Autopsy-Proven, Sporadic Pick Disease With Onset at Age 25 Years

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Context: Pick disease is uncommon and accounts for less than 2% of adult-onset dementias. Reports of Pick disease in young adults have apparently increased in the last decade.

Objective: To document the presentation and course of a patient with tau-positive Pick disease presenting at an extremely young age.

Setting: A university hospital.

Patient: A white woman with cognitive impairment that began at age 25 years. She experienced progressive dementia over an 8-year period with radiographic evidence of severe cerebral atrophy of the frontotemporal lobes. Autopsy findings confirmed the diagnosis of Pick disease characterized by tau-positive Pick bodies in the neurons of the fascia dentata.

Conclusion: Pick disease should be considered in the differential diagnosis of young adults presenting with behavioral symptoms, especially those of frontal impairment.

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A white woman had normal development and was known as a high achiever in high school and college. The member of a large family, there was no family history of dementia or other neurological disorders. She began to develop memory problems at the age of 25. Initially, she was unable to recall the details necessary to function at work. Her job required attention to fine detail and strong interpersonal skills. Over the next 2 years, stark personality changes and behavioral problems were noted. She began smoking and drinking heavily and neglected normal daily activities such as bathing and eating. She was unable to remember the date without a watch. A computed tomographic scan of the brain at age 27 showed no abnormalities. Results of a visit to a physician showed vitamin B12 deficiency. She was appropriately treated with no improvement in mental function. She lost her job at age 28 because of progressive memory problems and lack of trustworthiness.

A psychological evaluation at age 29, because of continued alcohol abuse, demonstrated severe memory impairment and behavioral disinhibition that interfered sig-
ificantly with her ability to function independently. On a Wechsler Adult Intelligence Scale–Revised, her verbal IQ score was 87; the performance IQ, 82; and the full-scale IQ, 83. She was unable to learn new information despite repeated trials. Although it was felt that these symptoms could be due to Korsakoff syndrome or alcoholic dementia, the rapidity of onset, along with the disinhibition, perseveration, loose associations, and flight of ideas suggested possible frontal lobe involvement.

Multiple laboratory tests were done at this time to look for possible viral diseases, toxins, or clotting abnormalities. Findings from tests for herpes simplex viruses 1 and 2, measles, cytomegalovirus, varicella-zoster virus, and Epstein-Barr virus were negative, and the examination of the cerebral spinal fluid gave normal results. The VDRL test findings were negative. Test results for anti-cardiolipin antibodies and an anti-nuclear antibody were negative. The levels of folate, vitamin B12, thyroxine, and triiodothyronine were normal. Toxicology screening was positive for ethanol at 103.2 mg/dL, but it was negative for benzodiazepines, opiates, salicylates, acetaminophen, tricyclic antidepressants, stimulant amines, cocaine, and barbiturates.

Three months after this evaluation, she began wandering off and was admitted to a hospital because of her progressive dementia and inability to take care of herself. A high-resolution magnetic resonance imaging (MRI) study showed significant volume loss involving the mesial temporal structures and frontal lobes bilaterally in a symmetric fashion. These included the hippocampal gyri bilaterally, the uncus, the anterior aspect of the temporal lobes, and the white matter (Figure 1 and Figure 2). There was some generalized cerebral and cerebellar atrophy.

Over the next 2 years, she continued to decline and would commonly pace while mumbling, repeating random numbers and her birthdate. She was under constant supervision. She was unable to dress herself or shower without being told each step. She refused to stop repeating numbers, and thus, had a difficult time eating. Another hospitalization at age 31 documented continued deterioration. She slept only 1 to 3 hours per night and would continually do repetitive tasks such as applying chapstick, blowing bubbles, or repeating numbers. At this time, findings from an electroencephalogram were within normal limits, while another MRI showed severe cerebral atrophy of the frontotemporal lobes. She died 1 year 9 months later.

**PATHOLOGICAL FINDINGS**

At postmortem examination the brain weighed 1170 g. There was marked atrophy of both frontal and temporal lobes with knifelike gyri. Coronal sections revealed severe cortical atrophy in the frontotemporal lobes (Figure 3). There was marked ex vacuo dilatation of the ventricles. The substantia nigra was pale. Histologically on hematoxylin-eosin–stained sections, the frontotemporal lobe cortices demonstrated severe loss of neurons with gliosis. Scattered ballooned Pick cells were found (Figure 4). Occasional Pick bodies were seen in the frontotemporal lobe sections. The hippocampi showed neuronal loss with numerous Pick bodies in the neurons of the fascia dentata (Figure 5). Numerous Pick bodies in the hippocampus demonstrated strongly positive expression when stained with antibodies to tau protein (monoclonal mouse anti–human paired helical filaments-tau, clone AT8 (Autogenbioclear, Calne, Wiltshire, United Kingdom) by immunohistochemistry (Figure 6). No senile plaques or neurofibrillary tangles were found. Both caudate nuclei demonstrated moderate neuronal loss with marked gliosis. The putamen and globus pallidus were mildly involved with neuronal loss and gliosis. The thalamus showed focal gliosis medially with mild neuronal loss. Severe neuronal loss and gliosis were present in the insular cortex. The substantia nigra showed severe loss of neurons with pigmented incontinence and gliosis in the pars compacta. There was gliosis around the aque-
duct of Sylvius. No Lewy bodies were found. Sections of the pons and the cerebellum were normal.

**COMMENT**

To our knowledge, this patient represents the youngest woman with sporadic Pick disease reported in the literature. Her diagnosis was confirmed by autopsy. Because of her young age, the diagnosis of Pick disease was not entertained until late in the disease course. By that time, many other possible causes had been ruled out and striking symmetrical atrophy of the frontotemporal lobes was obvious on MRI.

In general, the peak incidence of Pick disease is in the sixth decade of life, and unlike Alzheimer disease (AD), patients present before 65 years of age. This relationship was further supported by the European Concerted Action on Pick’s Disease Consortium’s data that showed in 50 cases of histologically confirmed Pick disease an earlier onset of disease than that found in AD. They also documented that Pick disease was relatively uncommon after 70 years of age.

There are 2 reports of familial Pick disease in which the patients, 2 brothers, were 21 and 25 years old when symptoms began. Several sporadic cases in younger individuals have been reported. Jacob et al described a woman who presented at age 27 and on biopsy had tau-positive inclusions. A 27-year-old man with biopsy-proven Pick disease was reported by Stewart et al. A third case reported by Mowadat et al described a 28-year-old woman with clinical and scanning evidence for Pick disease, but histological confirmation was not obtained. These 3 cases of sporadic Pick disease were all reported in the 1990s suggesting that Pick disease is being more frequently recognized in younger patients possibly because of better imaging techniques, lower risk of biopsy, and the ability to rule out other possible disorders.

Several studies have suggested features more commonly seen in young patients with Pick disease. These include a high incidence of familial occurrence, a short and progressive clinical course, severe basal ganglia disease, selective degeneration of the substantia nigra, and strong positive expression of tau protein in Pick bod-
ies. Our patient with sporadic Pick disease died 8 years following the onset of symptoms and had marked involvement of the caudate and substantia nigra with neuronal loss and gliosis. The putamen was also mildly involved. Diffuse Pick bodies revealed strong tau protein expression by immunohistochemistry.

Degenerative dementia with early onset is rare. It is possible that past cases have eluded detection or have been confused with psychiatric disorders or other organic disease processes. The differential diagnosis in a young patient presenting with dementia includes a long list of possible causes. This list includes not only the degenerative diseases but also metabolic imbalances, psychiatric illnesses, neoplasms, infections, posttraumatic sequelae, and vascular disease. The history and clinical workup will eliminate most of these causes and identify any treatable cause for the dementia.

After other diagnoses have been eliminated, Pick disease can often be suspected by lobar atrophy detected in radiographic studies. Importantly, Pick disease should be considered in the differential diagnosis of young adults presenting with behavioral symptoms, especially those of frontal impairment.

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REFERENCES