Neurodegeneration with Brain Iron Accumulation

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The recent advance in magnetic resonance imaging (MRI) and identification of causative genes led to the recognition of a new group of disorders, named neurodegeneration with brain iron accumulation (NBIA). NBIA is a group of inherited disorders characterized by abnormal iron deposition in the brain, usually in the basal ganglia, and share the clinical features of movement disorders accompanied by varying degrees of intellectual disability. In this review, the causative genes, clinical presentations, neuroimaging features, and pathological findings are summarized.

Key Words: Neurodegeneration, Iron, Basal ganglia, MRI

1. Causative genes

Over the last decade, ten causative genes which lead to NBIA have been identified: eight are autosomal recessive, one is autosomal dominant (neuroferrtinopathy), and one is X-linked dominant (Beta-propeller protein-associated neurodegeneration, BPAN).[1] Both neuroferritinopathy (*FTL* gene) and aceruloplasminemia (*CP* gene) are linked to mutations in genes directly associated with iron homeostasis.[2,3] The other forms are not directly involved in iron metabolism. They are involved in diverse cellular pathways: Pantothenate Kinase 2 (*PANK2*; Pantothenate kinase-associated neurodegeneration, PKAN), Phospholipase A2 group 6 (*PLA2G6;* Phospholipase-associated neurodegeneration, PLAN), *C19orf12* (Mitochondrial membrane protein-associated neurodegeneration, MPAN), Coenzyme A synthase (*COASY;* Coenzyme A synthase protein-associated neurodegeneration, CoPAN), and Fatty acid hydroxylase 2 (*FA2H;* Fatty acid hydroxylase-associated neurodegeneration, FAHN) genes seem to be related to lipid metabolism and to mitochondria functioning, *WDR45* (Beta-propeller protein-associated neurodegeneration, BPAN) and *ATP13A2* (Kufor-Rakeb syndrome) genes are implicated in lysosomal and autophagosome activity, while the *DCAF17* (Woodhouse-Sakati syndrome) gene encodes a nucleolar protein of unknown function.[2,3]

2. Phenotypic variability

NBIA patients commonly exhibit mixed dystonia, parkinsonism and spasticity.[1,4] However, the clinical features of NBIA range from global neurodevelopmental delay in infancy to mild parkinsonism in adulthood, with wide variation seen between and within the specific NBIA subtype, making the diagnosis of these rare diseases challenging.[1] The later onset forms of NBIA may also mimic the clinical presentations of other neurodegenerative diseases.[4]

PKAN accounts for about 50% of all NBIA cases and may present in age-dependent phenotypes; the classic with early onset and the atypical variant with later onset.[1] The classic form is characterized by pyramidal (spasticity, hyperreflexia, extensor toes) and extrapyramidal features with

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prominent dystonia, and rapid progression.[5] Gait and postural difficulties are often the presenting features developing around the first decade of life. Retinopathy are often present. The atypical variant presents in the second or third decade of life with less severe and slow-progressive extrapyramidal and pyramidal signs.[5] Difficulties with speech and psychiatric symptoms with cognitive decline are often observed. Similar age-dependent presentations have also been recognized in PLAN; early childhood-onset form results in infantile neuroaxonal dystrophy with severe progression, whereas later-onset PLAN may be milder and present commonly with dystonia-parkinsonism without cerebellar or sensory abnormalities.[1,4] These examples highlight the marked variability in clinical phenotype, and NBIA should be considered as a possible diagnosis in patients of any age and irrespective of family history.[4]

3. MRI Clues for diagnosis

The diagnosis of NBIA is typically suspected once compatible magnetic resonance imaging (MRI) features are identified along with representative clinical features.[6] Iron-sensitive sequences such as T2* and susceptibility-weighted imaging are more sensitive for demonstration of brain iron accumulation.[1,7] The established hallmark MRI features include hypointense lesions in the globus pallidus and substantia nigra on T2-weighted images.[4] The SN and the GP naturally contain high iron concentrations and also have a high metabolic requirement, potentially predisposing these areas to iron-related damage.[2] After iron deposition is identified on the MRI, the pattern of iron accumulation should be evaluated.[6] In particular, the involvement of sites outside of the globus pallidus is important for diagnosis.

In PKAN, iron-related MRI signal abnormalities are restricted to the globus pallidus and substantia nigra, and almost invariably exhibit the 'eye of the tiger sign' in which a central hyperintense region in the globus pallidus is surrounded by a hypointense region.[5] In MPAN cases, pallidal hypointensity can be seen with hyperintense streaking in the region of the medial medullary lamina.[1,8] In BPAN, the hypointensity is most pronounced in the substantia nigra where it appears as a discrete linear streak. This same area on T1 sequences is surrounded by a hyperintense 'halo' extending to the cerebral peduncles.[1,8] Neuroferritinopathy shows iron deposition in the dentate nuclei together with the globus pallidus and putamen and occasionally the caudate, thalami, and red nuclei.[7] By contrast, aceruloplasminemia affects the simultaneous involvement of all nuclei, with no evidence of the cystic degeneration seen in neuroferritinopathy.[7]

However, cases of genetically proven PLAN and Kufor-Rakeb syndrome patients have been described with no evidence of iron deposition on MRI, questioning the pathogenic role of iron.[4] In some NBIA subtypes, additional features including cerebellar atrophy which is the most common neuroimaging finding in PLAN,[1] diffuse T2 white matter hyperintensities, and thinning of the corpus callosum may be seen especially in more advanced disease.[4,6,7,8]

4. Neuropathology

On a pathological level, iron accumulation may be accompanied by protein aggregates (e.g. Lewy bodies, hyperphosphorylated tau) and axonal swellings depending on NBIA subtype.[2] For example, widespread alpha-synuclein-positive Lewy body pathology has been described in patients with PLAN.[4] In addition, neuropathological examination of a patient with the MPAN has shown the presence of Lewy bodies, spheroids, and tau-positive tangle pathology.[4]

References

1. Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. *J Mov Disord* 2015;8: 1-13.
2. Arber CE, Li A, Houlden H, Wray S. Insights into molecular mechanisms of disease in neurodegeneration with brain iron accumulation: unifying theories. *Neuropathol Appl Neurobiol* 2015 Apr 14.
3. Levi S, Finazzi D. Neurodegeneration with brain iron accumulation: update on pathogenic mechanisms. *Front Pharmacol*

2014;5:99.
4. Keogh MJ, Chinnery PF. Current concepts and controversies in neurodegeneration with brain iron accumulation. *Semin Pediatr Neurol* 2012;19:51-56.
5. Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, et al. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med* 2003;348:33-40.
6. Kruer MC, Boddaert N. Neurodegeneration with brain iron accumulation: a diagnostic algorithm. *Semin Pediatr Neurol* 2012;19:67-74.
7. McNeill A, Birchall D, Hayflick SJ, Gregory A, Schenk JF, Zimmerman EA, et al. T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation. *Neurology* 2008;70:1614-1619.
8. Amaral LL, Gaddikeri S, Chapman PR, Roy R, Gaddikeri RS, Marussi VH, et al. Neurodegeneration with Brain Iron Accumulation: Clinicoradiological Approach to Diagnosis. *J Neuroimaging* 2015;25:539-551.