Published in final edited form as:

Neurologist. 2010 January ; 16(1): 16–22. doi:10.1097/NRL.0b013e3181b1d5c6.

Update on Frontotemporal Dementia

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Abstract

Background—Frontotemporal dementia has recently been recognized as a common cause of young-onset dementia.

Objective—To review the current approach to the clinical evaluation, understanding of pathophysiology, and management of frontotemporal dementia.

Results—Two main clinical presentations are: 1) behavioral, with impulsive behaviors and disinhibition, change in personality such as apathy and indifference, and poor judgment, and 2) language, with a non-fluent aphasia with anomia (primary progressive aphasia), or a fluent aphasia with early loss of word meaning (semantic dementia). The differential diagnosis includes other neurodegenerative dementias, vascular and other conditions affecting the brain, and psychiatric diseases. Investigations, including neuropsychological testing, and structural and functional brain imaging, may help support the diagnosis. Recent advances in understanding the pathophysiology have suggested that most cases have underlying ubiquitin-positive inclusions, while some have tau-positive inclusions. Genetic mutations, particularly on chromosome 17 in the tau or progranulin genes, have been identified. Management includes a trial of symptomatic medications and a multi-faceted approach, including environmental modification and long-term care planning.

Conclusion—Medical researchers studying frontotemporal dementia aim to identify disease-modifying drugs and, ultimately, a cure for this devastating disease.

Keywords

Frontotemporal dementia; primary progressive aphasia; ubiquitin; tau; chromosome 17

INTRODUCTION

US national statistics of the twentieth century show a steady trend of increasing life expectancy. In 2000, the average life expectancy for both sexes and all races was about 77 years.¹ With the increase in the number of older persons, the prevalence of common conditions of aging is increasing, in particular that of dementia. Indeed, a major risk factor for dementia is increasing age. Studies suggest that the prevalence of dementia is about 5% in persons older than 65 years of age, and up to 50% in persons older than 85 years.²

The clinician's ability to recognize different causes of dementia and to make a specific diagnosis is improving with advances in medical research and technology. Nevertheless, making accurate diagnoses remains a challenge, particularly for less common forms of dementia. Having a practical approach to recognizing and managing all forms of dementia, including the relatively less common forms such as frontotemporal dementia, will allow the practicing neurologist to make an accurate and timely diagnosis and implement a tailored

plan of care. Also, improving our understanding of the less common forms of dementia may contribute to our understanding of the more common forms such as Alzheimer's disease, and may thus have a large positive impact on public health. Here, we review frontotemporal dementia, a less common form of neurodegenerative dementia and a condition for which our understanding of diagnosis, pathophysiology, and management has deepened in recent years.

PUBLIC HEALTH IMPACT

Although clinical syndromes with cognitive impairment resulting from frontal and temporal lobe dysfunction have been recognized for centuries (e.g., case descriptions of traumatic brain lesions and stroke), the dementia resulting from frontal and/or temporal lobe neurodegeneration has only been systematically examined more recently. To date, there is little data on the epidemiology of frontotemporal dementia. In specialty dementia clinics, some believe frontotemporal dementia to be the third most common cause of neurodegenerative dementia overall (after Alzheimer's disease and Lewy body disease), and the second most common cause in persons less than 65 years of age (after Alzheimer's disease). While large clinic-derived neuropathologic series suggest that frontotemporal dementia is relatively frequent,³ it is likely far less common in the general population, as suggested in a recent clinical-pathologic study of neuropathology of dementia in older community-dwelling persons.⁴ Its prevalence has been estimated to be 4–9/100,000 individuals in a province of the Netherlands.⁵ Individuals affected by frontotemporal dementia are often in their mid-to-late adulthood and have a slowly progressive course resulting in death, which is estimated, in most cases, to be approximately 6 years after the diagnosis is made.⁶ However, variability in disease duration has been observed and further study is needed to clarify prognosis. In general, prognosis seems to be worse in cases with early motor involvement, including cases with motor neuron disease.⁶ Over the course of the illness, patients invariably progress to become mute, bed bound, and totally dependent for all activities.

NOMENCLATURE

Frontotemporal dementia is a clinical syndrome with various clinical presentations and various associated underlying pathologies, including the relatively rare pathology of Pick's disease. Varying clinical presentations and pathologies have contributed to a range of nomenclature referring to this entity (Table 1). Overall, the current approach is to use the term "frontotemporal dementia" when referring to the clinical entity, and to use the term "frontotemporal lobar degeneration" when referring to the pathological entity.⁷ Terms referring to specific clinical diagnoses (e.g., primary progressive aphasia⁸) or pathologic diagnoses (e.g., Pick's disease) can be used once detailed clinical or pathologic data are available. Although the use of these specific terms is encouraged in research settings, their use in clinical settings has been discouraged and, to date, has had little bearing on the management of individual patients. Some researchers prefer to group together several neurodegenerative cognitive-motor diseases (including frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy), using the term "Pick complex": this emphasizes the overlap of clinical and pathological features.⁹ However, this approach is not been widely accepted.

CLINICAL FEATURES

Clinical diagnostic criteria for frontotemporal dementia have been proposed.^{7, 10, 11} The key feature is a slowly progressive dementia that presents with a predominant behavioral or language disturbance (Table 2), with relative preservation of memory and spatial skills early in the course of the illness.⁷ Intact memory is worthwhile noting, and one should assess for preserved ability to keep track of day to day events (e.g., timing of when spouse leaves for/

returns from work, timing of television programming). Also, spatial orientation is relatively preserved in frontotemporal dementia (e.g., patients do not get lost). These features raise suspicion that the dementia is atypical for Alzheimer's disease and that other causes of dementia should be sought. Another unusual feature in frontotemporal dementia is that affected individuals may have a young age of onset: several reports have found that the typical age of onset is in the late 50's.^{5, 6}

Of the two presentations of frontotemporal dementia, the more common is that of a behavioral disturbance which is associated with a change in personality: the individual displays difficulty with modulating behaviors (e.g., disinhibition, perseveration, and lack of initiative) and inappropriate behaviors (e.g., inappropriate sexual or eating behaviors), as well as marked personality changes such as emotional blunting and loss of insight. The less common presentation of frontotemporal dementia is that of a progressive and relatively isolated language disturbance. This language presentation can either be that of difficulty with expression and naming, suggestive of primary progressive aphasia (usually a non-fluent aphasia), or that of difficulty with word meaning, in keeping with a semantic dementia (usually a fluent aphasia in the initial stages). The different clinical presentations of frontotemporal dementia are believed to be associated with the initially focal pattern of atrophy of the brain.¹² However, as the disease progresses over the years, persons with frontotemporal dementia develop a more global pattern of cognitive impairment, displaying both behavioral and language impairment,¹³ as well as memory dysfunction, inattention, and other cognitive deficits.

On examination, early signs include "frontal lobes release signs", such as the presence of a grasp, snout, or palmomental reflex. Further, disinhibition and utilization behaviors (such as repeatedly using remote controls or other devices without purpose, but only because they are accessible) can be observed. Spoken language, reading and writing, and other tests of language would help identify significant anomia and other features of aphasia (e.g., semantic paraphasias). The presence of other neurological abnormalities may suggest the diagnosis, including the presence of early motor neuron disease or parkinsonism.^{6, 14} There are no widely accepted bedside cognitive or behavioral tests for frontotemporal dementia, although some tests have been proposed for detection of either abnormal behavioral or language function.^{15, 16} Tests like the Mini-Mental State Examination¹⁷ are insensitive to change in behavior, aphasia detection, and evaluation of executive function. If the index of suspicion is high, a more extensive neuropsychological battery should be completed and the patient followed closely.

DIFFERENTIAL DIAGNOSIS

The diagnosis of frontotemporal dementia may be difficult, as this syndrome shares important similarities with other more common causes of dementia. In particular, overlap with other neurodegenerative dementias makes the diagnosis challenging. In the early stages of the disease, common features include a gradual onset and slowly progressive course, impairment in social and occupational functioning, and decline from previous level of functioning. In later stages, common features include aphasia, dependence for activities of daily living, weight loss, and parkinsonism and impaired mobility.

The main consideration in the differential diagnosis of frontotemporal dementia is other neurodegenerative diseases (Table 3). The most common cause of neurodegenerative dementia is Alzheimer's disease.² This can mimic frontotemporal dementia, especially when it is associated with early semantic difficulties or personality changes (e.g., apathy), but usually differs by the prominent and early memory difficulties. In Alzheimer's disease, episodic memory, or memory for specific autobiographical events (e.g., a recent party) is

impaired.¹⁸ But frontotemporal dementia may often be distinguished early in the course from Alzheimer's disease by significant behavioral or language abnormalities with preservation of memory and spatial orientation, as well as the presence frontal lobes release signs and early motor neuron disease or parkinsonism. In addition to different patterns of abnormalities on neuropsychological testing, structural and functional brain imaging can help distinguish these two neurodegenerative dementias.¹⁹

Other neurodegenerative diseases are in the differential diagnosis. Lewy body disease should be considered in the face of behavioral changes and parkinsonism, but these patients often have a different pattern of behavioral problems with early well-formed visual hallucinations, cognitive fluctuations, and REM sleep behavior disorder.¹⁸ Creutzfeldt-Jakob disease or Huntington's disease presenting with isolated early personality changes and psychiatric problems, can mimic frontotemporal dementia, but have other distinguishing features. In Creutzfeldt-Jakob disease, the course is that of a rapidly progressive dementia with characteristic motor signs (such as myoclonus and ataxia) and abnormal tests (e.g., the presence of 14-3-3 protein in cerebrospinal fluid). In Huntington's disease, motor impairment is characterized by chorea, there is often a positive family history of a neurodegenerative condition, and diagnostic genetic testing is available.

Conditions to consider in the differential diagnosis of frontotemporal dementia include other diseases affecting the brain (Table 3). Vascular processes are common in aging and can lead to a dementia syndrome, although the course of illness would typically be more abrupt and stepwise, and there may be interval periods with improved or normal cognition and affect. Other considerations in the differential are diseases affecting the frontal or temporal lobes, such as brain tumors and paraneoplastic syndromes and infectious diseases (e.g., herpes encephalitis targeting the temporal lobes, a focal abscess affecting the frontal lobe), and others. Psychiatric conditions, including schizophrenia, manic-depression, and major depression, can mimic frontotemporal dementia, but there is often a longstanding history of psychiatric disease and differences in specific patterns of abnormal social behaviors.²⁰ Rarely, white matter diseases (leukoencephalopathies) can present in adulthood with an atypical dementia syndrome. Further, metabolic diseases (thyroid disease, hepatic encephalopathy, porphyria, etc.), toxins, inflammatory and immune diseases, head trauma, genetic diseases (such as Wilson's disease), and other conditions can produce behavioral and cognitive difficulties and should be in the differential diagnosis of frontotemporal dementia.

INVESTIGATIONS

There is no single specific test for routine use in making the clinical diagnosis of frontotemporal dementia. A thorough history that is suggestive of this syndrome remains essential to making the diagnosis. For most cases of frontotemporal dementia, the evaluation of the dementia is similar to that for Alzheimer's disease.¹⁸ In addition to the history and physical examination, the neurologist should consider ordering tests to support the diagnosis and rule out treatable causes of dementia.¹⁸ Neuropsychological testing, with particular focus on executive and language functions, increases diagnostic accuracy.²¹ The pattern of abnormality may reveal relatively isolated dysfunction of frontal lobe abilities (e.g., impaired set shifting or shifting from one set of rules to another) or dysfunction of language abilities (e.g., naming). Further, repeated neuropsychological testing may show an increased rate of cognitive decline in executive and language domains, helping to distinguish frontotemporal dementia from other more common forms of dementias.²² As there may be challenges that may preclude obtaining a full detailed battery of neuropsychological tests, brief (e.g., 15 minute) screening tools have been proposed.²³

Brain imaging is often helpful, and should target the frontal and anterior temporal lobes. Structural imaging may support the diagnosis, despite sometimes being interpreted as normal early in the course of the illness by non-expert clinicians. Structural brain imaging can demonstrate focal, and sometimes very marked, atrophy of the frontal and/or anterior temporal lobes, which is often asymmetric. Magnetic resonance imaging (MRI) is more useful than computed tomography to demonstrate subtle focal atrophy, and routine clinical MRI may differentiate frontotemporal dementia from other causes of dementia.²⁴ Asymmetric enlargement of the lateral ventricles, for example of the temporal horns, can be quite striking. The cortical ribbon is thinned in the affected brain regions. Functional brain imaging, such as single photon emission computed tomography (SPECT) or positron emission tomography (PET) imaging, can be particularly useful in showing abnormalities in the face of normal structural imaging. Functional imaging shows impaired function in affected cortical brain areas (frontal, anterior temporal regions). A recent study suggested that functional imaging was associated with a high negative predictive value in frontotemporal dementia.²⁵ Another study with longitudinal 18F-fluorodeoxyglucose (FDG) PET imaging has found that anterior hypometabolism progresses to include parietal and temporal regions over time,²⁶ which may confuse the interpretation (as parietal and temporal hypometabolism is observed in Alzheimer's disease). Performing functional imaging should, therefore, probably be done early in the course of suspected frontotemporal dementia, when it is more likely to assist in differentiating frontotemporal dementia from Alzheimer's disease.²⁷ Of practical relevance, PET imaging has recently been approved for coverage by Medicare to distinguish these two neurodegenerative dementias.

Blood testing for screening of other common conditions of aging that can present as dementia is recommended (e.g., thyroid screen and vitamin B12 level).¹⁸ Other tests, such as blood or CSF tests, or an electroencephalogram, are low yield in the clinical setting.²⁸ Although there are reports of up to fifty percent of individuals having a family history of dementia, only a small number of patients have a causative genetic mutation that can be identified on DNA testing. Genetic testing is not recommended, or available, for routine evaluation of patients suspected of having a frontotemporal dementia.

PATHOPHYSIOLOGY

The pathophysiology of frontotemporal dementia is not well understood. The neuropathology associated with the clinical syndrome of frontotemporal dementia often includes changes on gross anatomy (frontal and anterior temporal lobe atrophy) and microscopic changes (superficial cortical spongiosis and gray and white matter gliosis). However, overall, there is variable phenotypic-pathologic correlation.^{29, 30} The pathology of frontotemporal dementia has been classified according to molecular characteristics,⁷ and a recent consortium has proposed revised neuropathologic criteria based on advances in molecular genetics, biochemistry, and neuropathology.³¹ Some cases are found to have tau inclusions, and are then referred to as tauopathies³² (such as Pick's disease, corticobasal degeneration, and progressive supranuclear palsy), and other cases are without inclusions (such as dementia lacking distinctive histology,³³ now recognized as a relatively rare condition). More recently, it has been suggested that a non-tauopathy entity, "frontotemporal lobe degeneration with ubiquitin-positive inclusions", may be the most common pathology associated with the clinical syndrome of frontotemporal dementia: this entity may or may not be associated with motor neuron disease. The term "Pick's disease" is now reserved for cases with Pick cells (alpha-B-crystalline positive neurons) and Pick bodies (tau-positive round neuronal inclusions) in the brain. Rarely, other conditions, including hippocampal sclerosis, have been reported in cases of individuals who had clinical frontotemporal dementia.³⁴ Finally, the clinical syndrome of frontotemporal dementia may be caused by underlying Alzheimer's disease pathology,³⁵ in the absence of pathological changes of

frontotemporal lobar degeneration. Clinico-pathologic studies are expected to contribute to improved recognition of the clinical features of frontotemporal dementia and to a more accurate clinical diagnosis. Recently, a study of 90 patients with pathological confirmation of the diagnosis found that cases with tauopathy were more likely to have parkinsonism, and cases with ubiquitin inclusions were more likely to have motor neuron disease.³⁶ Further research in this area, including with animal models of frontotemporal dementia,³⁷ is needed to explore clinico-pathologic correlations.

The genetics of frontotemporal dementia are complex, yet ongoing research has shed light on important aspects of pathophysiology and may, one day, pave the way to developing improved therapies. Also, some research suggests that there may be some phenotypic-genetic correlation.^{38, 39} Most mutations causing frontotemporal dementia studied to date are on chromosome 17, including mutations of the microtubule-associated protein tau gene and the progranulin gene. More than 100 families with mutations involving the microtubule-associated protein tau (MAPT) gene on chromosome 17¹⁴ have been identified: the clinical entity has been termed frontotemporal dementia and parkinsonism linked to chromosome 17.^{40, 41} Tau is a protein that is critical for microtubule stability and axonal transport.⁴² The presence of pathological tau in some forms of frontotemporal dementia has led to the designation of this entity as a tauopathy (a category of neurodegenerative diseases which includes, among others, Alzheimer's disease). Although several neurobiologic mechanisms resulting from mutations in the tau gene have been proposed in frontotemporal dementia, some lines of work suggest that pre-fibrillar pathologic tau may play a role in neurodegeneration and behavioral disturbance.⁴³

More recently, mutations of the progranulin gene on chromosome 17 have been implicated in the pathogenesis of frontotemporal dementia,^{44–49} and have been associated with ubiquitin-immunoreactive lentiform intranuclear inclusions in the neocortex and striatum.⁵⁰ Progranulin is a growth factor with multiple functions, and is believed to play a role in neuronal survival, wound repair, tumorigenesis, and other physiologic and pathologic processes, including abnormal metabolism of an ubiquitinated protein, TDP-43,⁵¹ which may be important in some but not all⁵² forms of frontotemporal dementia with ubiquitin inclusions. Other than mutations linked to chromosome 17, several other chromosomes have been implicated in frontotemporal dementia, including mutations on chromosome 3^{53, 54} and chromosome 9 (inclusion body myopathy and Paget disease^{55, 56}). Although mutations of the presenilin 1 gene on chromosome 14 has been described in persons with frontotemporal dementia,⁵⁷ whether these mutations are pathogenic in frontotemporal dementia has been unclear.⁵⁸ These mutations have, however, been implicated in pathogenesis of early-onset Alzheimer's disease.

MANAGEMENT

As with the other neurodegenerative dementias, the management of frontotemporal dementia is multifaceted. Pharmacologic treatment is currently aimed at symptomatic treatment, with a focus on management of difficult behaviors and cognitive impairment (Table 4). To date, there is no approved disease modifying drug or cure for frontotemporal dementia. Few double-blind, randomized, controlled trials in frontotemporal dementia have been published, and further study is needed to identify effective treatments.

Atypical neuroleptics have been prescribed for aggressive or inappropriate behaviors, and can often have beneficial effects using low doses. Risperidone may help control difficult behaviors, and quetiapine fumarate may also be tried, especially when a more sedating neuroleptic is needed. Important to discuss with patients and families before drug initiation, is that atypical neuroleptics are not approved for treatment of patients with dementia-related

psychosis, and these drugs have been associated with increased risk of death compared to placebo. Also, monitoring for side effects such as motor complications, including parkinsonism, is necessary.

There are several studies of antidepressants in frontotemporal dementia. Although some suggest that selective serotonin reuptake inhibitors may improve behavior,^{59, 60} a recent small double-blind, randomized, placebo-controlled crossover trial of paroxetine hydrochloride showed that behavioral symptoms were not improved and that cognitive function, in fact, worsened.⁶¹ On the other hand, a similarly designed study found that trazodone hydrochloride, another antidepressant, was effective.⁶² In addition, a small open label trial of moclobemide, a monoamine oxidase type A (MAO-A) inhibitor, also suggested a benefit for patients with frontotemporal dementia with regards to affect, behavior, and speech.⁶³

Recently, several studies evaluated the use of drugs that are approved for Alzheimer's disease, including several of the acetylcholinesterase inhibitors. Some of these small open label studies seem to suggest that some patients may benefit from these agents, including donepezil hydrochloride and rivastigmine tartrate.⁶⁴ However, in a more recent small study, persons taking donepezil hydrochloride had worse behavioral symptoms over a six month period, compared to those not taking an acetylcholinesterase inhibitor.⁶⁵ A study of 36 patients found that persons with a behavioral form of frontotemporal dementia did not benefit from glantamine, while there was a trend for improvement in those with primary progressive aphasia.⁶⁶ In addition to acetylcholinesterase inhibitors, there has been interest in examining the use of memantine, an NMDA receptor antagonist, in frontotemporal dementia. A recently published small open-label study of 16 patients with frontotemporal dementia provided mixed results.⁶⁷ Clearly, there is a need for larger multi-centered trials to evaluate these and other treatments for frontotemporal dementia.

Ongoing research efforts offer increased understanding of frontotemporal dementia and the potential for identification of novel treatments, particularly disease-modifying treatments.⁶⁸ Recently, researchers have demonstrated that a microtubule-binding drug, paclitaxel (used clinically as an anticancer drug), could offset losses of tau function in a transgenic mouse model of tauopathy.⁶⁹ this provides the first evidence ever of a drug with the potential to reverse the loss of normal tau function and could have therapeutic benefits in human tauopathies. Advances in research provide hope for better treatments,⁷⁰ and maybe one day, a cure, for this devastating neurodegenerative dementia.

Management of the frontotemporal dementia includes important non-pharmacologic interventions for the patient and their caregiver. If possible, this is best achieved using a multidisciplinary team approach, including input from the family, nurse, speech therapist, and social worker.⁷¹ For the patient, environmental modification can help maintain quality of life. Providing a structured environment is important (e.g., keeping the same daily routine, not moving objects or furniture around, etc.). Safety issues that warrant particular attention include safety around the home (e.g., in the kitchen, bathroom, pool) and in public (e.g., whenever inappropriate behaviors may trigger a dispute), as well as driving safety and knowing when it is no longer safe to drive.⁷² Early in the course of the disease and if judgment is not impaired, the patient may be able to engage in decision-making about their long-term plans for medical care, living arrangements, and finances. This may be particularly difficult for patients who have lack of insight and impaired judgment. When appropriate (e.g., the patient is disabled from the dementia and is too young to qualify for Medicare), the caregiver should assist the patient in applying for social security disability. Getting approval for disability has often been challenging, given the young age of the patient and atypical presentation of the dementia. However, in 2008, the Social Security

Administration made changes to include frontotemporal dementia in the Compassionate Allowance program, which now facilitates and expedites application for social security disability.⁷³ In addition to these measures, as the disease progresses, maintaining physical and cognitive activities, a balanced diet, as well as comfort and dignity become increasingly important issues.

For the caregiver, obtaining accurate and up-to-date information about the disease will provide a sense of understanding and heightened control over this stressful situation.⁷⁴ Also, caregivers benefit from support from health care providers, and possibly even more so, from other caregivers experiencing similar issues. Useful handouts, books, and websites (which include information on clinical trials) are available (Table 5). Further, recognizing one's limits and knowing when to ask for help is crucial for the well-being of the caregiver. The multidisciplinary team should be on the alert for signs of burn out and depression in the caregiver.⁷⁵

Acknowledgments

Dr. Arvanitakis was supported by the National Institute on Aging, grant K23 AG023675.

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TABLE 1**Nomenclature of Frontotemporal Dementia**

Pick's disease
Frontal lobe degeneration of the non-Alzheimer type
Dementia lacking distinctive histology
Primary progressive dementia
Semantic dementia
Frontotemporal dementia *
Frontotemporal lobar degeneration
Pick complex
Frontotemporal dementia and parkinsonism linked to chromosome 17
Frontotemporal lobe degeneration with ubiquitin-positive inclusions

* Preferred term for designating clinical entity

TABLE 2**Two Clinical Presentations of Frontotemporal Dementia**

Presentation	Features
Behavioral *	<ul style="list-style-type: none"> Impulsive behaviors and disinhibition (e.g., inappropriate sexual behaviors) Change in personality (e.g., indifference, apathy, mental inflexibility) Poor judgment and poor insight into consequences of behaviors (e.g., driving) Repetitive, compulsive, stereotypic behaviors (e.g., hyperorality) Loss of personal hygiene (e.g., wearing same clothes for days) Loss of social graces (e.g., making jokes during a funeral)
Language	<ul style="list-style-type: none"> Non-fluent aphasia, with anomia, agrammatism, phonemic paraphrasias, impaired word repetition, alexia and agraphia Fluent aphasia, with early loss of word meaning (empty speech), poor comprehension, semantic paraphrasias, prosopagnosia and associative agnosia

* More common of the two presentations

TABLE 3

Differential Diagnosis of Frontotemporal Dementia

Category of disorder	Diagnosis
Neurodegeneration	Alzheimer's disease
	Lewy body disease
	Creutzfeldt-Jakob disease
	Huntington's disease
Vascular processes	Vascular dementia (e.g., strategic infarct, multi-infarct dementia)
	Cerebral vasculitis (primary and secondary)
Tumors	Primary (e.g., meningioma) and secondary (metastases)
	Paraneoplastic syndrome (e.g., limbic encephalitis)
Infections	Meningoencephalitis: syphilis, herpes simplex, HIV
	Abscess: tuberculoma
Psychiatric disorders	Schizophrenia
	Major affective disorder: depression, bipolar disorder
Leukoencephalopathies	Demyelinating: multiple sclerosis
	Dysmyelinating: metabolic diseases (e.g., adult metachromatic leukodystrophy)
Metabolic disorders	Thyroid disease: hyper- and hypothyroidism
	B12 deficiency
Toxins	Alcohol overuse (Wernicke-Korsakoff syndrome)
	Drugs (prescription, such as narcotics and chemotherapies, and illicit)
	Heavy metal intoxication
Inflammatory disorders	Temporal arteritis
	Neurosarcoidosis
Immune disorders	Hereditary diffuse leukoencephalopathy
	Various rheumatologic diseases (e.g., lupus)
Head trauma	Accidental (e.g., motor vehicle accidents)
	Non-accidental (e.g., dementia pugilistica, physical abuse)
Genetic disorders	<i>Mitochondrial DNA disorders</i> : mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
	<i>Trinucleotide repeat disorders</i> : spinocerebellar ataxias, fragile X syndrome
	<i>Other</i> : microangiopathies such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy, Wilson's disease (hepatolenticular degeneration)
Other	Normal pressure hydrocephalus
	Status epilepticus
	Radiation to the brain

TABLE 4**Classes of Drugs to Consider**

Atypical neuroleptics
Selective serotonin reuptake inhibitors
Acetylcholinesterase inhibitors

TABLE 5

Web Resources

General information	Association for Frontotemporal Dementias www.ftd-picks.org
	National Aphasia Association www.aphasia.org
Clinical trials	National Institute on Aging (NIA) www.nia.nih.gov/HealthInformation/ClinicalTrials.htm
	National Institutes of Health (NIH) www.clinicaltrials.gov