

Frontotemporal Dementia Treatment: Current Symptomatic Therapies and Implications of Recent Genetic, Biochemical, and Neuroimaging Studies

Adam L. Boxer, MD, PhD* and Bradley F. Boeve, MD†

Abstract: Frontotemporal dementia (FTD) is a common cause of dementia that encompasses 3 clinical subtypes: a behavioral/dysexecutive (frontal) variant and 2 variants with prominent language impairments. There are currently no Food and Drug Administration-approved medications for FTD although symptomatic treatments such as selective serotonin reuptake inhibitors and atypical antipsychotic agents are frequently used to manage behavioral abnormalities associated with this disorder. Evidence for the use of currently available symptomatic treatments in each FTD clinical subtype is reviewed. In addition, the implications of new genetic and neuropathologic information about FTD for the design of future clinical trials and the eventual development of FTD-specific disease-modifying treatments are discussed.

Key Words: frontotemporal dementia, semantic dementia, primary progressive aphasia, progressive nonfluent aphasia, treatment, frontotemporal lobar degeneration, selective serotonin reuptake inhibitor (SSRI), antipsychotic, cholinesterase inhibitor (*Alzheimer Dis Assoc Disord* 2007;21:S79–S87)

Although there are currently no Food and Drug Administration-approved medications indicated for the treatment of frontotemporal dementia (FTD), recent advances in the understanding of the clinical and pathologic correlates of FTD are beginning to suggest new avenues for treatment. Because FTD is in most cases pathologically distinct from Alzheimer disease (AD), new disease-modifying treatments under development that are targeted against β -amyloid are unlikely to be effective for the treatment of FTD. However, despite this limitation,

clinical methods for assessing treatment efficacy, management of target symptoms, and nonpharmacologic interventions developed for the treatment of AD and other disorders may be applied to the treatment of FTD. Moreover, recent advances in understanding the molecular neuropathology of FTD suggest new strategies for the development of disease-modifying FTD treatments. Currently available treatments for FTD broken down by clinical syndrome are reviewed below. In addition, the implications of new information from clinical pathologic and genetic correlations in different FTD subtypes and new biomarkers of neurodegenerative dementias are discussed.

CLINICAL VARIANTS OF FTD

Clinically, FTD presents either with changes in personality, behavioral problems, and/or executive impairment, or with language problems, as a primary progressive aphasia syndrome (PPA).^{1,2} The behavioral presentation of FTD is often referred to as “frontal variant” FTD (fvFTD; Fig. 1). The PPA associated with FTD pathology may be further subdivided into a fluent aphasia and a nonfluent aphasia (Fig. 2). The fluent PPA has often been referred to as semantic dementia (SD), reflecting a primary loss of knowledge about the world as the etiology of the aphasia, or as “temporal variant” FTD, reflecting the prominent anterior temporal lobe atrophy/pathology associated with this clinical FTD subtype. The nonfluent aphasia has been termed progressive nonfluent aphasia (PNFA).¹ A third type of PPA, termed logopenic progressive aphasia has also been included in some PPA classifications.³ In most cases, logopenic progressive aphasia may represent an atypical (language) presentation of AD, and for this reason will not be discussed in greater detail here.

The histopathologic correlates and neurobehavioral features of fvFTD and SD frequently overlap,⁴ suggesting that to a first approximation, treatment approaches to these 2 clinical subtypes can be considered together. In contrast, PNFA has more bland neurobehavioral features than fvFTD and SD, and is more frequently associated with tau pathology at autopsy.⁵ As discussed below, the varied but overlapping neuropathologic correlates of each clinical subtype will become an increasingly important considerations as new treatments are developed that target specific molecular pathologies associated with FTD.

From the *Memory and Aging Center, Department of Neurology, University of California, San Francisco, CA; and †Divisions of Behavioral Neurology and Movement Disorders, Department of Neurology, Mayo Clinic, Rochester, MN.

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Reprints: Adam L. Boxer, MD, PhD, Memory and Aging Center, Department of Neurology, University of California, Box 1207, San Francisco, CA 94143-1207 (e-mail: aboxer@memory.ucsf.edu). Copyright © 2007 by Lippincott Williams & Wilkins

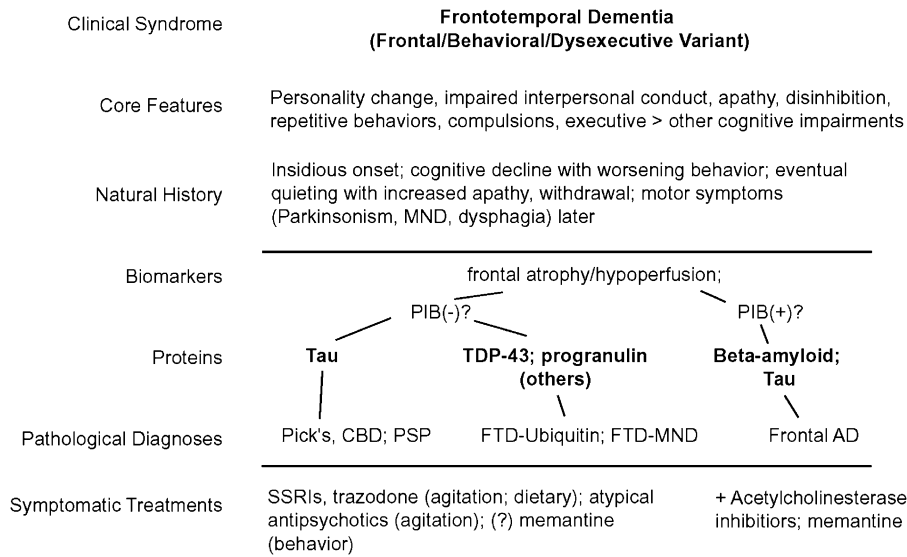


FIGURE 1. FTD (frontal/behavioral/dysexecutive variant): diagnosis and treatment.

SYMPTOM MANAGEMENT BY CLINICAL FTD SYNDROME

Behavioral/Dysexecutive FTD (Frontal Lobe Variant; fvFTD; Fig. 1)

Personality Changes

The insidious onset of personality changes and behavioral abnormalities are initially the most prominent features of fvFTD. Poor insight, loss of personal awareness, loss of social awareness, and blunting of affect are common behavioral changes that are seen early in

fvFTD. Patients may deny the existence of deficits and often show a lack of concern about their illness.⁶ Increased submissiveness, a lack of empathy, self-centeredness, emotional coldness, and decreased concern about family and friends is also common.⁷ Patients with evidence of right brain involvement on neuroimaging studies tend to have the most severe behavioral symptoms.⁸ These patients may undergo dramatic changes in beliefs, attitudes, and/or religious sentiment, leading to the emergence of a new personality as the disease progresses.⁹ Personality changes and declines in interpersonal conduct

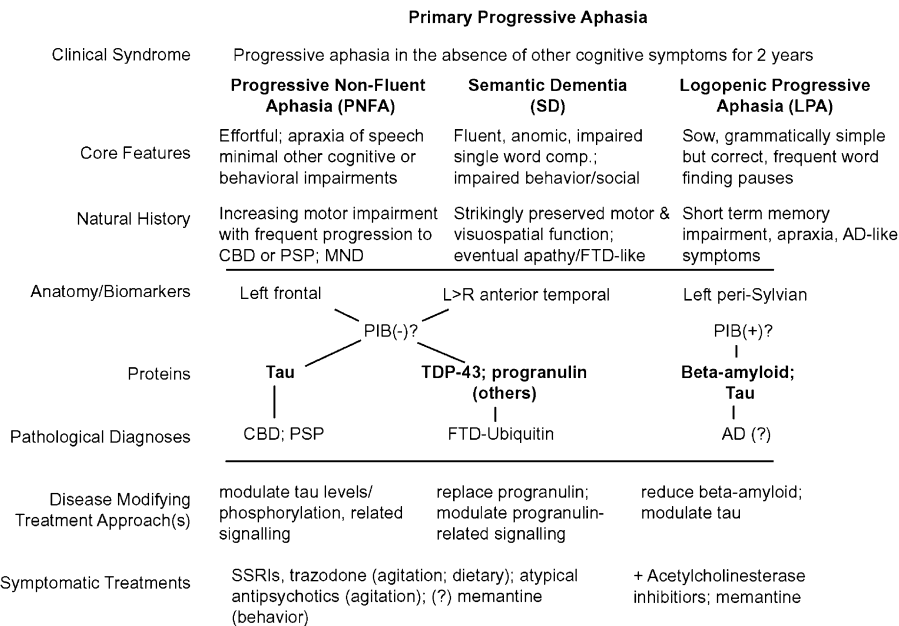


FIGURE 2. PPA: subtypes and treatments.

in fvFTD tend to be refractory to pharmacologic interventions.

Disinhibition and Other Inappropriate Behaviors

Orbitobasal (ventromedial) frontal lobe dysfunction leads to disinhibition, poor impulse control, antisocial behavior, and stereotyped behaviors. Disinhibition or distractibility may manifest as restlessness, pressured speech, impulsivity, irritability, aggressiveness, violent outbursts, or excessive sentimentality.⁶ Verbally inappropriate sexual comments and gestures are common in FTD. Despite these inappropriate behaviors, sexual drive is often reduced with impotence common in the FTD prodrome in men.¹⁰ Other socially inappropriate behaviors sometimes seen in FTD include theft, assault, inappropriate or offensive speech, and public urination or masturbation.¹¹ Many FTD patients exhibit stereotyped or perseverative behaviors such as repetitive cleaning, pacing, organizing objects into groups, use of catch phrases, impulse buying, hoarding, and counting. Features of obsessive-compulsive disorder are very common in fvFTD, and some patients may initially be given this psychiatric diagnosis.¹² Compulsions were the presenting symptoms in 30% to 60% of patients in 3 clinical series of FTD patients.¹³

A number of pharmacologic interventions may ameliorate or suppress disinhibition, poor impulse control, sexually inappropriate, and stereotyped behaviors in fvFTD. Selective serotonin reuptake inhibitors (SSRIs; fluoxetine, fluvoxamine, sertraline, or paroxetine) are often used as first line agents for the management of disinhibited, repetitive, sexually inappropriate behaviors, and dietary changes in FTD.^{14–17} Most descriptions of SSRI effects in FTD are based on open-label experience or cases series (Table 1). The few randomized, placebo-controlled trials that have been performed have produced mixed results. For example, although open-label experience suggests that paroxetine may be helpful for symptomatic management of FTD,¹⁶ a randomized, placebo-controlled trial failed to show efficacy.²¹ Trazadone has also been shown to be effective in treating the behavioral symptoms of FTD in a randomized, placebo-controlled trial²⁴; however, somnolence associated with trazadone use may limit its usefulness in some individuals. A meta-analysis of SSRI and trazadone effects on the Neuropsychiatric Inventory,³³ a measure of behavioral impairment in FTD, demonstrated a mean reduction (improvement) of 15.4 points in fvFTD,¹⁷ supporting the use of these drugs as first line agents for the management of behavioral symptoms in FTD.

Behavioral symptoms refractory to SSRI treatment are often responsive to atypical antipsychotic agents, although side effects including somnolence, weight gain, and emergence of Parkinsonism may limit efficacy.^{25,34} FTD patients may be particularly susceptible to extrapyramidal side effects of atypical antipsychotic agents.³⁴ Delusions are common in fvFTD, and tend to be jealous, somatic, religious, or bizarre, but are rarely persecutory. Euphoric symptoms, such as elevated mood, inappropriate

jocularity, and exaggerated self-esteem were found in 30% of FTD patients in 1 clinical series.³⁵ When severe, such behaviors may also be suppressed by treatment with an atypical antipsychotic agent.

An open-label study with the acetylcholinesterase inhibitor, rivastigmine reported modest improvements in mood and behavior in fvFTD.²⁸ However, the lack of cholinergic deficit in FTD¹⁷ and a recent case series documented worsening disinhibition and compulsions after donepezil treatment that resolved with medication withdrawal²⁹ suggest that acetylcholinesterase inhibitors should not routinely be used in FTD. A preliminary study of methylphenidate in FTD suggests a possible beneficial effect on risk taking behavior.³¹ More studies with this and similar medications are needed to assess the long-term safety and potential benefits of stimulant medications in FTD.

Dietary Changes

Dietary changes, especially cravings for sweets, are common in FTD.^{10,36} Decreased satiety and food cravings often lead to a weight gain in many patients. As the disease progresses, features of the Kluver-Bucy syndrome, such as hyperorality and oral exploratory behaviors may arise. Dietary changes, particularly food cravings, often respond to treatment with SSRIs.¹⁴ Dysphagia and gorging behaviors are less responsive to pharmacologic management and often require close caregiver supervision during meals.³⁷

Apathy

Apathy is frequently seen in patients with fvFTD who have involvement of the anterior cingulate and medial frontal lobes.³⁸ Symptomatic management of apathy is difficult, and there are few reports of successful management in the FTD literature. Apathy may be mistaken for depression in some patients; however, unlike in AD, depression is uncommon in fvFTD. Increased apathy may be related to caregivers' ratings of submissiveness in fvFTD.⁷ Apathy and emotional withdrawal are often punctuated with outbursts of disinhibited behavior,³⁹ which may respond to atypical antipsychotic treatment.

Cognitive Impairments

Impairments on tests of executive function or working memory are the most common cognitive deficits in fvFTD. Memory and visuospatial function are relatively spared and screening tests such as the Mini-Mental State Examination may remain normal even after patients require nursing home care.⁴⁰ Patients may have difficulty with set shifting, concept formation, abstraction and reasoning, inhibition of over-learned responses, response generation, organization, planning, self-monitoring, and using feedback to guide behavior.⁶ Tasks such as the Wisconsin Card Sorting Test, Trailmaking Test, Stroop Category Test, verbal and design fluency, and proverb interpretation are sensitive to frontal executive dysfunction in patients with fvFTD.⁴¹ Short-term memory impairments are an infrequent finding early in the course of fvFTD, but may become more prominent as the

TABLE 1. Summary of Published Open-Label and Randomized Clinical Trials in Patients With FTD (See Also Huey et al¹⁷ and Freedman¹⁸)

References	Subjects	Study Type	Study Duration	Main Findings
SSRIs				
Fluoxetine, fluvoxamine, sertraline or paroxetine Swartz et al ¹⁴	11	Open-label study	3 mo	Improvement in neuropsychiatric impairments in more than half of patients
Sertraline Mendez et al ¹⁹ Anneser et al ²⁰	18 1	Open-label study Case report	6 mo —	Decreased stereotypical movements Decrease in inappropriate sexual behavior and physical aggression in FTD-ALS patients
Paroxetine Moretti et al ¹⁶ Deakin et al ²¹	16 10	Randomized controlled trial Randomized controlled trial	14 mo 6 wk	Improvement in neuropsychiatric impairments and caregiver stress; few adverse events No improvement in neuropsychiatric impairments, mild worsening in cognitive function in treated group
Fluvoxamine Ishikawa et al ²² Ikeda et al ²³	2 16	Case series Open-label study	— 12 wk	Improved stereotyped behaviors, pain complaints Improved stereotyped and other behaviors
Other agents				
Trazodone Lebert et al ²⁴	26	Randomized, placebo-controlled trial	12 wk	Improvement in neuropsychiatric symptoms. No effect on cognitive status
Olanzapine Moretti et al ²⁵	17	Open-label study	24 mo	Improved agitation, misconduct, delusions; decreased caregiver distress
Risperidone Curtis and Resch ²⁶	1	Case report	—	Improved behavior
Aripiprazole Fellgiebel et al ²⁷	1	Case report	1 mo	Stabilization of clinical symptoms, improved frontal glucose metabolism on PET
Rivastigmine Moretti et al ²⁸	20	Open-label study	12 mo	Improvement in neuropsychiatric symptoms and caregiver burden, while cognitive function declined
Donepezil Mendez et al ²⁹	24	Randomized, open-label study	6 mo	No difference in cognitive function between treated/untreated. Neuropsychiatric impairments worse, reversible after drug removal in 33% treated subjects
Selegiline Moretti et al ³⁰	3	Open-label study	3 mo	Improved behavior, borderline improvement on 2 cognitive measures
Methylphenidate Rahman et al ³¹ Goforth et al ³²	8 1	Randomized, placebo-controlled trial Case report	One dose	Decreased risk taking behavior on gambling task Partial normalization of quantitative EEG pattern

PET indicates positron emission tomography.

disease progresses.⁴² At this time, there is no evidence to suggest that any medications can ameliorate cognitive dysfunction in FTD.

SUBTYPES OF FTD WITH EARLY LANGUAGE IMPAIRMENTS OR PPA (Fig. 2)

SD (Temporal Lobe Variant FTD or SD)

SD was originally defined as a syndrome of progressive loss of semantic knowledge, or knowledge

about people, objects, facts, and words.⁴³ The most common presenting complaint in SD involves language, and is often described as a loss of memory for words or a loss of word meaning. Although SD patients are aware of their expressive deficits, they are often unaware of their comprehension difficulties.⁴¹ Speech is fluent, but there are frequent semantic paraphasias, and use of substitute phrases such as “thing” or “stuff.” Repetition, prosody, syntax, and verb generation are preserved. Associative agnosia may lead to difficulty with object recognition.

This may manifest as misuse of or an inability to recognize household items such as a can-opener or pliers. Patients with more significant right temporal lobe damage may present with prosopagnosia, but more commonly with behavioral abnormalities such as irritability, impulsiveness, bizarre alterations in dress, and mental rigidity.^{44–46} An emergence of artistic talent has been observed in some patients with SD who have significant language impairment, but preserved visuospatial skills.⁴⁷

Many of the disinhibited and compulsive behaviors seen in fvFTD are also present in SD, as both groups have measurable damage to the orbitofrontal cortex.³⁸ The presence of such behaviors helps to distinguish SD from other forms of PPA.⁴ Patients with right-sided disease tend to have more severe behavioral abnormalities than patients with left-sided disease,⁴⁵ although most left-sided patients also develop such symptoms later during the course of disease.⁴⁶ As SD patients are often less apathetic than fvFTD patients, compulsive behaviors may be more prominent in SD than fvFTD. As with fvFTD, SSRIs may help to blunt compulsive behaviors, although severe cases, particularly those with more prominent right temporal lobe involvement, may require addition of an atypical antipsychotic. SD patients have deficits in emotion comprehension, especially for emotions with negative valence, such as sadness, anger, and fear.^{48,49} These deficits in emotion recognition may in part explain caregivers' reports of increased interpersonal coldness in SD.⁷ There are no known therapies for impairments in emotion recognition and interpersonal social interactions.

Owing to their language difficulties, patients with SD may score poorly on bedside screening measures such as the Mini-Mental State Examination. More detailed testing reveals a loss of semantic knowledge, with relatively preserved episodic memory for recent events.⁵⁰ In contrast to AD, recent memory tends to be preserved early in the course of SD, whereas many autobiographical events are lost. Thus in SD, some suggest that there is a reversal of the temporal gradient of memory impairment that is observed in AD.⁵¹ Neural networks that are damaged in SD are likely to be different than in AD, with less involvement of the posterior cingulate cortex.^{52,53} This coupled with the lack of cholinergic deficit in SD suggests that acetylcholinesterase inhibitors are unlikely to improve memory deficits.

PNFA

These patients present with changes in fluency, pronunciation, or word finding difficulty in the absence of other cognitive and behavioral abnormalities. Unlike fvFTD and SD, PNFA patients do not display typical behavioral abnormalities until later in the disease.¹ Insight and personal awareness can be exquisitely preserved, whereas depression and social withdrawal are common. Depression often responds to pharmacotherapy; however, there are no reported studies of antidepressant efficacy in PNFA. PNFA is a frequent presenting syndrome in patients who ultimately develop clinical

features of corticobasal degeneration (CBD) or progressive supranuclear palsy (PSP)^{5,54,55} and, less commonly, motor neuron disease (MND).^{56,57}

Episodic memory, semantic memory, and visuospatial function are preserved in PNFA. Executive function and working memory are often impaired. Language difficulties include agrammatism, phonemic paraphasias, and anomia. Other language problems may include stuttering, impaired repetition, apraxia of speech, alexia, and agraphia. Speech therapy may be of modest benefit to individuals with PNFA, particularly early in the course of disease.

THE IMPORTANCE OF NATURAL HISTORY OF FTD CLINICAL SYNDROMES

Symptomatic pharmacotherapy for all 3 subtypes of FTD is most frequently initiated when behavioral symptoms become intolerable to caregivers. With time, neuropsychiatric symptoms, such as agitation, aggressiveness, verbally and socially inappropriate behaviors, obsessive and compulsive symptoms, and sweet cravings eventually manifest in many FTD patients regardless of the initial clinical syndrome.⁵⁸ Such behavioral abnormalities often reach a peak during the middle-to-late stages of disease and depending on the rate of disease progression (which in turn may be dependent on the underlying neuropathology), symptomatic pharmacotherapy may be indicated for many years. However, as disease pathology progressively destroys medial frontal lobe structures involved in motivation,^{59,60} many patients display increasing apathy, become more withdrawn and experience fewer difficult-to-manage behaviors. This may allow for the withdrawal of symptomatic treatment in more advanced disease. Motor impairments, including atypical parkinsonism or weakness from motor neuron involvement are commonly observed with more advanced disease.⁶¹ These motor impairments may limit the expression of aberrant behaviors, and may allow for the withdrawal of symptomatic treatments such as atypical antipsychotics. FTD patients may be particularly sensitive to extrapyramidal side effects of antipsychotic medications,³⁴ thus clinicians should have a low threshold to reduce antipsychotic dose or stop such medications altogether in patients with worsening parkinsonism.

FUTURE DIRECTIONS IN THE SYMPTOMATIC MANAGEMENT OF FTD

The lack of randomized, placebo-controlled data on most symptomatic treatments for FTD limit clinicians' ability to determine the optimal therapy for this disorder. The data that are available are limited by the different clinical criteria for subject enrollment and the variable outcome measures used in each study. Clearly, more clinical trials of currently available symptomatic agents for the treatment of dementia are needed. However, such studies should use outcome measures that are sensitive to the cognitive and behavioral deficits associated with FTD, such as the Neuropsychiatric Inventory,³³ Frontal Behavioral Inventory,⁶² Executive Interview,⁶³ and

others.¹⁸ As suggested by Freedman,¹⁸ a greater consensus among investigators as to the optimal criteria for inclusion of FTD subjects, and the most appropriate outcome measures to measure treatment efficacy would greatly improve the validity of future studies and the ability to develop evidence-based treatment recommendations for FTD.

POSSIBILITIES FOR DISEASE-MODIFYING THERAPIES FOR FTD: IMPLICATIONS OF RECENT GENETIC, PATHOLOGIC, AND BIOCHEMICAL DATA

There is little evidence to suggest that current symptomatic treatments for FTD have any effect on disease progression or survival. However, as the molecular basis for each FTD clinical syndrome comes into focus, a number of possible targets for disease-modifying therapies, or treatments that treat the underlying neuropathologic causes of FTD, have become apparent. Future clinical trials of both symptomatic FTD treatments and potentially disease-modifying therapies will need to take into account the biochemical differences between each FTD subtype, and differences in their rates of progression. As new amyloid-imaging technology becomes more widely available, more accurate differentiation of FTD from AD in clinical trial participants will also improve the specificity of potential treatment effects for FTD.

Pathologic Correlates of FTD: Implications for Study Design and New Treatments

Recent clinical-pathologic series suggest that the most common pathologic correlates of the clinical fvFTD syndrome are FTD with ubiquitinated inclusions (FTD-U), including FTD-MND followed by tau-related diagnoses including most commonly Pick disease, and infrequently CBD or PSP.^{58,64–66} The most common pathologic correlate of SD is also FTD-U,⁶⁷ whereas PNFA is most commonly associated with CBD or PSP at autopsy.⁵ A small percentage of all 3 clinical FTD syndromes are found to have AD pathology at autopsy.⁶⁸

The primary constituent of ubiquitinated inclusions has been identified as TAR DNA-binding protein 43 kDa (TDP-43).⁶⁹ FTD individuals with concurrent MND represent the strongest clinical association with FTD-U pathology. Moreover, the strong heritability of FTD-MND suggests that genetic factors may be particularly important for developing this syndrome.⁷⁰ An association between FTD-MND and an as yet unidentified gene on chromosome 9p^{71,72} suggests that a new avenue for disease-modifying therapies for FTD-MND may soon exist: therapies targeted to biochemical pathways involving TDP-43 and possibly pathways that link the chromosome 9p-FTD-associated gene(s) to TDP-43.⁷³ In addition, the close clinical-pathologic association of FTD-MND with TDP-43(+) brain pathology and the rapid progression of FTD-MND, as compared with other FTD variants,^{74,75} suggests that FTD-MND may be a particularly attractive clinical syndrome on which

to focus future TDP-43(+)-related disease-modifying therapy clinical trials.

Progranulin Mutations

A significant proportion of cases of fvFTD, in most cases without MND,⁷⁶ have been found to have loss of function mutations in the progranulin (PGRN) gene.^{77,78} Progranulin is a peptide growth factor that plays important roles in mediating neuronal development and inflammation.⁷⁹ Clinically, such patients often have typical features of fvFTD, PPA, and/or Parkinsonism.^{80–84} Such individuals also display FTD-U/TDP-43(+) pathology at autopsy,^{73,85} suggesting that treatments that alter progranulin levels, either by restoring normal levels of PGRN gene expression, introducing exogenous progranulin or modulating the posttranslational modification of progranulin may be effective disease-modifying treatment strategies in the future, and may be useful even in FTD individuals without PGRN mutations. Strategies for normalizing expression of (or overexpressing) individual central nervous system proteins have been validated in human AD patients, suggesting that the technology for normalizing regional progranulin expression may be close at hand.⁸⁶

Finally, the identification of concurrent α -synuclein and/or AD pathology in a number of PGRN families with onset of symptoms as late as 75 years of age,^{84,87} the identification of TDP-43 pathology in approximately 20% of AD cases, and other possible roles for progranulin in mediating neuroinflammation in AD,⁷⁹ raise the possibility that future progranulin-targeted therapies may also be useful for treating non-FTD dementia pathologies.⁸⁸

Tau Mutations

Tau mutations have been recognized as an important cause of FTD for the past decade.⁸⁹ Alterations in splicing, posttranslational processing of tau, and tau expression levels may all contribute to altered tau isoform levels and tau deposition in different pathologic variants of FTD and related disorders.² Transgenic mouse and *Drosophila* models of a number of pathogenic tau mutations exist and are facilitating the development of potential disease-modifying agents that alter the phosphorylation of tau, such as lithium^{90,91} and interventions that affect the folding and metabolism of tau.^{92,93} Recent evidence suggests that reducing tau expression may also be a viable therapeutic strategy for tau-related neurodegenerative disorders.^{94,95} The variability of underlying tau-related neuropathology in fvFTD may limit the utility of tau-directed disease-modifying therapies until more specific biomarkers for tau versus TDP-43 related neuropathology are identified. This also suggests that clinical trials designed to test the efficacy of potential therapeutic agents targeted against tau should focus on FTD subtypes more closely associated with tau pathology, particularly PNFA (and CBD/PSP), and not fvFTD.

Biomarkers in Designing New Therapeutic Studies in FTD

In individuals who do not carry a pathologic mutation in 1 of the known disease-associated FTD genes, neuroimaging measurements are currently the best biologic markers for FTD both diagnostically and for assessing longitudinal responses to disease-modifying therapy. The most rigorous study of cerebrospinal fluid (CSF) findings in pathologically confirmed cases of FTD and AD suggests that a combination of markers, including CSF isoprostane levels and low CSF tau protein may be somewhat useful in differential diagnosis of FTD; however, more information is needed before CSF analysis can be routinely applied to diagnosis of FTD.⁹⁶

Functional neuroimaging of blood flow abnormalities using Tc₉₉-hexamethylpropyleneamine-single photon emission computed tomography shows bilateral frontal hypoperfusion early in the course of fvFTD, and reliably differentiates patients with FTD from patients with AD.⁹⁷ Unbiased analysis of T1-weighted magnetic resonance imaging (MRI) scans from patients with fvFTD has identified regions of significant cortical atrophy in the ventromedial frontal cortex, the posterior orbital frontal regions bilaterally, the insula bilaterally, the left anterior cingulate cortex, the right dorsolateral frontal cortex, and the left premotor cortex as compared with controls and patients with SD.^{98,99} Longitudinal measurements of MRI scans of patients with fvFTD show faster rates of frontal atrophy (4.1% to 4.5%/y), and similar rates of parieto-occipital atrophy (2.2% to 2.4%/y) as compared with patients who have AD (2.4% to 2.8%/y, globally).¹⁰⁰ Statistically significant atrophy of frontal and temporal lobe gray matter structures can be measured in annual MRI scans in relatively small groups of fvFTD or SD patients, using new methods such as Tensor-based Morphometry (TBM).^{101,102} These findings suggest that longitudinal measurements of brain volume may be useful outcome measures in future clinical trials of potential disease-modifying FTD therapies.

The advent of amyloid-sensitive positron emission tomography ligands, such as Pittsburgh Compound B (PIB),¹⁰³ may be useful for differentiation of FTD from AD, and particularly in identifying individuals with a clinical FTD syndrome caused by underlying AD pathology. Although most cases of clinically defined FTD syndromes show no PIB uptake, a small minority may display cerebral amyloid levels comparable with those seen in AD.^{104,105} Most likely, these individuals will be found to have unusual (often frontal) variants of AD¹⁰⁶; however, it is also possible that some of these cases will have both concurrent FTD-pathology and AD-pathology.⁸⁷ A definitive answer awaits the results of autopsy studies of PIB(+) FTD individuals. An exciting possibility is that PIB(+) FTD individuals will respond to amyloid-reducing, disease-modifying treatments for AD that are currently under development.

CONCLUSIONS

Although treatment options for FTD are currently limited to a small number of symptomatic agents, advances in understanding the biology of FTD have already suggested possibilities for new treatments designed specifically to interfere with FTD associated brain pathology. More large-scale, placebo-controlled trials are needed to establish the efficacy of currently available symptomatic treatments for FTD. Such studies will have the added benefit of establishing a set of optimal assessments for measuring efficacy of new FTD treatments and providing evidence-based clinical treatment recommendations for currently available drugs. On the basis of spectacular advances in the basic science of FTD, new treatments are rapidly progressing to the point of being ready for early stage human clinical trials. With these advances, the goal of specific disease-modifying therapies for FTD seems attainable within the not too distant future.

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