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Neuropathology Education

An 8-year-old boy with gait disturbance and the rapid increase of muscle tonus

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CLINICAL HISTORY

The patient is an 8-year-old boy with gait disturbance and rapid increase of muscle tonus. He was born uneventfully at 40 weeks gestation and weighed 3120 g. He was able to walk alone at the age of 18 months, but speech was delayed until 24 months. At 3 years, his speech became unclear and he began to fall frequently. At 6 years, he entered to an ordinary class at elementary school, and was able to run, walk down stairs using a handrail, as well as read, write and calculate normally. Walking disturbance with pes equinovarus and clumsy hands began at 7 years of age. By 8 years he was unable to walk and was referred to our hospital.

Neurological examination revealed a dystonic posture, athetotic movements, hyper-reflexia in the lower extremities and positive Babinski reflex. His speech was slurred and an articulation disturbance was noted. In addition, his swallowing was interrupted.

His clinical course worsened, with his dystonia, athetosis and opistotonic posture becoming aggravated at 3 months after admission to the hospital. He expired at the age of 8 years and 10 months because of choking on sputum.

Laboratory examination on admission revealed that complete blood count and blood chemistry were within normal ranges, including 52.3 mg/dL Fe, 108.2 mg/dL Cu, 38.2 mg/dL ceruloplasmin, 6.4 m/dL lactate and 0.27 mg/dL pyruvate. CSF showed no cell count, 12.7 mg/dL total protein and 59 m/dL sugar. Serum amino acid analysis, WBC and a lysosomal enzyme assay of eight enzymes were within normal ranges. Nerve conduction velocity and needle electromyograph were normal. Electroencephalography showed a dysrythmic awake pattern and no paroxysmal discharges. His intelligence quotient was 67 by the Tanaka Binet test. Fundoscopy showed a retinal pigment degeneration. CT scan revealed no abnormalities in the cerebral cortex and white matter, but symmetrical speckled high densities in the bilateral basal ganglia (Fig. 1). No MRI findings were available.

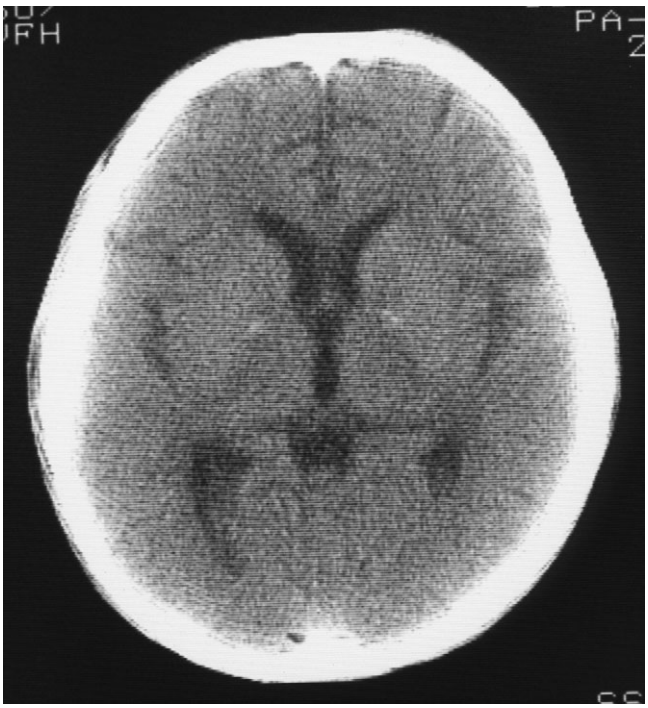

Fig. 1 CT scan of the patient at 8 years of age. CT scan shows symmetrical bilateral speckled high densities in the globus pallidus, although the cerebral cortex and white matter are normal.

NEUROPATHOLOGICAL FINDINGS

At autopsy, the brain weighed 1096 g, less than the expected weight of 1350 g. The brain was atrophic proportionally and each cerebral gyrus was preserved. On section, there was brown discoloration of the medial part of the internal segment of the globus pallidus (Fig. 2). The dark tone in the bilateral substantia nigra was normal.

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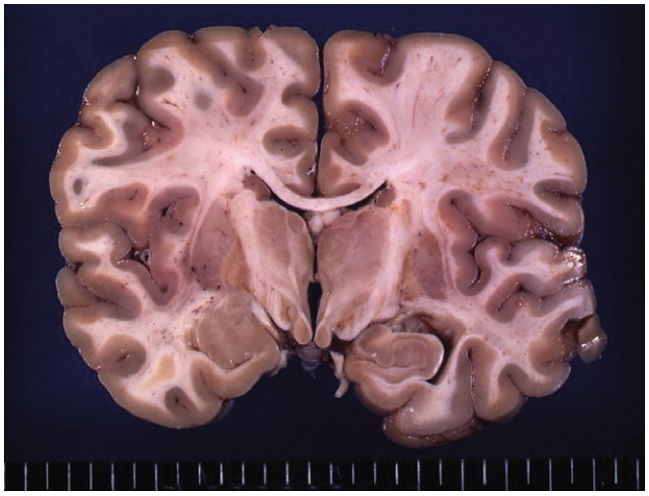

Fig. 2 Macroscopic findings of brain section. There is a brown discoloration of the internal segment of the globus pallidus (scale 5 mm).

Fig. 3 Macroscopic findings of basal ganglia by Berlin blue stain. Diffuse iron deposition is seen in the globus pallidus, and in part of the substantia nigra.

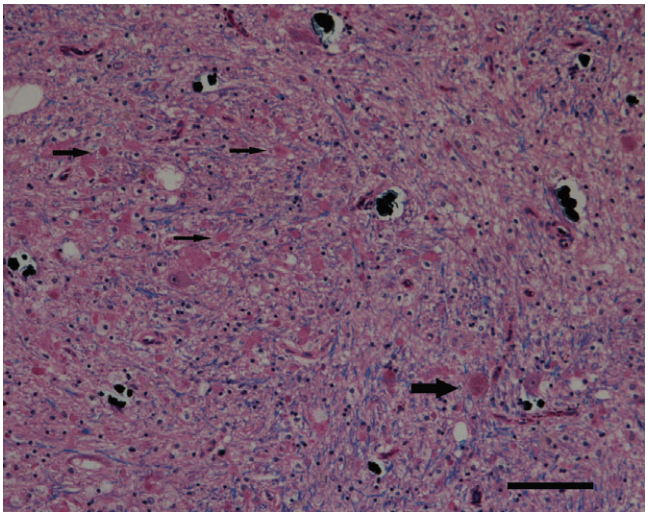

Fig. 4 Histologic findings of the globus pallidus by LFB–HE stain. Numerous round eosinophilic structures or "spheroid bodies" are seen in the globus pallidus (thin arrows). Large size eosinophilic granular bodies, called "foamy spheroid bodies", are observed (thick arrow). Many iron granules with variable size are black and are seen in the neuropil (bar = 100 μm).

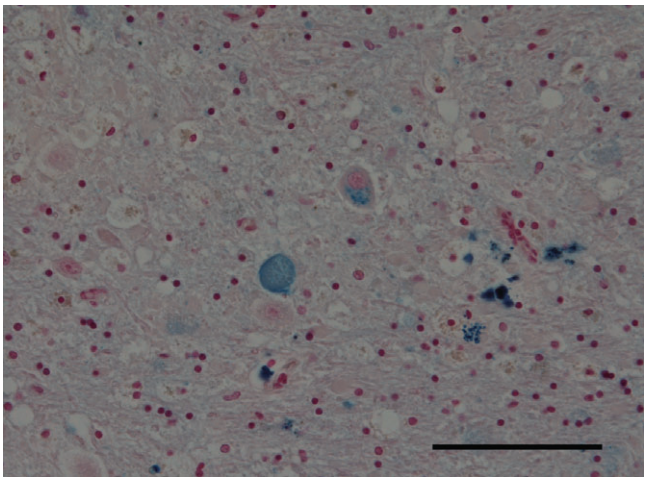

Fig. 5 Histologic findings of the globus pallidus by Berlin blue stain. Remarkable iron deposition is seen in the foamy spheroid and iron granules within the neuronal cell (bar = 100 μm).

Macroscopically, the globus pallidus and the part of the substantia nigra were stained diffusely by Berlin blue (Fig. 3). Microscopic examination revealed characteristic numerous small round eosinophilic structures called spheroid bodies, which were especially abundant between myelinated fibers in the globus pallidus (Fig. 4). Spheroid bodies were lightly positive by Bodian staining, so these were interpreted as axonal swellings. Mild neuronal cell loss and gliosis were observed, and there was rarefaction of the neuropil in the bilateral globus pallidus. Many variable-sized black–brown pigment granules were scattered in the

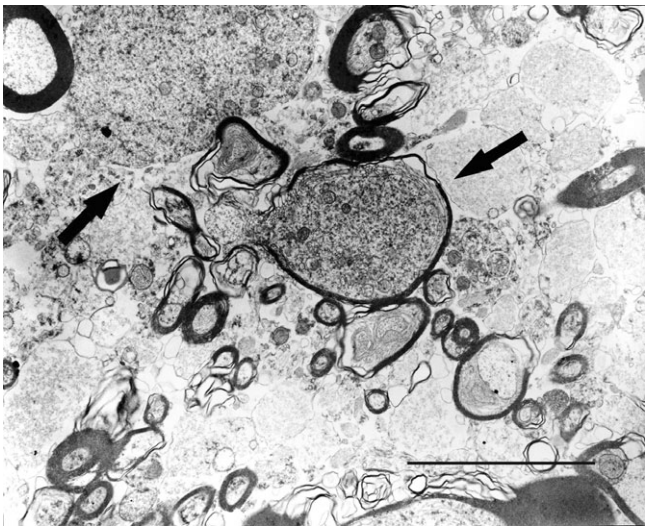

Fig. 6 Electron microscopic findings of the basal ganglia. The spheroid (arrows) is surrounded by myelin sheaths and contains a variety of materials such as mitochondria and dense bodies, but no specific abnormal structured materials (bar = 5 μm).

neuropil of this lesion. Some of these were positive with iron stain (Berlin blue stain). Also iron-positive granules were seen in the cytoplasm of some neuronal cells and glial cells. The large size eosinophilic granular bodies called "foamy spheroid bodies" that were also abundant in iron-positive pigments (Fig. 5) were observed in regions. A relatively small number of spheroids was found in the putamen, thalamus, caudate nuclei, hippocampus, frontal lobe and temporal lobe of the cerebrum. No spheroids were detected in the substantia nigra. Purkinje cells and granular cells in the cerebellum were well preserved. In an electron microscopic examination, spheroids were surrounded by myelin sheaths or some membranous layers and contained a variety of materials such as mitochondria and dense bodies (Fig. 6), but no specific structure, such as the tubulovesicular structures, which are usually seen in cases of infantile neuroaxonal dystrophy.

DIAGNOSIS

We diagnosed the patient initially as Hallervorden-Spatz syndrome (HSS), and more recently as panthothenate kinase-associated neurodegeneration (PKAN), which elucidates the biochemical mechanism.

DISCUSSION

This case was characterized clinically by the childhood onset of gate disturbance and dystonic posture, relentless progression of rapid increase of muscle tonus and a natural clinical course without any effective medication. Pathologically, the case was characterized by many spheroids and iron-containing pigments restricted to the globus pallidus. In general, the prominent pathological alterations were observed in both the globus pallidus and the substantia nigra in this syndrome. However, a previous report described an HSS patient who suffered from severe torsion dystonia from the age of 10, and the pathological findings were restricted to the pallidal nuclei.[1] Therefore, the pathologic alteration may relate to the onset of the disorder and neurological development.

Dooling *et al*. summarized 64 cases of clinicopathological descriptions of HSS from the literature.[2] The characteristic clinical features include: (i) occurrence at a young age, generally after earliest childhood; (ii) a motor disorder mainly of extrapyramidal type, characterized by dystonic postures, muscular rigidity, involuntary movements of choreoathetoid or tremulous type, but also at times corticospinal system dysfunction; (iii) mental changes indicative of dementia; and (iv) a relentlessly progressive course, extending over several years, leading to death in early adulthood. The neuropathological changes consist of: (i) a symmetrical, partially destructive lesion of the globus pallidus, especially its internal segment, and the pars reticulata of the substantia nigra, characterized by some loss of myelinated fibers and neurons, with gliosis; (ii) widely disseminated rounded or oval non-nucleated structures ("spheroids") identifiable as swollen axons, especially numerous in the regions indicated above as the site of destructive changes, but not confined to these areas; and (iii) accumulations of pigment, much of it iron-containing, in the regions that are chiefly affected.

Recently, Zhou *et al*. showed that an alteration of the pantothenate kinase gene (*PANK2*) is a cause of HSS.[3] The deficiency of phosphopantothenate leads to cysteine accumulation. In the normal brain, non-hem iron accumulates regionally and is highest in the medial globus pallidus and the substantia nigra pars reticulata. Perry *et al*.[4] described previously that highly accumulated cysteine in the globus pallidus was observed in HSS, and might act as a local chelating agent and may bind iron. The iron deposition in HSS might relate to secondary abnormalities. Cysteine, on the other hand, undergoes rapid autooxidation in the presence of iron, which results in free radical production, cytotoxicity and impaired cell membrane biosynthesis. Pantotenate also relates to the biogenesis of coenzyme A in mitochondria. PKAN is now considered a "neurodegenerative disorder with brain iron accumulation".[5]

Hayflick and colleagues investigated the genetic and clinical correlation of HSS.[6] Among 123 patients from 98 families, all patients with classic HSS and one-third of those with atypical disease showed PANK2 mutations. In all of the patients with a PANK2 mutation, brain MRI

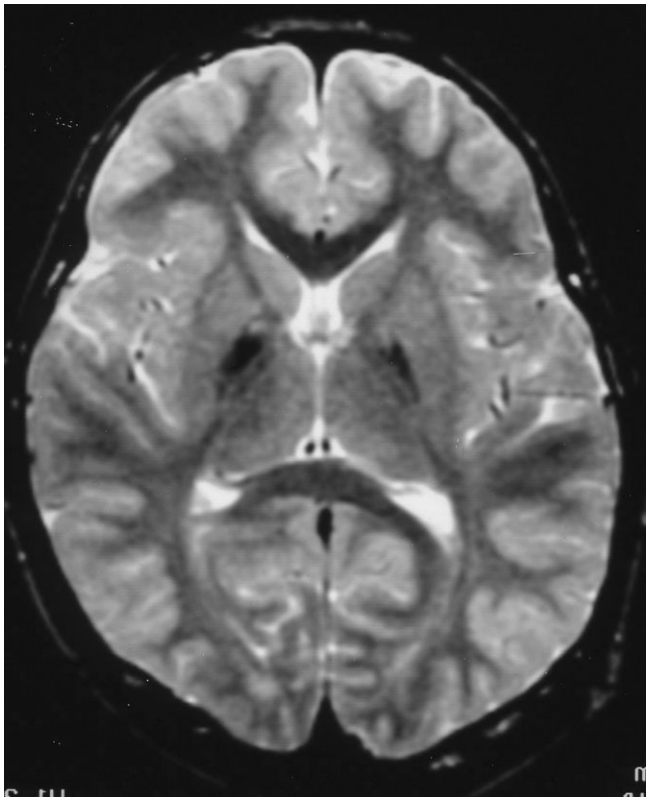

Fig. 7 MRI of another 5-year-old patient with panthothenate kinase-associated neurodegeneration. The brain T_2-weighted MRI shows the characteristic "eye of the tiger" sign which means hypointensity with a central region of hyperintensity in the medial globus pallidus.

showed the "eye of the tiger" sign (Fig. 7). Therefore, PANK2 protein correlates with severity of this disease.

We have experienced another PKAN patient over the last several years. The patient has not been examined for a known PANK2 mutation, and underwent deep brain stimulation into the bilateral globus pallidus. He is bedridden, but now the muscle tonus is controlled to allow for minimal functional daily living. We hope that these patients will be treated more effectively in the future.

ACKNOWLEDGMENT

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