Iron - Too Much of a Good Thing


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Iron is essential for oxygen transport and energy metabolism but excess iron accumulation within body organs can be detrimental. This is particularly true for the nervous system, where iron storage is tightly regulated and non-uniformly distributed. Excess iron, either from excess accumulation or from defects in iron metabolism, can lead to oxidative stress and protein aggregation, which may eventually lead to the formation of intracellular inclusion bodies often associated with neurodegenerative diseases. The syndromes of neurodegeneration with brain iron accumulation (NBIA) highlight the way in which clinically progressive neurologic dysfunction can be associated with distinct patterns of excessive iron deposition within the brain.

Neurodegeneration with brain iron accumulation disorders encompass a clinically heterogeneous spectrum of inherited childhood and adult-onset progressive neurodegenerative disease. Considerable work has been done since the original description of the Hallervorden-Spatz Syndrome (HSS) to differentiate and define specific NBIA disorders based on clinical, radiographic, pathophysiologic and genetic features. Currently, NBIA syndromes include the autosomal recessive neuroaxonal dystrophies pantothenate kinase-associated neurodegeneration (PKAN) and PLA2G6-associated neurodegeneration (PLAN), as well as Kufor-Rakeb Disease, FA2H-Associated Neurodegeneration (FAHN) and Woodhouse-Sakati Syndrome. It also includes the autosomal recessive disorder aceruloplasminemia and the autosomal dominant disorder neuroferritinopathy, in addition to the static neurodegeneration with brain iron accumulation (SNEDA) syndrome and other genetically yet undetermined conditions.

The unifying characteristic of the NBIA disorders is the excessive symmetric deposition of iron in key gray matter nuclei, which can be identified using specific magnetic resonance imaging (MRI) techniques. Areas rich in iron appear hypointense on T2-weighted MRI sequences, isointense on T1-weighted sequences and can be accentuated with T2* (gradient echo) sequences.

The exact pathophysiology and role of iron accumulation in these disorders is yet to be completely understood. Loss of PLA2G6 protein function in PLAN can result in axonal pathology and subsequent iron accumulation. Disruption of the PANK2 gene product in PKAN can lead to mitochondrial dysfunction, apoptosis and build up of metabolites such as cysteine, which is a potent iron chelator. The subsequent accumulation of iron results in further cellular injury through oxidative stress. Ultimately, many NBIA disorders may act on related metabolic pathways. For example, it has been proposed that these disorders may affect ceramide, which has a central role in sphingolipid metabolism. Ceramide has been implicated in mitochondrial processes of apoptosis and has been proposed to be associated with the formation of Lewy body inclusions, relating NBIA disorders to other neurodegenerative processes.

Indeed, iron accumulation has been noted in Parkinson disease and Alzheimer disease. However, as in NBIA disorders like PKAN, it is difficult to determine whether iron accumulation is a result of, or cause of, neuronal dysfunction.

Pantothenate kinase-associated neurodegeneration itself accounts for approximately half of all cases of NBIA and was the initial disorder characterized genetically from the original HSS patients. As with all NBIA disorders the clinical phenotype of PKAN can vary considerably from mild to severe. However, in general, the classic presentation of PKAN with childhood onset is much more severe than the atypical phenotype, which may present in adulthood. Classic PKAN presents with gait and postural difficulties, severe extrapyramidal dysfunction (e.g., limb, axial or oromandibular dystonia), pyramidal tract findings (i.e., spasticity and hyperreflexia), cognitive decline, and visual impairment (associated with retinitis pigmentosa). In contrast, atypical PKAN may present with speech difficulty (including dysarthria and palilalia), psychiatric symptoms, and cognitive decline. Extrapyramidal or pyramidal tract findings are less common and less severe in comparison to the classic phenotype.

Pantothenate kinase-associated neurodegeneration is associated with characteristic radiographic and genetic features. Iron accumulation is symmetric and predominantly concentrated within the globus pallidus. Other brain regions are relatively spared. On T2*-weighted sequences, iron deposition in the globus pallidus produces a central area of hyperintensity within a surrounding area of hypointensity, known as the "eye-of-the-tiger" sign. Although neither 100% specific nor sensitive, this radiographic sign is often associated with PKAN. Genetically, PKAN results from a mutation of the PANK2 gene on chromosome 20p13. Most mutations are missense mutations and can occur in any of the 7 exons of the PANK2 gene. Other mutation types, including deletions, duplications and splice-site mutations have also been reported.

The paper by Kim et al describes a case of adult-onset atypical PKAN that presented with jaw opening dystonia and characteristic "eye-of-the-tiger" MRI changes. Genetic analysis of the PANK2 gene revealed two heterozygous mutations; one previously established mutation and one novel variation. Descriptions of novel mutations are necessary to further characterize the disorder and provide genetic-phenotypic correlations. By further characterizing the gene and possible mutations, it may provide improved prognostic information to patients, more accurate genetic counseling and may uncover targets for future therapeutic trials.
REFERENCES