clinical subtypes. Behavioral variant FTD (bvFTD) accounts for about half of all FTD cases [2], and involves initial and progressive decline in social functioning and changes in personality. The behavioral variant is characterized by focal and prominent bilateral frontal atrophy, though some reports suggest more right-hemisphere involvement

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than left [5]. The remaining subtypes are classified as variants of primary progressive aphasia (PPA), and are marked by initial and prominent disturbance and decline of language functioning. Loss of semantic knowledge is associated with the semantic variant of primary progressive aphasia (svPPA), while agrammatism and motor–speech difficulties are associated with nonfluent variant of primary progressive aphasia (nfvPPA) [6,7]. The semantic variant is characterized by bilateral anterior temporal lobe atrophy, associated with language, compulsions and dysfunctions in emotional processing [8]. Most patients present initially with greater left hemisphere atrophy; however, approximately a quarter of cases present with initial right anterior temporal lobe atrophy, and is associated with a more behavioral presentation of symptoms, including: social awkwardness, loss of insight and difficulty with face recognition [9]. nfvPPA is accompanied by left inferior frontal and insular atrophy; expressive speech and syntax difficulties are characteristic of the disease early in its course.

This review summarizes the clinically relevant findings typically seen in each of the three FTD subtypes. Recent advances have shed more light on the specific cognitive, behavioral and socio-emotional deficits seen in these syndromes. This review underscores the importance of identification of these deficits to aid in early and accurate clinical diagnosis and management. We also discuss best practices for how to manage the challenges associated with FTD.

Epidemiology

Due to the diagnostic challenges associated with FTD, the true prevalence of this disease is likely underestimated. The number of psychiatric and neurological disorders that can resemble the spectrum of FTD symptomology may contribute to misclassification and underestimation. Recent epidemiological work estimates a range from 15 to 22/100,000 [10]. Independent studies investigating the prevalence of FTD in the UK estimated a prevalence of about 15 cases/100,000 in adults between 45 and 64 years of age, which was comparable to the prevalence of early-onset Alzheimer's disease [3].

Male predominance of bvFTD has been reported across a number of studies and centers. Of the PPA subtypes, male predominance has been reported in svPPA, with female predominance in nfvPPA [1–3]. Regarding progression, FTD is marked by shorter duration of survival and more rapid decline of cognition and function than Alzheimer's disease [11–13]. Average survival time of FTD ranges significantly depending on the subtype. The average survival time from diagnosis to death can be as brief as 3 years for bvFTD patients with motor neuron disease and up to 12 years in patients with svPPA [12].

Pathology, genetics & risk factors

Pathology

The nomenclature surrounding FTD has evolved over time. FTD encompasses the three clinical syndromes, while the term frontotemporal lobar degeneration (FTLD) specifies the underlying pathological aggregation of protein in the frontal and temporal lobes with microvacuolation, neuronal loss and astrocytic gliosis [14]. Immunohistochemical staining

has provided clarity to the underlying pathology of most FTD syndromes. Approximately 40% of FTD cases are caused by abnormal accumulations of the microtubule-binding protein tau (FTLD-tau). Pick's disease is associated with three microtubule repeats (3-R), while four microtubule repeats (4-R) are associated with progressive supranuclear palsy (PSP) and cortical basal degeneration (CBD). 3- and 4-R Tauopathies are also strongly associated with nfvPPA [15,16]. More than half of FTD cases are tau negative and characterized by the abnormal accumulation of the 43 kDA TAR DNA-binding protein (TDP-43; FTLD-TDP) [15,16]. There are four subtypes of TDP-43 pathology: Types A, B, C and D, and each of these proteinopathies correlate with different FTD syndromes. Patients with progranulin (GRN) gene mutations have Type A, though both bvFTD and nfvPPA syndromes are present even without *GRN* mutation. Type B pathology is associated with FTD with motor neuron disease (FTD-ALS). The majority of patients with svPPA have type C pathology, and TDP-43 type D is also associated with FTD-ALS [17]. The majority of the remaining 10% of cases are associated with accumulation of the fused in sarcoma protein (FTLD-FUS) [18,19].

The ability to predict the underlying pathology in FTD syndromes *in vivo* has been a major focus of research. Within the PPA syndromes, nfvPPA is more often associated with FTLD-tau, and svPPA is almost always associated with FTLD-TDP [16,20]. Of our pathology confirmed cases at the University of California San Francisco Memory and Aging Center, 21 of 23 svPPA patients showed TDP-43 type C aggregation. In bvFTD, however, FTLD-TDP and FTLD-tau variants are equally as likely [16,21].

Genetics

Approximately 40% of FTD cases include a family history of dementia and approximately 10% of patients are autosomal dominant (affecting first-degree relatives across two generations) [22–24], with *MAPT, GRN* and *C9ORF72* representing the most common genes responsible for autosomal dominant inheritance of FTD. Among FTD syndromes, svPPA is the least likely to be familial [23]. Mutations in the *MAPT* gene account for about 17% of autosomal dominant FTD in our center, though another series reported 32% of patients with both FTD and a positive family history [22]. *MAPT* mutation carriers tend to have more focal and symmetrical temporal lobe atrophy than other genetic forms [25]. Amyotrophic lateral sclerosis (ALS), bvFTD and FTD motor neuron disease are the most common syndromes associated with a hexanucleotide expansion in *C9ORF72*, with PPA subtypes being seen more infrequently [26]. Mutations in *C9ORF72* account for 13–26% of familial FTD cases [27]. Patients with a *C9ORF72* mutation often present with obsessive-compulsive behaviors, rituals and may also display psychotic features. A progression of this symptomology in younger patients may be indicative of early FTD [26,28]. Progranulin mutations account for about 8% of autosomal dominant forms of FTD, is characterized by asymmetrical cerebral atrophy and is strongly associated with bvFTD and nfvPPA [29].

Risk factors

More recent investigation into the roles of inflammation and the immune system have shown promise in identifying potential biomarkers involved in the pathogenesis and progression of neurodegenerative diseases [30]. Neuroinflammation may contribute to the underlying

pathology of FTD syndromes [31], and recent studies examining peripheral levels of tumor necrosis factor suggest a role for early dysregulation of inflammation mediators in neurodegeneration associated with bvFTD [32,33]. Another recent study posits the presence of autoimmune disorders with increased vulnerability for FTD syndromes. This study found that rates of nonthyroid-spectrum autoimmune disorders were twice as common in patients with svPPA and in individuals with a mutation in the GRN gene [34]. Other factors that have shown promise as potential risk factors for the language presentations include diagnosis of learning disability in patients and first-degree relatives [35,36]. Miller *et al.* also suggest the possibility of a relationship between atypical brain hemispheric lateralization and FTLD-TAU, with an increased number of nonright-handedness in svPPA patients compared with the general population [35].

Behavioral variant FTD

Neurobehavior findings

bvFTD presents distinct diagnostic challenges due to the presence of behavioral symptoms, even at a very mild disease stage [37]. The hallmark symptoms of bvFTD include progressive changes in emotional regulation, conduct and personality, and are harbingers of the underlying dysfunction of the salience network, a neural network responsible for socio-emotional awareness, reward processing and motivation [38,39]. Typically, patients do not have insight into these changes; as such, family members and friends are critical in establishing the earliest symptoms and attendant progression of symptomology.

Two discrete and not mutually exclusive behavioral syndromes have been described: an apathetic type, characterized by decreased volition and motivation, isolating behaviors, loss of socio-emotional awareness and increased latency to pain response; and a disinhibited type characterized by hyperorality, preference for sweet foods, perseverative behaviors and motor stereotypies [40]. Increased disinhibition and impulsivity can lead to inappropriate remarks (e.g., sexually explicit comments), embarrassing social behavior, overspending, pathological gambling and more rarely, hyperreligiosity [41–43].

Increasingly, a subset of patients also presents with clinical features of bvFTD without a progressive neurodegenerative condition. These patients are considered to have bvFTD ‘phenocopy syndrome,’ presenting with the behavioral features characteristic of bvFTD, without progressing to dementia. The profile of these patients as reported by family members mimics that of bvFTD, though activities of daily living (ADL) appear less impaired [44,45]. Phenocopy cases also exhibit intact memory and socio-emotional functioning, and normal or only mild deficits on measures of executive functioning [46]. On imaging, phenocopy cases display minimal or no atrophy on MRI, and normal glucose metabolism on PET [47]. While the etiology of bvFTD phenocopy is still unknown, its resemblance to other neuropsychiatric conditions has led to the postulation that these cases may have either personality disorders, or autism spectrum disorders with subclinical symptomology for formal diagnosis [48].

Functional capacity—Impaired functional capacity in bvFTD is primarily a function of the behavioral deficits present early on. For example, when compared with patients with

Alzheimer's disease (AD) matched on Mini-Mental State Examination (MMSE) score, bvFTD patients showed more functional impairment on the Clinical Dementia Rating scale (CDR) total score [49]. Patients with bvFTD are also more functionally impaired than AD patients on assessment of activities of daily living (ADL), and are often impaired in ADLs upon initial visit [11,13]. When compared with PPA subtypes, functional impairment in bvFTD is also typically more severe [50,51]. Little research exists related to driving and other areas of capacity in bvFTD. A recent review examining four articles investigating driving in bvFTD found that bvFTD drivers had more problems than control groups around issues of social cognition and behavior resulting in hit and run crashes, failure to stop at red lights and speeding [52].

Neurocognitive findings

One of the new diagnostic criteria for bvFTD is a pattern of cognitive performance showing relative sparing of memory and visuospatial functions with executive dysfunction present. However, there are conflicting reports concerning the extent to which episodic memory is spared [53]. Language also tends to be preserved initially. Executive dysfunction can be assessed using tasks of set-shifting (e.g., trail making), backward digit span, verbal and nonverbal fluency measures, inhibition (e.g., stroop task), as well as the Frontal Assessment and NIH EXAMINER batteries [54–56]. The EXAMINER is a recently developed executive function battery with strong psychometric properties, which incorporates item response theory to increase sensitivity. It is important to recognize that bvFTD patients may exhibit impaired performance for multiple reasons. Error monitoring is a crucial component of successful test performance. Impairments in error monitoring has been associated with right lateral prefrontal cortex atrophy [57], and is an area of neurodegeneration in bvFTD. Possin *et al.* (2012) also showed that bvFTD patients produce more repetition errors on tests of design fluency than other neurodegenerative disease patients [166].

Socio-emotional functioning

Deficits in emotional salience are part of the diagnostic criteria for bvFTD (e.g., loss of sympathy or empathy), though deficits in empathy are also seen in svPPA (see below) [58]. These deficits are partly explained by patients' inaccurate estimation of their ability to empathize [59], as well as impairment in detection and recognition of emotionally salient stimuli, particularly negative emotions [60, 61]. As the disease progresses, bvFTD patients exhibit stark changes in personality marked by declines in extraversion and warmth [37]. These deficits extend to impairments in social cognition and studies have demonstrated deficits in theory of mind (e.g., taking the point of view of someone else) [62], metacognition (e.g., awareness of one's own thought processes) [63], recognition of insincere communication [62] and moral reasoning [64]. Well-validated measures that track the progression of socio-emotional changes are needed given the role these symptoms play from the outset of the disease course [65].

Reward processing—Eating, financial decisions and social functioning are all impacted in bvFTD and these changes can be attributed to changes in reward processing. As mentioned above, the lack of warmth and isolating behaviors are suggestive of a lack of incentive for interpersonal connection [66]. Impulsive purchasing and overspending behavior

is also common, and on reward-related decision-making gambling tasks (e.g., the Iowa gambling task) bvFTD patients choose options with high risk of monetary loss but with large possible gains [66–69]. Changes in eating behavior can also be understood within the construct of reward processing. Impaired satiety is seen in bvFTD patients across cultures [70], despite hormone profiles that would suggest decreased food consumption [71]. Increased preference for sweet food is also commonly observed [70].

Diagnostic criteria

The international consortium proposed new criteria from 2011 provide three levels of diagnostic certainty for a diagnosis of bvFTD: possible, probable and definite [72]. A summary of these criteria can be found in Box 1. Possible bvFTD requires a patient to have a progressive deterioration of behavior accompanied by three out of six core features (disinhibition, apathy, loss of sympathy/empathy, eating behavior changes, compulsive behaviors and an executive predominant pattern of dysfunction on cognitive testing). Additionally, functional decline and neuroimaging consistent with bvFTD are required for a probable bvFTD diagnosis. Neuroimaging findings consistent with probable bvFTD include frontal, or anterior temporal atrophy, or both, on CT or MRI, or frontal hypoperfusion or hypometabolism on single-photon emission computed tomography (SPECT) or PET [72,73]. Definite bvFTD requires presence of the clinical syndrome with genetic or pathological confirmation of FTLD.

Semantic variant primary progressive aphasia

Neurobehavioral findings

Between 20 and 25% of patients diagnosed with FTD have svPPA [2]. While language is fluent, it is characterized by loss of object knowledge, with impoverished content, semantic and paraphasic errors [74]. The initial and prominent symptom is loss of object knowledge [7]. Semantic loss begins with finer distinctions between things such as types of cars, then to differentiating between kinds of vehicles and ultimately loss of semantic knowledge of what vehicles are [75]. While svPPA typically presents with left greater than right anterior temporal atrophy, about 25% of cases present with initial right greater than left involvement [9]. In either case, the contralateral anterior temporal lobe becomes affected with disease progression [76]. As the disease progresses, cross-modal loss of person recognition is also frequently observed [77]. Behavioral changes are present initially in right predominant patients, including lack of interpersonal engagement, lack of empathy, compulsive behaviors (e.g., crossword puzzles) and increased rigidity expressed by strict schedules, restricted food preference and consumption and clock watching [78,79]. The prominence of behavioral symptoms early on may meet criteria for bvFTD, and apathy and disinhibition symptoms similar to bvFTD are visible 5–7 years after symptom onset [80]. It is noteworthy that some patients experience newfound interest and productivity in the verbal arts or visual arts and music as a result of asymmetric neurodegeneration of the anterior temporal lobes [81–83].

Functional capacity—As would be expected, semantic loss and difficulty with voice and facial recognition can be devastating to one's ability to engage socially, whether through written correspondence, on the phone or face-to-face [6]. While these ADLS are often

impaired initially, the typically slower rate of progression means that svPPA patients have preservation of basic ADLs for much longer when compared with bvFTD and nfvPPA patients [84,85]. Driving skills may remain intact until more moderate stages of the disease [86], and language-mediated activities may remain intact, despite a patient's inability to name items or communicate their intentions [86].

Neurocognitive findings

On formal testing svPPA patients show semantic knowledge loss [9,72], with relatively preserved episodic memory, particularly visual memory, visuospatial abilities and executive functions early on. Tests of confrontation naming, single-word comprehension, category fluency and word-picture matching are helpful in isolating the principal object knowledge loss deficit associated with svPPA [6,87]. Additionally, svPPA patients make regularization errors when asked to read aloud or engage in written dictation, where irregular words are read or spelled according to letter-sound rules [88,89].

Socio-emotional functioning

While early changes in personality and behavior are frequently present in svPPA patients [79,90], right predominant anterior temporal lobe dysfunction has been more strongly associated with loss of empathy, social awkwardness, loss of insight, occupational difficulties and face recognition problems [9,76,91]. Restricted diet and food fads may also be present. In comparison to bvFTD patients, right predominant svPPA patients are more rigid, and exhibit unique compulsions and eating disorders [6]. Right anterior temporal lobe dysfunction has also been implicated in theory of mind deficits [92]. In contrast, left predominant dysfunction is accompanied by more frank object knowledge loss.

Diagnostic criteria

With respect to svPPA and nfvPPA, recent international consortium criteria from 2011 also provide three levels of diagnostic certainty for a diagnosis of svPPA or nfvPPA: clinical diagnosis, neuroimaging-supported diagnosis and definite [7]. A summary of these criteria can be found in Box 2. Inclusion criteria for any of the three PPA variants requires the presence of three core features: language difficulty as the most prominent clinical feature, language difficulty as the cause of impaired daily living activities and the presence of aphasia as the most significant deficit at symptom onset and during the initial phase of the disease. Additionally, there can be no prominent initial behavioral disturbance, episodic or visual memory impairments or visuoperceptual difficulties, and the symptoms cannot be better accounted for by psychiatric or nondegenerative nervous system or medical disorders.

Clinical diagnosis of svPPA requires both impaired confrontation naming, and single-word comprehension, with at least 3 out of 4 additional core features (impaired object knowledge, surface dyslexia or dysgraphia, spared repetition and spared speech production). In addition, neuroimaging consistent with svPPA is required for an imaging-supported diagnosis of the syndrome, and must show either predominant anterior temporal lobe atrophy, or predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET, or both. Definite svPPA requires presence of the clinical syndrome with genetic or pathological confirmation of FTLD.

Nonfluent variant primary progressive aphasia

Neurobehavioral findings

In keeping with PPA syndromes, language is the initial and prominent symptom marked by apraxia of speech (AOS) resulting in interrupted speech with pauses both within and between utterances [93]. Agrammatism and para-phasic errors can be present [7], and distortion of prosody (the pitch pattern used to provide emotional content and alert the listener of questions and emphasis) [94]. Difficulty with comprehension of syntactically complex sentences may also be present. As the disease progresses, the patients may become mute [95]. Acquisition of a speech sample is the best clinical measure to capture agrammatism and diminished rate of speech [96]. Aberrant behavior is not usually present in the initial presentation of nfvPPA, with neuropsychiatric inventories comparable to the logopenic variant of primary progressive aphasia (lvPPA) and AD [79], though may manifest as the disease progresses [97,98]. As in svPPA, some nfvPPA patients experience newfound interest and productivity in the verbal arts or visual arts and music as a result of asymmetric neurodegeneration of the anterior temporal lobes [83]. Seeley *et al.* has hypothesized the gradual loss of function in the language-dominant anterior temporal lobe leads to the release or remodeling of function in the nondominant hemisphere posterior structures [99].

Functional capacity—Similar to svPPA patients, the frank impairments in speech, writing and reading present early on in nfvPPA patients and significantly impact their ability to engage in interpersonal interactions [6]. These impairments can be severe by the second year into disease course [100]. In contrast, basic ADLs remain comparatively preserved for many years. As the disease progresses, patients may become mute and immobile, with more severe impairments in sentence comprehension and following of multistep instruction. Advanced stage of the disease has also been associated with features of bvFTD [101].

Neurocognitive findings

In conjunction with language difficulties, nfvPPA patients can exhibit executive dysfunction including: verbal fluency (e.g., letter fluency), working memory (e.g., digits backward) and set-shifting (e.g., Trail Making) [102]. Episodic memory and visuospatial functioning are relatively preserved in nfvPPA, but may deteriorate over the disease course [102], as well as in cases where nfvPPA is secondary to cortical basal degeneration (CBD) [103].

Socio-emotional functioning

nfvPPA patients exhibit fewer deficits in socio-emotional functioning than svPPA patients, though recent research has demonstrated that individuals with nfvPPA have selective deficits interpreting emotion from vocal prosody [104,105]. Couto *et al.* showed differential patterns of regional gray matter atrophy associated with social cognition deficits between bvFTD and nfvPPA patients, suggesting that socio-emotional function deficits in nfvPPA may be a consequence of more basic dysfunction of face and emotion recognition [106].

Diagnostic criteria

A clinical diagnosis of nfvPPA requires either agrammatism in language production or effortful, halting speech with inconsistent speech sound errors and distortions (AOS), along

with two of the three remaining core features (impaired comprehension of syntactically complex sentences, spared single-word comprehension and spared object knowledge). An imaging-supported diagnosis of nfvPPA requires neuroimaging consistent with this syndrome, and must show either predominant left posterior fronto-insular atrophy on MRI, or predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET, or both [7]. See Figure 1 for representative MRI imaging of each of the FTD subtypes. Finally, definite nfvPPA requires presence of the clinical syndrome with genetic or pathological confirmation of FTLD.

Syndromic overlap

Psychiatric syndromes—FTD can overlap in presentation with a number of psychiatric disorders, such as: late onset bipolar disorder, borderline personality disorder, late onset schizophrenia, obsessive-compulsive disorder and depression [107–109]. For example, in a study of 69 patients diagnosed with bvFTD, 51% received a prior psychiatric diagnosis. Younger age, higher education and a family history of psychiatric illness increase the likelihood of a prior psychiatric diagnosis. It is difficult to retrospectively invalidate the diagnosis of a psychiatric disorder, and it is possible that psychiatric conditions may represent a risk factor for bvFTD. Nevertheless, the preponderance of psychiatric diagnoses given to individuals ultimately diagnosed with bvFTD underscores the complexities of the disease course, and the overlap with many psychiatric conditions. In addition, genetic mutations have been implicated with psychiatric disease in FTD. The presence of the *C9ORF72* mutation has been associated with a family history of psychiatric illness in both FTD and motor neuron disease [110,111].

Cortical basal degeneration & progressive supranuclear palsy—The clinical syndrome of FTD overlaps with several other FTLD and AD pathological syndromes [112–115]. The atypical parkinsonian spectrum disorders of PSP and CBD can both exhibit cognitive and behavioral changes characteristic of bvFTD (e.g., executive dysfunction, apathy and impulsivity). They may also show language impairment similar to that of nfvPPA. Extrapyramidal features are characteristic of PSP, along with supranuclear gaze restriction, constrained vertical gaze and slowed saccades. CBS presentation can include apraxia, cortical sensory deficits, rigidity and bradykinesia. While movement findings are typical in these syndromes, a behavioral syndrome without attendant movement disorder can be present with both PSP and CBS pathology.

Frontal variant Alzheimer's disease—While rare, an atypical frontal variant Alzheimer's disease (fvAD) can also present as a behavioral and dysexecutive syndrome [116–119]. When compared with typical AD patients, performance on tests of executive function are more impaired, and pathology confirmed cases of fvAD show marked plaque and neurofbrillary tangle deposition in the frontal cortex.

Motor neuron disease—The clinical syndrome and underlying pathology of FTD can also be present in motor neuron disease, including amyotrophic lateral sclerosis (ALS) [120–122]. ALS typically progresses faster than FTD with time-dependent survival at 5 and 10 years from diagnosis of 23.4 and 11.8%, respectively [123]. As many as half of ALS patients

present with executive dysfunction [124,125], and about 15% of bvFTD patients eventually develop symptoms of ALS [122]. In cases of familial ALS, approximately a third are due to *C9ORF72* expansion [126]. A distinct clinical profile is associated with *C9ORF72* expansion carriers, including loss of empathy, disinhibition, apathy and psychotic behaviors, which can resemble aspects of the FTD clinical profile [126]. Research and assessment of patients with ALS provides the opportunity to better understand prodromal symptoms of bvFTD given their likelihood of developing the syndrome over their disease course.

Logopenic variant primary progressive aphasia—lvPPA represents a third PPA variant; however, this syndrome it is not classified as an FTD given the predominance of Alzheimer's pathology associated with this syndrome [127–129]. The clinical presentation of lvPPA includes minimal verbal output and intermittent disruptions in fluency, with relatively spared grammar and oral motor speech. On neuroimaging focal neurodegeneration is found in the left temporoparietal junction [7,67,130]. Diagnostic criteria for lvPPA include impaired single-word retrieval in spontaneous speech and confrontational naming, and impaired repetition of sentences and phrases. It is hypothesized that problems of short-term auditory phonological memory is a key cognitive deficit contributing to most language impairment in lvPPA, as verbal immediate recall is a core factor in sentence and phrase repetition, and comprehension of longer and grammatically complex sentences. Spontaneous speech (phonologic) errors are also common in lvPPA.

Differentiating lvPPA from svPPA and nfvPPA can be difficult, but comparison of the quality of spontaneous speech is a useful diagnostic technique. Specifically, lvPPA can be differentiated from svPPA by the absence of agrammatism and spared single-word comprehension and object knowledge, and it can differentiated from nfvPPA by the sparing of motor speech [131]. While both lvPPA and nfvPPA patients tend to present with slowed spontaneous speech and hesitations, there are distinct qualitative differences in speech presentation. Patients with lvPPA have been described as having frequent word-finding pauses with syntactically simple, though intact, utterances [132]. These patients tend to have pauses between words and often exhibit phonological paraphasias, but with motor capabilities intact. By contrast, patients with nfvPPA tend to exhibit stuttering, slurring or pausing within words due to oral motor articulation difficulties.

Pharmacological intervention

To date, no disease-modifying treatments exist that change the course of this neurodegenerative disease, and as such, the focus of treatment across subtypes is necessarily symptomatic. Behavioral symptoms are usually the focus of intervention, though executive dysfunction and working memory deficits can also be a treatment focus [133,134]. Treatment with antidepressants has fewer potential side effects than neuroleptics, and modest behavioral improvement has been shown with selective serotonin reuptake inhibitors [135,136] and trazodone [137]. The use of neuroleptics such as olanzapine has been shown to treat aggression, agitation and psychosis, with case studies supporting the efficacy of risperidone and aripiprazole [138–140]. While studies on anticholinesterase inhibitors in FTD have been limited, research to date leaves its status as a pharmacological treatment suspect. Treatment with Donepezil led to worsening neuropsychiatric symptoms without

cognitive improvement [141]. Rivastigmine has been reported to improve neuropsychiatric symptoms, with concomitant gains in caregiver stress [142]. A trend toward efficacy of Galantamine has been reported in a subset of aphasic FTD and PPA patients, though this effect may have included lvPPA patients with underlying Alzheimer's pathology [143]. Large studies administering Memantine have shown no treatment gains [144,145]. Importantly, while no approved pharmacological treatments exist, advances in knowledge of the underlying molecular and genetic causes of FTD have clarified the foci of research for randomized control trials. Targets of clinical development for specific FTD therapies include progranulin replacement and immunomodulation in svPPA [31,146–148].

Caregivers

There are important implications for family caregivers of patients with FTD, as care and management of these patients can be demanding. Studies evaluating caregiver stress in FTD have found caregivers of FTD patients report higher levels of generalized distress burden and report feeling less competent than caregivers of AD patients [149–152]. One study found that caregivers of patients with svPPA and nfvPPA reported similar distress as caregivers of AD, while bvFTD caregivers reported the most distress [153]. In bvFTD, changes in behavior regardless of disease severity have been correlated with caregiver distress [151], and caregiver burden has been shown to increase across FTD syndromes as a result of the combination of disease progression, relationship changes and caregiver depression [153]. One study found that FTD caregiver report of depression accounted for 58% of the variance of generalized stress scores within the caregiver sample, suggesting a significant role for personal health in caregiver stress and coping [152]. A study comparing bvFTD with svPPA found that caregivers of bvFTD patients reported poorer sleep quality and more frequent use of sleep medications [154]. Apathy and its association with lowered daytime activity resulted in increased emotional distress for bvFTD caregivers [155].

Caregiver reporting of symptomology and treatment gains from therapeutic interventions is critically important in the management of care for persons suffering from FTD [134]. To that end, specialty nurse clinics educating caregivers about the best nonpharmacologic behavioral strategies, identification of triggers for problematic behaviors and increase coping skills have shown success in reducing caregiver stress and improving caregiver tools for the management of behavioral symptoms [156,157]. Five weekly, one-on-one sessions focused on building skills in mindfulness and positive appraisal improved positive affect and psychological outcomes for family caregivers of FTD patients [158]. Recent reviews have comprehensively outlined therapeutic recommendations for PPA patients and caregivers, addressing issues such as cognitive rehabilitation, speech therapy, meal preparation, telephone communication, driving, shopping, financial matters, written correspondence, medications, leisure activities and issues of constitution [84,159,160]. Resources such as The Association for Frontotemporal Degeneration [161], the Frontotemporal Dementia Research Group [162] and the Association for Frontotemporal Dementias [163] provide peer caregiver support and information for those caring for a loved one with FTD.

Conclusion & future perspective

FTD is a common cause of early-onset dementia, and is often accompanied by psychiatric symptoms of depression, obsessions, compulsions, mania, as well as psychotic symptoms. In the case of svPPA or nfvPPA, initial and prominent language difficulties are present. The progressive deterioration of socio-emotional and language abilities – two uniquely human abilities – is devastating, particularly when onset of the disease is in late middle age. Awareness and recognition of the diversity of possible presentations associated with FTD can aid in early and accurate diagnosis.

The combination of comprehensive history, neuropsychological testing, measures of social cognition, as well as advances in neuroimaging modalities, all aid in earlier and more accurate diagnosis of FTD. The last decade has also seen a dramatic increase in our understanding of the distinct kinds of molecular changes responsible for the pathology involved in frontotemporal neurodegenerative processes; yet, accurate prediction of the underlying neuropathology responsible for FTD syndromes during life remains a challenge. The development of increasingly sensitive psychiatric and cognitive diagnostic measures and identification of salient biomarkers in the next decade may improve the predictive power of underlying neuropathology. Close longitudinal monitoring of patients may also provide additional data relating patterns of cognitive, behavioral and socioemotional functioning to underlying neuropathology.

Progressive monitoring of speech and language impairments has been developed for PPA syndromes [164]. Given the prominent socioemotional and behavioral symptoms associated with FTD syndromes throughout disease course, there is a great need to further develop clinical tests to operationalize decision-making impairments [165], methods for tracking progression of impairment [84] and ways to prospectively identify patients at greatest risk of harm in the presence of these impairments.

To date, no disease-modifying agents have been developed that effectively prevent, cure or slow the progression of FTD. While current pharmacological treatments focus on symptom management and support, we hope to see the development of pharmacological interventions in the next decade. Specifically, the creation of neuroprotective medications for those patients at risk for developing FTD may help delay the onset of disease. The characterization of distinct proteinopathies, including tau and TDP-43, has led to the development of clinical trials targeting these molecular abnormalities. While trials have yet to successfully report significant treatment gains, future trials hold out hope for remediating the effects of FTD disease processes.

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Box 1

Summary of international consensus criteria for diagnosis and classification of behavioral variant frontotemporal dementia

Neurodegenerative disease

- Must be present for any FTD clinical syndrome
  - Shows progressive deterioration of behavior and/or cognition by observation or history

Possible bvFTD

- Three of the features (A–F) must be present; symptoms should occur repeatedly:
  - A. Early (within first 3 years) behavioral disinhibition
  - B. Early (within first 3 years) apathy or inertia
  - C. Early (within first 3 years) loss of sympathy or empathy
  - D. Early (within first 3 years) perseverative, stereotyped or compulsive/ritualistic behavior
  - E. Hyperorality and dietary changes
  - F. Neuropsychological profile: executive dysfunction with relative sparing of memory and visuospatial functions

Probable bvFTD

- All the following criteria must be present to meet diagnosis
  - A. Meets criteria for possible bvFTD
  - B. Significant functional decline
  - C. Imaging results consistent with bvFTD (frontal and/or anterior temporal atrophy on CT or MRI or frontal hypoperfusion or hypometabolism on SPECT or PET)

Definite bvFTD

- Criteria A and either B or C must be present to meet diagnosis:
  - A. Meets criteria for possible or probable bvFTD
  - B. Histopathological evidence of FTLD on biopsy at post mortem
  - C. Presence of a known pathogenic mutation

Exclusion criteria for bvFTD

- Criteria A and B for possible bvFTD must both be answered negatively; criterion C can be positive for possible bvFTD but must be negative for probable bvFTD:

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

bvFTD: Behavioral-variant frontotemporal dementia; CT: Computerized tomography; FTD: Frontotemporal dementia; FTLD: Frontotemporal lobar degeneration; SPECT: Single-photon emission computed tomography.

Adapted with permission from [72].

Box 2

Summary of international consensus criteria for clinical diagnosis and classification of primary progressive aphasia

PPA

- Most prominent clinical feature is a difficulty with language (object knowledge loss, word-finding difficulties, paraphasias, effortful speech and grammatical deficits)
- Language deficits are the principal cause of impaired daily living activities
- Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease (prominent behavioral, memory and/or visuospatial deficits should not be present at the onset)
- No other conditions better account for the language deficits present (i.e., nondegenerative or psychiatric conditions)

svPPA

- Impaired confrontation naming and single-word comprehension, explained by semantic knowledge loss
- At least three of the following additional features:
- Impaired object knowledge, particularly for low-frequency items
- Surface dyslexia or dysgraphia
- Spared repetition
- Spared speech production (grammar and motor speech)

nfvPPA

- Either agrammatism or motor speech disorders with effortful, halting speech and inconsistent speech sound errors (apraxia of speech)
- At least two of the following additional features:
- Impaired comprehension of syntactically complex sentences
- Spared single-word comprehension
- Spared object knowledge

lvPPA

- Impaired single-word retrieval in spontaneous speech (speech fluency interrupted by word finding pauses) and confrontational naming, and impaired repetition of sentences and phrases
- At least three of the following additional features:
- Speech (phonologic) errors in spontaneous speech and naming

- Spared single-word comprehension and object knowledge
- Spared motor speech
- Absence of frank agrammatism

lvPPA: Logopenic variant primary progressive aphasia; nfvPPA: Nonfluent variant primary progressive aphasia; PPA: Primary progressive aphasia; svPPA: Semantic variant primary progressive aphasia.

Adapted with permission from [7].

Practice points

- Frontotemporal dementia is currently divided into three subtypes: behavioral variant frontotemporal dementia, semantic variant of primary progressive aphasia and nonfluent variant of primary progressive aphasia.
- Diagnosis of patients with suspected frontotemporal dementia should include: detailed history from patient and informant; neurologic examination; neuropsychological evaluation; structural brain imaging with MRI and assessment of socioemotional functioning and speech and language.
- Treatment is supportive and symptomatic with targeted pharmacologic interventions, and nonpharmacologic approaches, including: exercise, psychosocial therapy, physical therapy and speech therapy.
- Referral for enrollment in research studies at specialized medical centers should be considered.

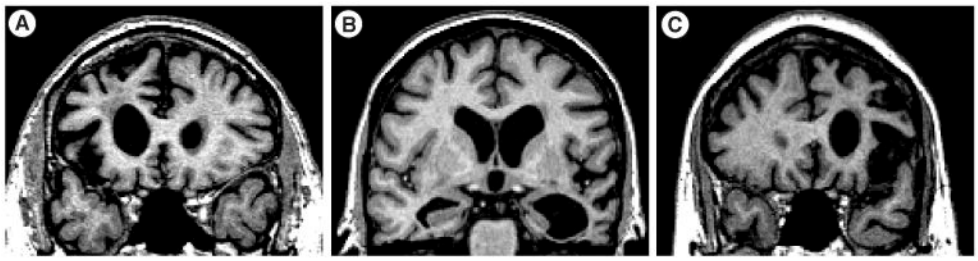

Figure 1. T1-weighted structural MRI in patients with behavioral variant frontotemporal dementia, semantic variant primary progressive aphasia and nonfluent variant primary progressive aphasia

(A) Behavioural variant frontotemporal dementia **(B)** semantic variant frontotemporal dementia and **(c)** nonfluent variant primary progressive aphasia. Images are in radiological view (right hemisphere is on the left side of the image).