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Neurodegeneration with Brain Iron Accumulation

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Recent advances in magnetic resonance imaging 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. The disorder shares the clinical features of movement disorders and is accompanied by varying degrees of neuropsychiatric abnormalities. In this review, the causative genes, clinical presentations, neuroimaging features, and pathological findings are summarized.

Key words: Neurodegeneration, Iron, NBIA

REVIEW ARTICLE

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INTRODUCTION

Neurodegeneration with brain iron accumulation (NBIA) is a group of inherited disorders with hallmark features that include abnormal iron accumulation in the basal ganglia, mainly the globus pallidus and substantia nigra, and progressive movement disorders that include dystonia, spasticity, parkinsonism, and varying degrees of intellectual disability, as well as other neuropsychiatric abnormalities [1]. Prevalence data is incomplete, but all forms of NBIA are rare, between one and three per million individuals in the general population [1,2].

Ten genes associated with different NBIA subtypes have been identified: *PANK2*, *PLA2G6*, *C19orf12*, *WDR45*, *COASY*, *FA2H*, *ATP13A2*, *FTL*, *CP*, and *DCAF17* [3,4]. The four most common NBIA disorders include pantothenate kinase-associated neurodegeneration (PKAN; NBIA1, MIM#234200), phospholipase A2-associated neurodegeneration (PLAN; NBIA2B, MIM#610217), mitochondrial membrane protein-associated neurodegeneration (MPAN; NBIA4, MIM#614298), and beta-propeller protein-associated neurodegeneration (BPAN; NBIA5, MIM#300894) [5]. Inheritance pattern of most NBIA disorders is autosomal recessive [1]. Neuroferritinopathy (NBIA3, MIM#606159) is the only autosomal-dominant subtype. BPAN is inherited in a dominant X-linked manner. Recently, a number of new NBIA subtypes are being recognized as a result of next-generation sequencing (NGS) [5]. *SCP2*, *GTPBP2*, *AP4M1*, *REPS1*, and *CRAT* can be considered NBIA genes [2,6].

Here, we review the known NBIA genes and their proposed disease mechanisms, and summarize the clinical, magnetic resonance imaging (MRI), and pathological features of NBIA disorders.

MOLECULAR MECHANISMS

Only two genes, *FTL* in NBIA3 and *CP* in aceruloplasminemia (MIM#604290), are directly associated with iron homeostasis [3,4]. The other forms are not directly involved in iron metabolism; instead, they are involved in diverse cellular pathways: *PANK2* in PKAN) and *COASY* in Coenzyme A synthase protein-associated neurodegeneration (CoPAN; NBIA6, MIM# 615643) code for enzymes responsible for coenzyme A (CoA) synthesis; *PLA2G6* in PLAN), *FA2H* in fatty acid hydrolase-associated neurodegeneration (FAHN; SPG35, MIM#612319), and *C19orf12* in MPAN appear to be related to lipid metabolism, membrane integrity, and mitochondrial function; *WDR45* in BPAN and *ATP13A2* in Kufor-Rakeb syndrome (MIM#606693) are implicated in autophagosome and lysosomal activity, while the *DCAF17* in Woodhouse-Sakati syndrome (MIM#241080) encodes a nucleolar protein of unknown function [2-4].

Although the presence of excessive iron accumulation enables these diseases to be included in the NBIA disorders, pathogenic processes leading to iron dyshomeostasis are still not fully elucidated [2,3]. The contribution of iron to disease pathophysiology also remains unclear owing to the lack of experimental models that fully recapitulate the human phenotype [2].

CLINICAL FINDINGS

Patients with NBIA commonly exhibit mixed dystonia, parkinsonism, and spasticity [1]. However, the clinical features of NBIA range from global neurodevelopmental delay in infancy to mild parkinsonism in adulthood, with wide variation between and within the specific NBIA subtype, making the diagnosis of these rare diseases challenging [1,5]. The late-onset forms of NBIA may also mimic the clinical presentations of other neurodegenerative diseases [7].

PKAN may present in age-dependent phenotypes: the classic form with early onset and the atypical variant with later onset [8,9]. The classic form is characterized by pyramidal and extrapyramidal features with prominent dystonia and rapid progression [8]. Gait and postural difficulties are often the presenting features developing in the first decade of life. Retinopathy is often present. The atypical variant presents in the second or third decade of life with less severe and slow-progressive extrapyramidal and pyramidal signs [8]. Speech difficulties 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 [1,7,9]. These examples highlight the marked variability in clinical phenotype and suggest that NBIA should be considered as a possible diagnosis in patients of any age and irrespective of family history [7].

MPAN typically occurs in the first decade of life to early adulthood. The phenotype is characterized by spastic gait with upper motor neuron findings, followed by lower motor neuron signs; electrophysiologically, it is characterized as a motor neuronopathy/axonopathy, dystonia, and parkinsonism, commonly accompanied by optic atrophy and neuropsychiatric features [1,9,10].

BPAN is a biphasic disease: global developmental delay in childhood and further regression in early adulthood with progressive dystonia, parkinsonism, and dementia [1,9,11]. BPAN typically presents with seizures, spasticity, and Rett syndrome-like features [11].

Clinical features of FAHN comprise childhood-onset spasticity, ataxia, and dystonia [9]. FAHN is a disorder allelic to hereditary spastic paraplegia type 35 (SPG35). Kufor-Rakeb syndrome, also known as PARK9, is caused by mutations in the *APT13A2* and is characterized by a syndrome of juvenile-onset parkinsonism, spasticity, and cognitive decline [9]. Woodhouse-Sakati syndrome presents with hypogonadism, diabetes mellitus, alopecia, extrapyramidal movement disorders, intellectual disability, and sensorineural hearing loss [1].

Similar to PKAN, CoPAN due to mutations in the *COASY* presents with early-onset gait difficulty and learning disabilities, followed by progressive spasticity and extrapyramidal features [1,6].

Neuroferritinopathy and aceruloplasminemia typically present in mid-life with the average age of onset much later than other NBIA subtypes [1,9]. Neuroferritinopathy, often thought of as one of the Huntington-like disorders [9], is a dominantly-inherited syndrome of chorea, dystonia, parkinsonism, cognitive decline, and low serum ferritin. Aceruloplasminemia is characterized by diabetes, retinal disease, and a movement disorder consisting of facial dystonia, chorea, tremor, parkinsonism, ataxia, cognitive decline, and low or absent serum ceruloplasmin. Systemic iron accumulation results in peripheral retinal degeneration and liver iron storage [9].

MRI FEATURES

The diagnosis of NBIA is typically suspected when compati-

ble MRI features are identified along with representative clinical features [12]. Iron-sensitive sequences such as T2* and susceptibility-weighted imaging are more sensitive for demonstration of brain iron accumulation [13]. The established hallmark MRI features include hypointense lesions in the globus pallidus and substantia nigra on T2-weighted images [7,14].

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 [13,15]. In MPAN cases, pallidal hypointensity can be seen with hyperintense streaking in the region of the medial medullary lamina [1,16]. 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 [1,18]. Cavitation involving the globus pallidus and putamen is unique to neuroferritinopathy [15]. However, the morphological patterns of these lesions can vary according to the patient's age [13,17]. Typical findings do not appear until adolescence or early adulthood.

Widespread brain iron accumulation involving the basal ganglia nuclei, thalami, dentate nuclei, and cerebral and cerebellar cortices may develop in aceruloplasminemia and neuroferritinopathy [15]. However, cases of genetically proven PLAN and Kufor-Rakeb syndrome with no evidence of iron deposition on MRI have also been described [7].

In addition to excessive iron, non-iron MRI abnormalities are helpful in diagnosis [14,16]. Cerebellar atrophy is a hallmark feature of PLAN [16,18]. Hypertrophy of the clava has been proposed as an important early feature of PLAN and may precede cerebellar atrophy [19, 20]. T2 hyperintense white matter abnormalities are prominent in FAHN, Woodhouse-Sakati syndrome, and aceruloplasminemia [16]. Thinning of the corpus callosum is seen in FAHN, PLAN, and BPAN [11,16].

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 [4]. For example, widespread alpha-synuclein-positive Lewy body pathology has been described in patients with PLAN [21]. In addition, neuropathological examination of a patient with the MPAN has shown the presence of Lewy bodies, spheroids, and tau-positive tangle pathology [10]. Tau-positive neurofibrillary tangles are common in the brains of patients with BPAN [4,11].

CONCLUSIONS

NBIA is a phenotypically and genetically heterogeneous group of disorders. There have been significant advances in identifying new genes/mutations involved in NBIA as a result of the development of technology based on NGS [5,6], which has also facilitated early detection of patients with nonspecific phenotype. Due to their clinical and pathophysiologic overlap with common neurodegenerative diseases, such as Parkinson's and Alzheimer's disease, NBIA disorders may stand at the forefront of understanding the common pathways in neurodegeneration [22].

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CONFLICTS OF INTEREST

The author has no financial conflicts of interest.

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