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Patient Care and Management of Frontotemporal Lobar Degeneration

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Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease that affects frontal and temporal regions of the brain. Two proteins indicated in the pathology are tau and the recently discovered TDP-43. Major manifestations include progressive aphasia and a disorder of social comportment. The diagnosis of a patient includes a detailed cognitive exam, clinical testing, and neuroimaging techniques. The current goal of therapy for FTLD is symptomatic management with medications borrowed from other conditions. Nonpharmacologic management such as behavioral interventions and environmental engineering are also efficacious in optimizing quality of life.

Keywords: frontotemporal lobar degeneration; TDP-43; symptomatic management; nonpharmacologic management

Introduction

Frontotemporal lobar degeneration (FTLD) is a neurodegenerative disease that affects frontal and temporal regions of the brain. FTLD is remarkable for its early onset, presenting typically in the fifth or sixth decade of life.[1] Although epidemiological studies of FTLD are limited, the prevalence of FTLD is estimated to be comparable with that of Alzheimer's disease (AD) among individuals with dementia who are younger than 65 years at onset.[2]

Many individuals presenting with an FTLD spectrum disorder have histopathologic disease at autopsy that identifies the condition as a *tauopathy*. Tau, a microtubule-associated protein present in neurons, serves 2 crucial functions: maintaining the shape of the cell and transporting metabolic substances throughout the neuron. Tauopathies include conditions like dementia with Pick bodies, corticobasal degeneration, progressive supranuclear palsy, and argyrophilic grain disease.[3] Other individuals with FTLD are said to have a tau-negative disease at autopsy. The most common histopathology seen in these patients is frontotemporal lobar degeneration with ubiquitin-positive immunoreactive inclusions (FTLD-U).[4] Until recently, the ubiquinated protein was unknown. TDP-43 is now known as the signature pathology in FTLD-U,[5] as well as amyotrophic lateral sclerosis and FTLD accompanied by amyotrophic lateral sclerosis. Other causes of FTLD that are tau-negative include dementia lacking distinctive histopathology and neuronal intermediate filament inclusion disease.

Approximately 60% of FTLD cases are sporadic, where there are no other family members with an FTLD spectrum disorder, and relatives do not appear to have an increased risk of developing the disease. However, the remaining 40% of patients appear to have some family history of dementia or neurodegenerative disease,[6] and up to 30% of FTLD is inherited in an autosomal dominant pattern. In a small percentage of cases, FTLD is due definitively to an identifiable mutation.[7] Mutations in the tau gene (*MAPT*) account for 7% to 50% of FTLD cases with an autosomal dominant pattern of inheritance.[8-14] Goldman and colleagues explain that the large variation in occurrence of genetic profiles of FTLD patients with tau mutations is because of differing criteria among

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centers for a positive family history.[7] Recently, mutations in familial FTLD have been discovered in a gene that codes for progranulin (PGRN). This too is located on chromosome 17, the same chromosome as the tau mutation,[15] although there is no known relationship between these 2 genes on chromosome 17. Mutations in the PGRN gene are associated with FTLD-U pathology.[16]

Clinically, FTLD presents with a number of distinctive phenotypes that may be linked to the specific frontal and temporal distributions of disease caused by tau-positive and tau-negative disorders.[17,18] Neary and colleagues published clinical criteria that delineate 3 FTLD syndromes.[19] Patients with damage to ventral and inferolateral temporal lobe structures experience profound deficits in word comprehension and object knowledge. These patients are said to have semantic dementia. In contrast, patients with significant disease burden in left frontal lobe structures experience progressively effortful speech. This is accompanied by a disorder of motor speech that includes articulatory approximations and groping as well as grammatical comprehension difficulty. These patients have a syndrome known as progressive nonfluent aphasia. Patients with damage to the right frontal and temporal lobes, by comparison, show behavioral disinhibition and other changes in personality and social comportment. This includes a disorder of social conduct involving loss of insight, decline in personal hygiene, mental rigidity, distractibility, hyperorality, and perseveration.

This great diversity in phenotype makes FTLD difficult to diagnose. Recent clinical-pathological studies suggest that diagnostic inaccuracy in experienced clinicians ranges from 15% to about 33%.[20-22] Furthermore, there is no single in vivo diagnostic test with sufficient specificity to discriminate FTLD from other forms of dementia, although advances are being made in terms of antemortem diagnosis.[23] This diagnostic issue is complicated by the fact that there are also clinical features that overlap with those of more common conditions such as AD, small-vessel ischemic disease, and Parkinson's disease.[24,25] In this article, we briefly review FTLD from a clinical perspective and discuss treatment options that are currently available.

Diagnosis

The diagnosis of FTLD requires great attention by the physician because of the neurologic and psychiatric features that are shared with other disorders that can mimic FTLD. For example, serum studies like B12 level, sedimentation rate, and thyroid function are important to obtain to reduce the likelihood of a metabolic cause. A magnetic resonance imaging (MRI) scan will help rule out structural disease that can masquerade as FTLD such as normal pressure hydrocephalus and small vessel ischemic disease. A lumbar puncture is useful to eliminate conditions such as lymphomatous meningitis and other nonbacterial meningitides.

A major obstacle in an accurate diagnosis is distinguishing FTLD from more common neurodegenerative conditions such as AD. A variety of biomarkers are beginning to demonstrate some utility in increasing the reliability of the diagnosis of FTLD.[23] A detailed cognitive and behavioral assessment is an essential element of the neurological exam.[1] Neuropsychological assessments are generally quite good at identifying specific patterns of impairment in these patients, but these lengthy evaluations are not very practical. Nevertheless, several studies appear to show specific patterns of neuropsychological impairment in patients with autopsy-proven FTLD.[26,27] Brief screening instruments like the Mini-Mental State Examination[28] do not appear to be sensitive for capturing patients with FTLD, and these patients often have a normal Mini-Mental State Examination when they first present.[29,30] However, several brief instruments have been developed recently that attempt to capture disease severity in non-Alzheimer's forms of dementia such as FTLD.[31,32] For example, the Philadelphia Brief Assessment of Cognition is a brief instrument that measures 5 domains of cognition: executive, language, visuospatial, social, and memory functioning. In recent analyses from our lab, the Philadelphia Brief Assessment of Cognition was useful for distinguishing patients with FTLD from AD and other neurodegenerative conditions such as corticobasal syndrome (Libon et al., unpublished data, 2007).

Abnormalities on imaging studies can contribute to the diagnosis of FTLD.[33] Each clinical syndrome of FTLD appears to manifest a relatively distinct MRI pattern. The behavioral or social form is associated with atrophy that is most evident in right frontal and temporal regions, including medial orbital frontal cortex.[34] In contrast, patients with language disorders tend to have more prominent left hemisphere disease. Atrophy associated with progressive nonfluent aphasia is found in brain regions supporting speech production such as inferior frontal gyrus, insula, and superior

temporal gyrus of the left hemisphere.[35] Ventral and lateral atrophies of the anterior temporal lobe are frequently described in semantic dementia.[36] Functional neuroimaging with positron emission tomography or single photon emission computed tomography can be useful if the MRI is within normal limits or the atrophy is too subtle.[37] Perhaps the most sensitive imaging studies are longitudinal, in large part because of the increased variance in normal MRI volume and normal glucose metabolism found in healthy aging. A longitudinal positron emission tomography study of 22 patients with a clinical diagnosis of frontal variant FTD showed a significantly lower glucose metabolism in the frontal cortical areas than healthy controls at baseline, for example.[38] Follow-up visits conducted 19.5 (±7.5) months later showed significantly lower glucose metabolism in frontal, inferior and middle temporal, and inferior parietal cortical areas as well as the caudate nuclei, insula, and thalamus. Similar findings have been reported in a longitudinal MRI study using a fully automated registration and high-dimensional normalization procedure.[39]

Other biomarkers also may be useful in diagnosing FTLD. In one large series, cerebrospinal fluid tau was found to be significantly low in 34% of individual FTLD patients, an effect that was never seen in AD cases.[40] A follow-up study confirmed that cerebrospinal fluid total tau and the ratio of tau/β-amyloid are significantly lower in autopsy-confirmed FTLD than in AD (H. Bian et al., unpublished data, 2007).

Treatment

Medication Treatments

The current goal of therapy for FTLD is symptomatic management. Unfortunately, there is no etiologically based curative treatment available at present that will change the natural history of FTLD, although several labs are actively pursuing the development of medications targeted at the abnormally accumulating proteins responsible for the condition. Some medications may be helpful in managing the clinical manifestations of FTLD, and behavioral treatments may also contribute substantially to patient care.

Social abnormalities are very common in FTLD. Depression, anxiety, and obsessive behavior are observed frequently. These symptoms are associated with decreased 5-H1AA receptor activity.[41] There have been a small number of double-blind, randomized, placebo-controlled trials of serotonin-supplementing agents for treatment of FTLD. One trial suggested that patients who receive the serotonin-specific reuptake inhibitor paroxetine at a dosage of 20 mg/day show improvement in behavioral symptoms after 14 months of drug therapy.[42] However, another trial of paroxetine failed to show any efficacy.[43] A small double-blinded, placebo-controlled study using trazodone up to 300 mg/day demonstrated an improvement in behavioral symptoms.[44] None of these trials showed an improvement in cognition.

Agitation and psychosis are most often treated with neuroleptic drugs. There have been no studies to date that evaluate the effectiveness of antipsychotics in FTLD. Traditional neuroleptic agents—particularly high-potency medications—are frequently avoided in FTLD because of the associated extrapyramidal side effects. Low-potency neuroleptics, on the other hand, have significant soporific side effects that limit their usefulness. In a large multisite, double-blind, placebo-controlled trial with AD patients, atypical antipsychotic drugs were efficacious, and their advantages offset adverse effects in the treatment of psychosis, agitation, and aggression.[45] However, other less well-controlled studies failed to show any benefit from this class of medication.[46] Clinicians and family members must consider preexisting medical conditions and known side effect profiles before beginning a regimen of medication.

Anticonvulsant therapy may be used alone or in conjunction with antipsychotics to treat aggressive behavior. Medications such as valproic acid have been shown to have efficacy in treating behavioral disturbance in various dementia populations (only in uncontrolled studies),[47] although this medication can be associated with weight gain and confusion. Carbamazepine is another useful anticonvulsant, but gait disturbance is a worrisome dose-dependent adverse reaction in an already vulnerable population.

Cholinesterase inhibitors have been approved by the Food and Drug Administration to treat mild to moderate AD in the hope of delaying cognitive decline. Medications in this class such as donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne) are widely used in the treatment of AD. In the AD population, this class of medications has been shown to be efficacious in slowing the decline in cognition and behavior.[48] There have been a few small studies that examine the usefulness of these drugs in FTLD patients. Some authors note that patients will experience a worsening of symptoms.[49]

Others report that patients improve their scores on behavioral rating scales.[50] Neither study found improvement in cognitive performance.

Other medications may be useful in the management of specific symptoms. For example, medroxyprogesterone may help calm sexual urges.[51] Dopaminergic supplementing agents may help treat some forms of involuntary movement that can occur in FTLD. Small doses of methylphenidate may contribute to the management of an amotivational syndrome.[52]

Nonpharmacologic Management

Nonpharmacologic treatments, such as behavioral or environmental interventions, play a crucial role in the management of FTD.[53] Strategies reviewed below should be discussed with caregivers throughout the course of the illness.

Behavioral symptoms can be quite distressing for loved ones and caregivers of patients. Environmental strategies can help limit unwanted behaviors. For example, avoid situations that provoke the unwanted behavior. If crowded places or large family gatherings provoke confusion and agitation, expose the patient to social interactions only in a calmer and more controlled situation where there are small numbers of visitors. It is also useful to structure the environment to limit the burden of decision making and minimize the confusion associated with multiple choices. This can involve development of a structured curriculum of planned activities every hour throughout the day. A daily schedule will keep the patient occupied and control the sleep-wake cycle so that the patient is not awake and agitated in the evening but sleeping during the day. Control access to foods containing large amount of sugar, particularly in patients who are hyperoral.

Impairment in executive function can also be problematic in patients. Limitations in planning and organization often lead to significant frustration for both patients and caregivers. Likewise, apathy can be a substantial impediment to health and quality of life. Decreased attention and disinhibition can emerge as perseveration, ritualistic behavior, or echolalia.[24] Encourage activities while providing a plan for executing the activities. Multistep activities that involve complex contingencies should be divided into simple steps. Make a list and cross each step off as it is performed. Provide guidance and redirection to facilitate the performance of activities. Limiting options is not a restriction of freedom but instead allows individuals to perceive clear choices and optimize the selection of the most desirable choice.

A variety of strategies can be implemented to optimize communicative efficacy. Strategies that promote language comprehension include speaking in context, speaking at a slower pace, using grammatically simple sentences, speaking redundantly by using different words to articulate the same message, and using gestures. Computerized assistive devices and personalized picture vocabulary cards are also helpful when expression is a problem.

Management of physical features of visuospatial functioning is important, particularly in patients with corticobasal degeneration. Limb apraxia is common and can produce awkward, clumsy movement even with simple tasks.[54] Occupational therapy can play an important role in identifying orthotic devices and adaptive clothing to assist with activities of daily living such as dressing and using implements for eating. Bright-colored tape can be used to mark spatial problem areas such as stairs and ovens. Remove throw rugs and toys from walkways to reduce the risk of falls. Physical therapy and passive range of motion exercises are useful to maintain joint mobility in the face of a limited range of motion and minimize pain because of contractures.

Aspiration pneumonia is a major source of morbidity and mortality. This may be related to difficulty coordinating swallowing, a reduced gag reflex, or inattention while eating. A swallowing study can help confirm swallowing difficulty. Recommended procedures include modifying the diet to include mechanically ground solid foods (eg, porridge consistency) or soft foods like scrambled eggs, and thickened liquids that are of nectar consistency. Eating should occur slowly to control shoveling food into the mouth, possibly by providing multiple small portions one at a time. Patients should not be distracted while eating. Surgical procedures that facilitate tube feeding without swallowing are often ineffective because oral secretions continue to be produced and remain a challenge.[55]

Another source of morbidity and mortality is related to reduced mobility. In some patients, gait may be unstable. Physical therapy can be useful in providing a regimen of lower extremity exercises and identifying devices that can assist gait stability such as a multipronged cane or a walker. In other patients who are apathetic, there may be limited postural adjustment. The minimal spontaneous movement can be a risk for the development of pressure sores

or decubitus ulcers. Patients should be repositioned frequently during the day and should be turned in bed in the middle of the night if they cannot roll over independently themselves. Specialty beds and mattresses are also available to reduce pressure, but a regimen of turning is still indicated.[56]

As patients become increasingly dependent on others for activities of daily living such as bathing and toileting, the risk of infection increases in the urinary tract and in sacral pressure sores. A regular regimen of bathing should be instituted, and careful skin care is essential following bathing as well as toileting.

FTLD is a challenging disease. Clearly a great deal remains to be learned. Although recent advances help improve diagnostic accuracy, FTLD is often confused with other neurodegenerative conditions. Medical management is currently aimed at symptomatic treatment and involves mostly medications borrowed from other conditions. As we come to understand more about the underlying pathology from autopsy studies, curative treatments will increasingly become the focus of further research. The combination of a judicious medication regimen, together with effective management of the environment, will optimize the patient's quality of life and minimize the risk factors associated with morbidity and mortality.

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