
Practical Issues With Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration is a group of neurodegenerative disorders whose clinical presentations and neuropathologic features are heterogeneous. There are three subtypes of frontotemporal lobar degeneration, namely: frontotemporal dementia, progressive non-fluent aphasia (primary progressive aphasia) and semantic dementia. Some have suggested that these subtypes may be distinct entities. Several genetic mutations, particularly on chromosome 17 in the tau gene, have been associated with this disorder.

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Frontotemporal lobar degeneration is a group of disorders where patients display behavioral changes and/or language function. Arnold Pick provided the first description of a patient who had language impairment. On macroscopic examination of the brain, there was atrophy of the frontal and temporal lobes.¹ Upon microscopic examination, some neurons had intracytoplasmic inclusion bodies, that were named “Pick bodies,” and ballooned neurons that were named “Pick cells.”^{2,3} Onari and Spatz called this condition “Pick’s disease” (“Picksche Krankheit”).⁴ This entity was thought to be rare. However, the Manchester-Lund Group provided a clinical and pathological description of a group of neurodegenerative disorders they called “frontotemporal dementia.”⁵ They suggested that

this disorder was relatively common, particularly in patients younger than 65 years of age. Neary et al, provided consensus criteria for frontotemporal lobar degeneration.⁶ They proposed three subtypes, namely: frontotemporal dementia, progressive non-fluent aphasia and semantic dementia. They suggested that frontotemporal dementia was clinically characterized by behavioral change. Progressive non-fluent aphasia was previously described under the name “primary progressive aphasia.”⁷ Semantic dementia was previously described as a disorder characterized by the loss of semantic knowledge.⁸ However, the nosology, clinical criteria and neuropathologic criteria need further refinement. For example, it has been suggested that all these disorders, including frontotemporal

dementia, progressive non-fluent aphasia, semantic dementia, corticobasal degeneration and other diseases have overlapping clinical, neuropathological and genetic aspects, and hence they should fall under the rubric of “Pick Complex”.^{9,10} Furthermore, it has been suggested that the use of the term “frontotemporal dementia” as a common designation for frontal lobe dementia and primary progressive aphasia may be too inclusive and should be separated because of the presence of distinct signs and symptoms.¹¹ Nonetheless, current consensus criteria provide a reasonable framework for assessment and management of these patients.

Characteristics of Frontotemporal Lobar Degeneration as a Group

It has been suggested that about 25% of individuals with dementia under age 65 years have frontotemporal lobar degeneration.¹² It affects men and women about equally, and the mean duration of the illness is about eight years. It is estimated that up to half of these cases have a first degree relative with this disorder.¹³

Characteristics of Frontotemporal Dementia

Patients with frontotemporal dementia can be categorized into three subgroups. Patients in the first subgroup predominantly

exhibit disinhibition, inattention and overactivity. Those in the second subgroup predominantly display apathy and social withdrawal. Patients in the third subgroup show ritualistic, stereotyped behavior. In addition to this, some patients may have a change in dietary habits. For example, they may show hyperorality and preference for certain foods, such as sweets. They may also exhibit a

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decline in personal hygiene, restlessness, impulsivity, irritability, aggression, hypersexuality and sexual disinhibition. A small percentage of these patients also has motor neuron disease.

From a neuroimaging perspective, there may be atrophy of the frontal and/or temporal lobe on MRI scanning. It is reported that Single Photon Emission Computed Tomography (SPECT) scanning may show hypoperfusion in the frontal and/or temporal regions.¹⁴

Neuropathologically, those with disinhibited, impulsive, antisocial behavior and stereotypical features usually have involvement of the orbitofrontal cortex. Those with deficits in planning and organization primarily have involvement of the dorsolateral prefrontal cortex, and those with apathy have

involvement of the medial frontal and anterior cingulate gyrus.¹⁵

Characteristics of Non-fluent Progressive Aphasia (Primary Progressive Aphasia)

Although progressive aphasia was described approximately 100 years ago,^{16,17} Mesulam described this disorder in more detail under the name of “primary progressive aphasia” and

provided further diagnostic criteria.^{7,11,18} For the first two years, these patients display insidious onset and gradual progression of fluent or non-fluent speech, anomia, agrammatism, phonemic paraphasic errors and they may have some comprehension deficit. They have difficulty with repetition, reading and/or writing over the course of the disease. They do not have significant apathy or disinhibition. They have preserved recent memory and visuospatial function. They may, however, have acalculia, ideomotor apraxia and perseveration. After two years, all cognitive domains can be affected, but language remains prominent and deteriorates faster. Most of these patients have focal involvement of the left frontal lobe.

The most common neuropathologic features of this disorder are neuronal loss, gliosis, and spongiosis of the superficial layers of the cortex, although Pick bodies and

memory. In addition to this, these patients may exhibit difficulty recognizing faces (prosopagnosia) and/or associative agnosia, whereby they have

protein gene, located on chromosome 17, have been described.²² The tau protein is found in the normal brain and is thought to be important in the maintenance of neuronal cytoskeleton and axonal transport. In families with a tau mutation, the phenotypic expression of the disease has varied among family members. For example, different family members may exhibit psychiatric disorders, behavioral disturbances (such as social withdrawal, alcoholism, hyperreligiosity and hypersexuality), dementia, parkinsonism and amyotrophy.^{23,24} In addition, some members may have predominant language disturbance, while others may have parkinsonism.²⁵

The most common neuropathologic features of non-fluent progressive aphasia are neuronal loss, gliosis, and spongiosis of the superficial layers of the cortex, although Pick bodies and Pick cells have also been described in some cases.

Pick cells have also been described in some cases.¹⁹ In very few cases, pathology of Alzheimer's disease (AD) has been observed.²⁰

impairment in object recognition. In contrast to AD, patients with semantic dementia have preserved episodic memory. They are usually oriented and are able to relate to recent events, although they may have difficulty recalling more distant events.

Characteristics of Semantic Dementia

Semantic dementia was first described by Warrington.⁸ These patients lose the meaning of words. They have difficulty with naming and comprehension. In addition, they have problems with object recognition. They may have preserved repetition, particularly single words. They may also have preserved ability to read and to write to dictation. They may have idiosyncratic usage of words. There is an absence of phonemic paraphasic errors (e.g. "cope" for "coat") but these patients do exhibit semantic paraphasias (e.g. "pencil" for "pen"). They generally have insight into their difficulties. This disorder is thought to be due to a loss of semantic

From a neuroimaging perspective, there may be hypoperfusion in one or both temporal lobes on SPECT scanning.²¹ Temporal lobe atrophy is much more significant and there is usually an asymmetric involvement, with the left temporal lobe being more involved.

Genetic Aspects of Frontotemporal Lobar Degeneration

It has been reported that as much as 38% to 45% of all the frontotemporal lobar degeneration cases are hereditary,¹³ and that 80% to 90% of these cases can have an autosomal dominant pattern of inheritance. Mutations in the tau

Neuropathologic Aspects of Frontotemporal Lobar Degeneration

Neuropathologic changes are found predominantly in the frontal and temporal lobes, symmetrically or asymmetrically. There can be neuronal loss, gliosis and spongiosis in the superficial layers of the cerebral cortex.²⁶⁻²⁸ In those with Pick's disease, there are ballooned neurons (Pick cells) and intraneuronal argyrophilic ubiquitin-positive and tau-positive neuronal inclusion bodies (Pick bodies). From a neurochemical perspective, the involvement of both serotonergic and catecholergic systems have been observed.²⁹

Pharmacologic Treatment of Frontotemporal Lobar Degeneration

Serotonergic systems are involved in some behavioral syndromes, such as apathy, depression and impulsivity. As a consequence, drugs such as fluvoxamine, fluoxetine, paroxetine and sertraline, that enhance the serotonergic tone, have been used. These drugs have exhibited variable effects on these symptoms.³⁰⁻³² Low dopaminergic tone has been suggested. Consequently, bromocriptine, a D-1 and D-2 dopaminergic agonist, has been tried. However, the role of selective serotonin reuptake inhibitors (SSRIs) and dopaminergic agonists need to be examined further.

Because of cholinergic deficit in AD, cholinesterase inhibitors are currently used to treat the symptoms of this disease.³³ Although deficits in cholinergic markers have been observed in frontotemporal lobar degeneration,³⁴ there is no evidence that cholinesterase inhibitors are beneficial in the treatment of this disorder.

Nonpharmacologic Management of Frontotemporal Lobar Degeneration

Since behavioral disturbances in these dementias include environment exploratory behavior,

disinhibition, aggression, hyperorality, loss of personal hygiene, and poor judgement, management of these patients includes behavioral strategies directed at educating the caregivers to adopt strategies that can help deal with these behavioral symptoms. An essential component of planning behavioral management is to ask caregivers to keep a log of behavioral disturbance, including the type of

disturbance, the severity and the possible circumstances that might have triggered the problem. This allows individualized interventions and the setting of realistic goals, which can be key to effective non-pharmacological management.^{35,36} These targeted strategies may include provisions of structured environments or removal of environmental cues that could potentially trigger behavioral disturbance. Furthermore, safety issues must be addressed. This may include cessation of driving and making important financial decisions, each of which can put a great burden on caregivers. In this regard, caregiver education and support groups are vitally important. Management of these patients, like other chronic illnesses, is best provided by a

multidisciplinary approach. This includes physicians, nurses, occupational therapists, physiotherapists, social workers, speech-language pathologists and other allied health professionals.

Conclusion

Frontotemporal lobar degeneration refers to a heterogeneous group of disorders in which there is a range of impairments, from a

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dysexecutive syndrome to impairment of semantic knowledge to language disturbance. The clinical impairments and neuropathological manifestations of frontotemporal lobar degeneration can overlap with many other disorders, such as motor neuron disease. Genetic factors, such as mutations in the tau gene on chromosome 17, appear to show some biologic basis for these disorders. There is, however, difficulty in attributing a mutation in one gene to the varied clinical manifestations seen in these disorders. Careful clinical, neuropathological and genetic profiles need to be undertaken to further refine our understanding of this disorder and to provide satisfactory diagnostic criteria to improve management thereof.

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