Pick Disease: Navigating the Frontotemporal Dementia Diagnosis

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The clinical diagnosis of Pick disease can be one of the most difficult facing the neurologist. Those patients found to have lobar atrophy usually present clinically with bouts of irrational behavior, bulimia, marked reductions in speech, abulia, and apathy.

In contrast with Alzheimer disease (AD), Pick disease generally is not associated with symptoms of memory loss or disorientation in regard to time and space. Aphasia is a prominent feature. Psychiatric features that often accompany Pick disease but are not seen in AD include obsessive-compulsive disorder, delusions, and paranoia. Common noncognitive features of AD, such as blindness, sensory loss, and weakness, are not usually encountered in Pick disease.\(^1\)

**DIFFERENTIAL DIAGNOSIS**

Pick disease is characterized by frontotemporal lobar degeneration (FTLD). It can take on a variety of clinical presentations that make a differential diagnosis difficult. With the advent of specialized immunohistochemical staining techniques and insights gleaned from molecular genetics, researchers have found that FTLD is closely related to and often overlaps with other neurodegenerative disorders, such as motor neuron disease, progressive supranuclear palsy, and corticobasal ganglionic degeneration.

Because the pathogenesis of FTLD has been associated with the tau protein—which plays a central role in microtubule-associated neuronal destruction—FTLD has become classified as a tauopathy.\(^2\) Tau proteins have been associated with the formation of intraneuronal, neurofibrillary, filamentous lesions that are found in a number of neurological diseases.\(^3\)

"If you consider Pick disease as a postmortem neuronal pathology demonstrating cytoplasmic inclusion bodies [ie, Pick bodies], that's one thing," commented Howard Crystal, MD, professor of neurology and pathology at the State University of New York Downstate Medical College in Brooklyn. "For the clinician, the question arises about whether patients presenting with progressive frontal lobe dysfunction with anterior temporal lobe dysfunction have FTLD or whether they are just presenting with a kind of primary aphasia."

**BASIC PATHOLOGY**

The postmortem appearance of the brain of patients with classic FTLD is unique. Notable is its highly demarcated reduction in cortical mass, which is often so severe that it has been given the name "knife-blade" atrophy. This remarkable atrophy, generally confined to the frontal and temporal lobes, has led to the widespread use of the alternative term, "frontotemporal lobe atrophy," as another name for Pick disease.

When compared with the conspicuous general atrophy noticed in the brains of patients with AD, most cases of Pick disease demonstrate a marked sparing of the parietal lobe, the occipital lobe, the temporal gyrus, and the posterior two thirds of the superior temporal gyrus. However, there are cases in which the characteristics of both AD and Pick disease are present in the same brain.\(^4\)

**TAU PROTEIN AND GENES**

Tau proteins have been studied extensively. Advanced techniques in molecular biology have produced a more complete understanding of their involvement in the pathogenesis and histopathology of FTLD.\(^5,6\) The tau protein is located on chromosome 17q21, and mutations in this tau gene cause frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). An autosomal dominant inherited syndrome that expresses the clinical features of FTLD develops in patients carrying the mutated tau gene. Mutations of the tau gene responsible for the clinical syndrome of Pick disease are clustered around exon 10.\(^7\)
"Two genes have been associated with frontotemporal dementia. The most important one is the tau protein gene. Some families express this gene in the form of parkinsonian features accompanied by some eye-movement problems in progressive dementia," Crystal explained. "The other gene that was identified about a year ago is called progranulin. It would appear that the genome mapping is irregular, so that the clinical phenotype is not consistent." He added that some forms of Pick disease are probably autosomal dominant.

**CLINICAL PRESENTATION**

FTLD can present as 3 types of syndromes. All are characterized by progressive aphasia. The most common syndrome is primary progressive aphasia. The patient's speech becomes progressively nonfluent, but the patient's comprehension skills are intact. "The family will often say, 'He's fine, but he just can't seem to get his words out,'" Crystal noted. Dementia eventually develops in many of these patients but it can take 5 or 10 years before it does.

In the case of the nonaphasic but demented patient, the typical scenario in the clinical setting would be for a wife to say that she suspects that her husband has AD, Crystal explained. "She might say: 'He can't do anything. His personality has changed. He just sits there. He doesn't remember what I tell him to do,'" Crystal noted.

In taking the medical history, the neurologist must decipher whether the described problem is arising because the patient's frontal lobes are not working (ie, Pick disease) or his memory-encoding system is not working (ie, AD). "Statistically speaking, most patients will have AD, even those in their 50s to 60s." After testing, if you find that the patient's memory is actually pretty good or very good, then you have to conclude that you are not dealing with AD," he said.

"Testing frontal lobe function can be difficult at the bedside or in the office because there is no really perfect test for frontal lobe dysfunction," Crystal remarked. "I would say that the most important discerning factor is the relative preservation of recent memory and the relative exaggeration of personality changes, including apathy and the problems with executive function that characterize frontal dementia."

Imaging studies often help because they can at least identify or rule out AD, according to Crystal. Single photon emission CT and positron emission tomography scans will show a temporal-parietal decrease in glucose utilization in the patient with AD. A pattern of frontal lobe decrease in glucose consumption will be seen in frontal lobe disorders, Crystal said.

"A less common form of frontotemporal atrophy is semantic dementia," he continued. "The damage tends to occur somewhere around the Broca area in the inferior frontal region of the brain." Semantic aphasia tends to occur more posteriorly in the superior temporal lobe region, Crystal explained. Affected patients tend to lose their ability to name objects or recall the appropriate words for things. "For example, if you show them a picture of a helicopter, they may not be able to name what it is. If you ask them to name a kind of airplane that has a rotor on top and flies straight up and down, the patients will not be able to name the vehicle. If you ask them what the President uses to get from the White House to Camp David, they have no idea because their entire notion of helicopters is gone," Crystal said.

The third but fairly uncommon type of frontal dementia named by Crystal is corticobasal degeneration. It is often characterized by problems with language and executive function. Motor problems often develop as well and may even progress to motor neuron disease likened to amyotrophic lateral sclerosis. Indeed, supranuclear palsy develops in some patients, he noted.

"What we see here is a hodge-podge of diseases both with different syndromic qualities and different pathologies. One might ask whether there is a unifying or underlying pathology that holds them all together. I would have to say no. Some patients have abnormalities in tau protein, others may have abnormalities in progranulin," Crystal said. Indeed, the presence of Pick bodies is not a prerequisite for a diagnosis of Pick disease.

"The majority of postmortem brains do not show the presence of Pick bodies. Diagnostic terminology used about 15 years ago to describe this situation was 'dementia lacking distinctive histology.' Microscopically, no Pick bodies nor classic Alzheimer lesions were seen; however, conspicuous cell loss and marked gliosis was present," Crystal explained, noting that this feature clearly revealed why the person experienced dementia.

**TREATMENT APPROACHES**

There are currently no successful treatments that significantly alter the progression of FLTD. A few behavioral interventions and medications have been used to treat specific neuropsychiatric phenomena, but none have emerged as being particularly beneficial.

Similarly, acetylcholinesterase inhibitors that were developed to treat AD have provided no benefit for patients with Pick FLTD. Certain behaviors specific to FLTD, such as communication difficulties
associated with aphasia, poor insight, lack of empathy, and impaired executive functions, can become a highly stressful constellation of factors for caregivers of those with FTLD. Caregiver stress is often manifested in the earlier placement of patients with FLTD in long-term-care nursing facilities.  

"As far as I know, there are no successful interventions in the treatment of frontotemporal dementia." Crystal remarked. Research into tauopathies may provide some momentum for drug development, he added.

References: REFERENCES

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