Neurodegeneration with Brain Iron Accumulation: A Cautionary Tale

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Key Words

Brain iron accumulation • Neuroaxonal swellings • National Socialism • Research ethics

Abstract

Hallervorden and Spatz first described, in a sibship of 12, five sisters with clinically increasing dysarthria and progressive dementia, whose brains showed a brown discoloration of the globus pallidus and substantia nigra. Subsequently the basis has been shown to be a neurodegeneration with brain iron accumulation or pantothenate kinase-associated neurodegeneration due to mutations in the pantothenate kinase 2 (PANK2) gene. Progressive dystonia, Parkinsonism and dementia characterise the syndrome in children. The pathology comprises neuronal loss, axonal swelling, gliosis and iron deposits in the basal nuclei, disclosed by 'the eye of the tiger' sign on MR imaging. Since the criminal, unethical National Socialist activities of Hallervorden and Spatz came to light 'neurodegeneration with brain iron accumulation' has become the preferred nomenclature.

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Information about the alleged wartime activities of the eponymous contributors to this syndrome is based on published work cited here in [2, 11, 12].

Hallervorden and Spatz first described this rare condition in 1922 [1]. In a sibship of 12, five sisters showed clinically increasing dysarthria and progressive dementia, and at autopsy were found with brown discoloration of the globus pallidus and substantia nigra. The little-used eponym 'Martha-Alma disease' recalls the unfortunate sisters whose brains were dissected.

In 1921, Hallervorden came on sabbatical leave from the state psychiatric institution in Landsberg an der Warthe to work with Walther Spielmeier (1879–1935) at the Deutsche Forschungsanstalt für Psychiatrie (now Max-Planck-Institut) in Munich. He brought with him the brain of a girl. He met Spatz, with whom he described the syndrome. From January 1938, Hallervorden was head of the neuropathological department of the Kaiser-Wilhelm-Institut für Hirnforschung in Berlin-Buch, succeeding Max Bielschowsky who, as a Jew, had been dismissed in 1933. After the war Hallervorden was a neuropathologist at the Max-Planck-Institut in Frankfurt. Both he and his friend became notorious National Socialist war criminals. Shevell [2] recounts that a majority of the 700 brains Julius Hallervorden (1882–1965) investigated during the National Socialist period were victims of the Brandenburg-Görden 'euthanasia centre'.

Neurodegeneration with Brain Iron Accumulation

Neurodegeneration with brain iron accumulation (NBIA) or pantothenate kinase-associated neurodegeneration (PKAN) founds the nomenclature now favoured, ever since the criminal activities of Hallervorden and Spatz, who described this rare neuroaxonal dystrophy in 1922, came to light [3–5].

NBIA is characterized by a relentless progression of dystonia, Parkinsonism or other basal ganglia signs and intellectual decline in children. Pyramidal signs and retinal degeneration are frequently associated [6]. Characteristic pathological findings in HSD are neuronal loss, axonal swelling ('Axonschollen', 'neuro-axonal dystrophy' or 'axonal spheroids'), gliosis and iron deposits mainly in globus pallidi, substantia nigra, caudate nucleus, amygdala, hippocampus and pons with swelling and iron deposition in the globus pallidus [7]. Magnetic resonance imaging shows the 'eye of the tiger' sign in the globus pallidus on T₂-weighted imaging – a central hyperintensity, attributed to tissue necrosis and oedema, and a surrounding hypointensity due to iron deposition. This appearance is present [8] in all cases, but is not pathognomonic, as formerly asserted.

The classic form presents within the first decade of life with rapidly progressive, extrapyramidal syndrome often with pigmentary retinopathy and inability to walk (PKAN) within 15 years. The atypical form begins clinically in the second decade with slow progression, and after 15 years patients can still walk. The intermediate form subsumes patients with early onset and slow progression or later onset and rapid progression. Those with early onset often develop retinitis pigmentosa, whereas those beginning in late adolescence tend to have speech and psychiatric disorders.

Mutations in the same gene cause the rarer allelic disorder 'HARP': hypobetalipoproteinemia, acanthocytosis, retinitis pigmentosa and pallidal degeneration.

Differential Diagnosis

Several familial extrapyramidal disorders of childhood and adolescence enter the differential diagnosis. They include Wilson's disease, juvenile Huntington's chorea, olivo-ponto-cerebellar atrophy, Joseph's syndrome, Leigh's disease, mitochondrial encephalopathies and infantile bilateral striatal necrosis. Seitelberger's disease or infantile neuroaxonal dystrophy is

similar, characterized by pathologic axonal swelling and spheroid bodies in the central nervous system. Onset is within the first 2 years of life with death by age 10 years.

Classification and Mechanisms

This group of disorders has been labeled NBIA. The commonest type is due to mutations in the pantothenate kinase 2 (PANK2) gene (gene map locus 20p13-p12.3) and the term PKAN is preferred [9].

Predicted levels of PANK2 protein correlate with clinical severity. Perry et al. [10] have found deficiency of cysteine dioxygenase and subsequent cysteine accumulation in the globus pallidi in NBIA. The cysteine chelates iron, causing its slow and late deposition. Free iron radicals and cysteine damage neuronal cell membranes. The accumulation of the damaged cellular constituents leads to axonal spheroids, which destroy myelin sheaths.

On Hallervorden's role, Shevell commented:

Julius Hallervorden's important contribution to the practice of neuropathology over a long career cannot be underestimated. However, his work as a pathologist during the Third Reich put him in close proximity with the implementation of biologic solutions (i.e., euthanasia) targeting those individuals with significant intellectual or physical disabilities in chronic-care facilities. The Nazi program of active euthanasia provided a scientific opportunity to gain quick access to pathologic materials. This opportunity was recognized and used by Hallervorden to achieve personal scientific objectives and research efforts. These efforts resulted in a number of post-war scientific publications using materials obtained through the euthanasia program. The participation of distinguished academic physicians in such a program provides a cautionary tale... [11].

Similar were the human experiments of G. Schaltenbrand [12]. Ironically, the careers of neither Hallervorden nor Spatz were substantially impeded after the war. However, there have been demands for the removal of Hallervorden's eponymous name from the disease, which I have respected here.

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