OBSERVATION

Adult-Onset Neurodegeneration With Brain Iron Accumulation and Cortical α-Synuclein and Tau Pathology

A Distinct Clinicopathological Entity

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Background: Neurodegeneration with brain iron accumulation is a rare neurodegenerative disorder characterized by iron deposition in the basal ganglia and neuronalaxonal dystrophy. Familial cases with mutations in the pantothenate kinase gene are associated with a specific phenotype. In contrast, sporadic cases are heterogeneous in their clinical presentation.

Objective: To describe an atypical case of sporadic late-onset neurodegeneration with brain iron accumulation.

Design, Setting, and Patient: Case report of a patient who presented with psychiatric features at age 22 years followed by progressive gait disturbance, extrapyramidal symptoms, epilepsy, and corticospinal tract involvement.

Results: Magnetic resonance imaging showed iron deposition in the globus pallidus and substantia nigra. Cortical biopsy revealed Lewy bodies with predominant α-synuclein and less extensive tau-positive neurites.

Conclusions: Our findings in association with previously reported cases suggest that cortical neuritic and Lewy body pathology is a feature of atypical neurodegeneration with brain iron accumulation, clinically characterized by adult onset and psychiatric symptoms. These observations raise the possibility that these cases of atypical neurodegeneration with brain iron accumulation represent a distinct clinicopathological syndrome and suggest a molecular link between iron deposition and α-synuclein accumulation.

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N eurodegeneration with brain iron accumulation (NBIA), previously known as Hallervorden-Spatz disease, is a rare autosomal recessive or sporadic neurodegenerative disorder. The diagnosis of NBIA is based on clinical criteria and has been classified by the onset of symptoms into the following: (1) early-onset childhood type (diagnosis earlier than age 10 years), which includes both rapidly and slowly progressive types; (2) late-onset slowly progressive type with presentation between ages 10 and 18 years; and (3) adult-onset slowly progressive type. Genetic studies have identified mutations in the pantothenate kinase 2 (PANK2) gene in familial cases of NBIA that have specific clinical features (termed pantothenate kinase–associated neurodegeneration). In contrast, sporadic cases of NBIA have a heterogeneous clinical presentation and therefore may represent a distinct syndrome.

REPORT OF A CASE

A 27-year-old woman had normal motor and intellectual development and no family history of neurological disease. At age 22 years, she developed mood changes such as indifference and loss of impetus. Two days after an emergency appendectomy that was uneventful, she became irritable and aggressive. This was associated with transient auditory hallucinations. She was initially treated with haloperidol but developed extrapyramidal adverse effects. Within 9 months, she became mute and required electroconvulsive therapy, which lifted her mood transiently. Her extrapyramidal syndrome also improved on switching to clozapine. However, by age 24 years, her gait became shuffling and she experienced falls. She became bradykinetic and developed micrographia. She began receiving levodopa but within 7 months developed drug-induced orofacial and limb dyskinesias, which responded to treatment. At age 26 years, she had a single generalized convolution. Anticonvulsive therapy was initiated and was effective. A progressive decline in her language ability had been noted since age 24 years, and at about the time of her seizure, she was unable to engage in conversation and could only say occasional words. She is currently dependent for most...
activities of daily living. General examination was unremarkable apart from hypomimia and emaciation. Higher mental functions were severely impaired on verbal and nonverbal tests of reasoning. She had weak visual perceptual and visuospatial skills, comprehension difficulties, dyscalculia, and impaired memory skills. Pursuit eye movements were jerky and vertical saccades were slow. There was marked dystonic posturing in both arms and legs. The reflexes were brisk and the plantar responses were spontaneously extensor. Biochemical and hematological test results were normal. There were no acanthocytes in her peripheral blood. Cerebrospinal fluid examination results were unremarkable. Genetic test results were negative for Huntington disease, spinocerebellar ataxia 1, 2, 3, 6, 7, 12, and 14, dentorubropallidolysian atrophy, and PANK2, DYT1, ferritin light-chain gene, and α-synuclein gene mutations. Electroencephalography showed normal activity. Magnetic resonance imaging of her brain at age 27 years showed severe cerebral atrophy with a frontotemporal predominance. The T2-weighted images demonstrated low signal intensity, indicative of abnormal iron deposition in the globus pallidus, cerebral peduncles, and substantia nigra, although no “eye of the tiger” sign was seen (Figure, A). A computed tomographic scan excluded basal ganglia calcification. Muscle biopsy showed mild nonspecific myopathic features, and results of a muscle mitochondrial assay for respiratory chain function were normal. Results of liver biopsy for copper deposition were negative. Frontal cortical biopsy was also performed.

Microscopical examination of the sections revealed gliosis affecting the cortex and white matter. Numerous cortical Lewy bodies (Figure, B), which were positive for α-synuclein (Figure, C), were seen. In addition, anti-α-synuclein staining revealed severe Lewy neurite pathology throughout the thickness of the cortex (Figure, C). Sparse α-synuclein neurites were also seen within the white matter. Immunohistochemistry for tau revealed neuritic pathology throughout the neocortex but sparing the white matter (Figure, D). Neurofibrillary tangles were not seen. The appearance of these neurites was similar to those stained with α-synuclein antibodies. Double immunofluorescence staining showed that the 2 proteins very rarely colocalized within the same aggregates (Figure, E). No β-amyloid–positive pathology was seen. No glial inclusions (eg, coiled bodies or tufted astrocytes) were identified, and there was no morphological evidence of neuronal or glial cell apoptosis. No axonal swellings were identified; however, deep gray structures were not available for examination.

**COMMENT**

It is now well recognized that the diagnosis of NBIA applies to a spectrum of disorders. Following the identification of PANK2 mutations in familial NBIA, it has been shown that patients with deletion mutations have classic disease and present before age 6 years, commonly with gait or postural difficulties, early extrapyramidal symptoms, and involvement of the corticospinal tracts, whereas those with sporadic disease or some with point mutations have atypical late presentation with more frequent corticospinal tract involvement and prominent psychiatric symp-

toms with cognitive decline. There is also a striking correlation between the presence of PANK2 mutations and the eye of the tiger sign. The findings described earlier are consistent with the observations in our patient, who
had adult-onset disease with psychiatric presentation, iron accumulation in the basal ganglia without the eye of the tiger sign, and no mutation in the PANK2 gene.

Although a distinct phenotypic classification seems to emerge based on genetic screening, the pathological substrate for the clinical heterogeneity in NBIA is poorly understood. Until recently, the most prominent microscopic finding alongside iron deposition, neuronal loss, gliosis, and loss of myelin was the presence of widely disseminated, rounded or oval structures termed spheroids identifiable as swollen axons. It has now become apparent that neuropathologically, NBIA belongs to the growing list of α-synucleinopathies based on the identification of α-synuclein-immunoreactive Lewy bodies and Lewy neurites in a number of published cases. It is therefore possible that in NBIA, axonal spheroids and dystrophic neurites represent a pathological spectrum signifying a degenerative process affecting the neuronal processes and α-synuclein deposition represents a marker of axonal or dendritic injury. In contrast to α-synuclein pathology, the presence of neurofibrillary tangles is not a prominent feature of this disorder. We identified only 6 reports of NBIA with coexistent α-synuclein and tau pathology. It is noteworthy that in all of the reported cases as in our patient, dual pathology was associated with prominent cognitive decline. Furthermore, NBIA cases with cortical Lewy bodies share clinical features with our patient, such as adult-onset and prominent psychiatric features (cognitive decline, mood changes, dysphoria, blunted affect, and auditory hallucinations), which are distinct from classical dementia with Lewy bodies (prominent visual hallucinations and fluctuating cognition and alertness). The pathological findings described earlier suggest that patients with atypical disease are more likely to develop widespread α-synuclein with or without tau pathology especially in cortical regions, which could explain the prominence of psychiatric symptoms in this group.

In this respect, adult onset and protracted course could represent the clinical corollary to a slow retrograde neurodegenerative process with the axonal terminals being the anatomical substrate of the primary insult. When iron accumulates in excess, as in NBIA, it generates reactive free radicals and damages lipid membranes. Oxidation of α-synuclein, a presynaptic protein that binds to lipid membranes, induces conformational changes and aggregation of the protein. It is therefore possible that cortical projections to areas where iron accumulates are damaged by oxidative stress, inducing aggregation of α-synuclein and neuritic pathology. With time, this may disrupt axonal transport leading to accumulation of α-synuclein and other proteins such as tau (an axonal protein involved in stabilization of microtubules) proximally, formation of perikaryal aggregates, and cellular demise. Our findings of α-synuclein and tau neuritic depositions with minimal colocalization may help to explain dual α-synuclein and tau pathology, which is increasingly being recognized in a number of other neurodegenerative diseases.

In summary, our findings in association with those of previously reported cases suggest that cortical involvement is a feature of atypical NBIA characterized clinically by psychiatric features and pathologically by extensive neuroaxonal dystrophy. These observations may help in understanding the neurodegenerative process and raise the possibility that atypical NBIA represents a distinct clinicopathological syndrome. Further pathological and molecular studies are necessary to characterize this syndrome, which in turn may help in understanding the pathogenesis of other α-synucleinopathies.

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