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Genetics of Neurodegeneration with Brain Iron Accumulation

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Abstract

The condition originally called Hallervorden-Spatz syndrome is a collection of related disorders involving abnormal iron accumulation in the basal ganglia, usually manifesting with a movement disorder. To date, mutations in the following genes have been associated with neurodegeneration with brain iron accumulation (NBIA) phenotypes: *PANK2*, *PLA2G6*, *FA2H*, *ATP13A2*, *C2orf37*, *CP*, and *FTL*. This collection, now classified under the umbrella term NBIA, continues to evolve as new genes and associated phenotypes are recognized. As this body of information continues to grow, better approaches to diagnosis and treatment have become available. Continued investigations of the underlying pathogenesis of disease, with a focus on lipid, iron, and energy metabolism, will lead to the identification of new therapeutic targets.

Keywords

Neurodegeneration with brain iron accumulation; NBIA; Pantothenate kinase-associated neurodegeneration; PKAN; Neuroaxonal dystrophy; INAD; Dystonia-parkinsonism; PLAN; Fatty acid hydroxylase-associated neurodegeneration; Woodhouse-Sakati syndrome; Kufor-Rakeb syndrome; Aceruloplasminemia; Neuroferritinopathy; *PANK2*; *PLA2G6*; *FA2H*; *ATP13A2*; *C2orf37*; *CP*; *FTL*

Introduction

The condition originally described as Hallervorden-Spatz syndrome, characterized by the hallmark features of high levels of basal ganglia iron and axonal spheroids, has been steadily delineated since the first gene was identified in 2001 [1]. The discovery of the *PANK2* gene and characterization of the corresponding clinical condition, pantothenate kinase-associated neurodegeneration (PKAN), provided a model for future gene discovery and description of clinical subtypes for what is now called neurodegeneration with brain iron accumulation (NBIA) [2]. Significant progress was made in 2009 to 2010 in differentiating types of NBIA according to genetic, radiologic, and clinical findings. These discoveries have begun to

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provide a diagnostic approach for cases of possible NBIA. Advances in gene discovery and sequencing techniques have aided in this process and will contribute to more complete clinical testing. As our understanding of NBIA genotypes and phenotypes has rapidly expanded, intriguing exceptions to the rules have also been recognized. This review will provide an update on key findings in each subtype of NBIA and conclude with overarching recommendations for approaching and treating this complex group of disorders.

Pantothenate Kinase-Associated Neurodegeneration (PKAN)

Historically, PKAN has been described as either classic or atypical, but evidence continues to mount showing that the phenotype includes a broad spectrum between these two points. Classic PKAN remains quite homogeneous, with early onset and rapid progression. Children commonly present with gait abnormalities and later develop progressive dystonia, dysarthria, and rigidity with corticospinal tract involvement that results in spasticity, hyperreflexia, and extensor toe signs. By definition, atypical cases have later onset (late childhood to teenage years) and slower progression. Speech difficulty is often the presenting feature and psychiatric symptoms (including depression, emotional lability, and impulsivity) are more common than in early-onset cases [2]. Pigmentary retinopathy is common in PKAN, and abnormal electroretinography results may precede onset of ophthalmological symptoms by several years, particularly in slowly progressive cases [3]. Now that molecular genetic testing has been available for several years, cases with unusually late onset are being recognized, including one at age 37 who presented with arm tremor, recently reported by Aggarwal et al. [4]. Our International NBIA Research Registry includes a PKAN patient who presented with hand tremor at 23 years and is still living with minimal symptoms at 77 years, as well as three others who also presented in their mid-20s and are still living in their 40s to 50s.

MRI is particularly useful in separating PKAN cases from other forms of NBIA. Specifically, on T2-weighted imaging the medial globus pallidus shows hypointense signal with a central region of hyperintensity. In presymptomatic patients the hyperintense central lesions predominate. With disease progression, the hypointensities appear and eventually dominate [5], in rare cases to the point that the hyperintense regions have been reported to disappear [6]. Other forms of NBIA have been reported to exhibit an eye-of-the-tiger sign [7], but have subtle differences in the appearance of the globus pallidus lesion, including asymmetry, irregular contour, and lateral displacement.

PKAN is an autosomal-recessive inborn error of coenzyme A metabolism caused by mutations in the gene encoding pantothenate kinase 2 (*PANK2)*. Pantothenate kinase is a key regulatory enzyme in the biosynthesis of coenzyme A, critical to energy metabolism, fatty acid synthesis and degradation, and other functions. Molecular diagnosis is currently offered by two clinical laboratories in the United States, other international laboratories (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests), and through the National Ophthalmic Disease Genotyping Network (eye-GENE, http://www.nei.nih.gov/resources/eyegene.asp). The decision to order molecular testing should be guided by whether brain MRI indicates the presence of an eye-of-the-tiger sign. Many families tested by sequence analysis will have at least one rare or private mutation [2]. In these instances, clinical

laboratories use mutation databases and algorithms to predict the pathogenicity of each variant. Limited data suggest 3% to 5% of *PANK2* mutations are large deletions or duplications [8]; separate assays are now routinely performed to search for these alterations that can be missed by sequence analysis.

PLA2G6-Associated Neurodegeneration (PLAN)

The phenotype associated with *PLA2G6* mutations has broadened substantially since molecular diagnosis became clinically available in 2007, and this group of autosomal-recessive disorders is now referred to as PLAN [9••]. Prior to the gene discovery, diagnosis was challenging and was confirmed by nerve biopsy showing the presence of peripheral nerve axonal spheroids [10]. The most common form, infantile neuroaxonal dystrophy (INAD), is a severe psychomotor disorder with early onset and rapid progression of hypotonia, hyperreflexia, and later tetraparesis. Psychomotor regression is the most frequent presentation; ataxia or gait instability is also frequent in early disease. Cerebellar atrophy is observed in the majority of cases and abnormal brain iron accumulation, mainly in the globus pallidus, is observed in at least half of mutation-positive cases. The combination of cerebellar atrophy and high brain iron is strongly predictive of a *PLA2G6* mutation [11••]. Even without evidence of high brain iron, cerebellar atrophy in a young patient with psychomotor slowing or regression merits *PLA2G6* analysis.

The spectrum of atypical NAD continues to expand as more individuals undergo molecular testing. These are typically patients with later onset and slower progression whose features overlap with PKAN, including progressive dystonia and dysarthria not usually observed in the infantile form. Speech delay and diminished social interaction are common at onset. Cerebellar atrophy and optic atrophy remain distinguishing features [9••, 11••]. Since our publication of six atypical NAD cases in 2008, we have ascertained another unusual patient who recently died at the age of 36. At age 2 she had mild developmental delay, particularly affecting language. It was not until age 30 that she began to regress, with gait slowing, spasticity, and behavioral changes including aggression and depression. One splice site mutation was identified in *PLA2G6*, and autopsy findings included iron accumulation and axonal spheroids in the globus pallidus and substantia nigra (Mark Tarnopolsky, personal communication).

In 2008, Paisan-Ruiz et al. [12] described two inbred families with dystonia-parkinsonism found to have homozygous mutations in *PLA2G6* without high brain iron. The described individuals had onset in the second to third decades of life, with rapid decline and several features overlapping with atypical NAD, including gait abnormalities, dystonia, dysarthria, and psychiatric disturbances. Yoshino et al. [13] recently reported two additional families with early-onset parkinsonism and *PLA2G6* mutations. However, these patients did not have dystonia and one did have iron accumulation in the substantia nigra and striatum. This is the first evidence of iron accumulation in this population, linking these rare patients to the more typical PLAN presentation. Engel et al. [14] recently showed that *PLA2G6* mutations associated with INAD impair the catalytic activity of the PLA2G6 protein, whereas the mutations associated with milder dystonia-parkinsonism do not. Supporting this correlation, Tonelli et al. [15] described a novel in-frame deletion of exons 5 and 6 in *PLA2G6* that

deletes the ankyrin repeat region of the gene associated with enzymatic activity. This large deletion, compounded with a known nonsense mutation, resulted in unusually rapid disease progression.

The *PLA2G6* gene encodes iPLA$_2$-VIa, a calcium-independent phospholipase. The iPLA$_2$ enzymes are critical in cell membrane homeostasis, which may underlie the axonal pathology observed in *PLA2G6*-associated disease [16]. Common mutations have not been identified in *PLA2G6* and most families will be found to have private mutations [17]. For this reason, diagnosis depends on strong clinical correlation and assessment of each gene variant with predictive algorithms. Sequence analysis of the coding region and splice sites is thought to identify approximately 87% of mutations [11••]. The presence of individuals in whom only one mutation is identified by mutation scanning suggests large intragenic deletions or duplications may account for some additional cases, and preliminary studies support this (Eden Haverfield, personal communication). Rarely, an individual with strong clinical evidence of NAD, including documented peripheral nerve axonal spheroids, will fail to have any mutations identified in *PLA2G6*.

Additional cases consistent with the PLAN phenotypic spectrum have not been associated with *PLA2G6* and are likely caused by mutations in other genes. Although the original Karak syndrome family was found to have *PLA2G6* mutations [17, 18] and we believed this to no longer be a separate phenotype, we have more recently ascertained additional Karak families who are negative for mutations in *PLA2G6* (cases provided by Saeed Bohlega). We have also ascertained two cases of severe, prenatal-onset neuroaxonal dystrophy characterized by fetal akinesia, arthrogryposis, and pathologic findings similar to INAD that screened negative for *PLA2G6* mutations (clinical and pathologic information provided by Catherine Fallet-Bianco, Brigitte Gilbert, and Fabien Guimiot). Rakheja et al. [18] recently published a similar case of fetal contractures, arthrogryposis, hypoplastic cerebellum and lungs, and small optic nerves that also tested negative for *PLA2G6* mutations. A strikingly similar disorder involving fetal akinesia, arthrogryposis, pulmonary hypoplasia, and cerebellar hypoplasia with evidence of peripheral nerve spheroids in a colony of laboratory dogs may provide an opportunity for additional gene discovery relevant to these human cases [19].

Fatty Acid Hydroxylase-Associated Neurodegeneration (FAHN)

FAHN is a new subtype of NBIA caused by mutations in fatty acid-2 hydroxylase (*FA2H*) [20•]. To date, mutations have been detected in five patients from two separate families, and sequencing of 50 additional idiopathic NBIA families did not reveal other cases, suggesting *FA2H* mutations are a rare cause of NBIA. The two affected families have quite similar phenotypes with specific MRI changes that will provide guidance for the diagnosis of future cases.

FAHN typically begins with focal dystonia in the legs and feet and gait impairment during preschool years. Ataxia follows, and dysarthria and progressive spastic quadriparesis with pyramidal tract signs develop. Strabismus and nystagmus may occur, along with optic atrophy leading to progressive loss of visual acuity. In our index family, cognitive function

was preserved in all three affected children who did well in school with adaptive measures. In the second case mild cognitive impairment did not become evident until the early 20s. Seizures may be observed later in the disease course. Similar to other forms of NBIA, death in the early 20s occurred secondary to respiratory complications in two individuals. Neuroimaging features of FAHN include abnormal iron accumulation in the globus pallidus, and the substantia nigra may be affected to a lesser degree. Other distinguishing features include confluent subcortical and periventricular white matter T2 hyperintensities along with thinning of the corpus callosum. Cerebellar and brainstem atrophy increase with time and may be profound.

FA2H produces 2-hydroxylated fatty acids incorporated into ceramide species necessary for the production of normal myelin [21]. Interestingly, mutations in *FA2H* have also been associated with a familial leukodystrophy and a hereditary spastic paraplegia that appear clinically distinct [22, 23]. Both FAHN families reported to date had homozygous mutations in *FA2H*. The index family has a missense mutation, c.460 C>T, that replaces a highly conserved arginine residue (R154C), whereas the second family has a nonsense mutation causing premature protein truncation (Y170X). Gene sequencing is available on a research basis, although clinical testing is in development.

Kufor-Rakeb Syndrome

Schneider et al. [24] recently suggested that the rare, autosomal-recessive Kufor-Rakeb syndrome might be classified as a form of NBIA based on novel findings in a previously described family. This syndrome was first described in five siblings from the Jordanian village of Kufor-Rakeb [25]. It is characterized by juvenile-onset parkinsonism, pyramidal signs, dementia, and supranuclear gaze palsy. Williams et al. [26] identified additional distinguishing features, including facial-faucial-finger myoclonus, visual hallucinations, and oculogyric dystonic spasms. Only a few families with this diagnosis have been reported, and little is known about the phenotypic spectrum, including imaging findings.

Striking overlap with NBIA features led Schneider et al. [24] to do a more thorough investigation of their case using T2*-weighted MRI to look for iron deposition. This imaging showed generalized brain atrophy, reported previously in Kufor-Rakeb syndrome, and hypointense signal in the putamen and caudate nuclei, consistent with iron deposition. Using T2* imaging, Behrens et al. [27] also found evidence of iron accumulation in the caudate and lenticular nucleus in one individual from a large Chilean family. Iron accumulation has not been detected in the limited number of other cases in the literature, and it is unclear what portion of patients with Kufor-Rakeb syndrome will have brain iron accumulation [28, 29]. Similar to PLAN cases, Chien et al. [30] have suggested that only a portion may have iron accumulation, this feature may develop late in disease course, or it may only occur with more severe *ATP13A2* mutations. Postmortem studies have not been performed to date but may eventually provide more information about overlap between NBIA and Kufor-Rakeb syndrome.

Mutations in a lysosomal type 5 P-type ATPase (*ATP13A2*) have been found in the original Jordanian family and a handful of other families worldwide [27, 31–34]. Clinical testing is

available through European laboratories (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests).

Woodhouse-Sakati Syndrome

Woodhouse-Sakati syndrome is a rare, autosomal-recessive condition characterized by hypogonadism, alopecia, diabetes, mental retardation, hearing loss [35], and additional neurologic findings later characterized by Al-Semari and Bohlega [36]. In 12 Saudi families, including one of the original Woodhouse-Sakati families, they described a neurologic phenotype that included a progressive extrapyramidal disorder, generalized dystonia and focal dystonia, dysarthria, and cognitive decline. They also reported decreased signal in the globus pallidus, substantia nigra, and other regions of the basal ganglia on T2-weighted MRI in all the patients who had imaging, presumed to be iron. White matter disease was also common. Through Dr. Bohlega we were able to review the images from one of these families and agreed that they are consistent with iron accumulation.

Alazami et al. [37] used two unrelated Saudi families for linkage analysis and found a 1-bp deletion in *C2orf37* that was later confirmed to be homozygous in six additional families and appears to be a founder mutation in Saudi Arabia. The group subsequently found different mutations in other ethnic groups, suggesting that the syndrome is not limited to the Saudi Arabian population. Although this appears to be a rare cause of NBIA, the phenotype is distinguished by the additional endocrine abnormalities and should be recognized with relative ease. Gene testing may be available on a research basis.

Aceruloplasminemia

Unlike other forms of NBIA, in autosomal-recessive aceruloplasminemia, iron accumulates in both the brain and viscera. The combination of retinal degeneration, diabetes mellitus, and neurologic disease occurs with onset in adulthood (25–60 years) [38]. Neurologic findings include blepharospasm, facial and neck dystonia, dysarthria, tremors, chorea, and ataxia. Unlike other forms of NBIA, serum iron and copper are low, with high serum ferritin concentration.

Brain MRI shows hypointense signal in the globus pallidus, striatum, thalamus, and dentate nucleus on T2-weighted images. Abnormal hypointensities in the liver are also common, and iron content in the liver is even greater than in the basal ganglia.

Aceruloplasminemia is caused by mutations in the *CP* gene that encodes ceruloplasmin [39]. This leads to absence of serum ceruloplasmin in affected individuals. Gene sequencing is reported to find mutations in 92% of individuals of Japanese heritage with clinical evidence of aceruloplasminemia [40]. Molecular diagnosis may be available on a research basis.

Neuroferritinopathy

Neuroferritinopathy is the only autosomal-dominant form of NBIA and may present similarly to Huntington’s disease with adult-onset chorea or dystonia and cognitive change [41]. It progresses from involving the limbs to a more generalized movement disorder [42].

Most affected individuals will develop a characteristic orofacial action-specific dystonia related to speech. Serum ferritin is low in the majority of males and postmenopausal females, but will be normal in younger females.

Brain MRI shows excess iron storage in the basal ganglia and later cystic changes in the caudate and putamen that can distinguish neuroferritinopathy radiographically from other forms of NBIA [7]. The ferritin light (*FTL*) gene is the only gene associated with neuroferritinopathy [43]. A common adenine insertion in exon 4 has been found in approximately 80% of families, and clinical testing may be done sequentially with sequencing performed when the common insertion is not found initially. Clinical genetic testing is available through one US laboratory and several in Europe (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests).

Idiopathic NBIA

Despite the progress made to date, a significant portion of patients with clear clinical, radiologic, and sometimes pathologic evidence of NBIA fail to have mutations identified in known causative genes. Based on our experience to date, it is likely that several additional, rare genes remain to be discovered. For the most part, the clinical features within the remaining patients do not stratify into clear phenotype groups, making gene hunting a challenge, although new technologies that enable rapid and affordable exome sequencing will enable discovery of even these culprit genes.

One exception is the identification of a distinct NBIA subpopulation with static encephalopathy of childhood with neurodegeneration in adulthood (SENDA) [44]. These patients have early childhood intellectual impairment that appears nonprogressive. During adulthood, affected individuals have relatively sudden onset of progressive dystonia-parkinsonism and spasticity. In addition to iron deposition in the globus pallidus and substantia nigra, SENDA has a distinct pattern on MRI of T1-weighted signal hyperintensity of the substantia nigra with a central band of hypointensity [44]. Significant cerebral and milder cerebellar atrophy also occur. Interestingly, the SENDA patients we have found to date are each single cases within their families, suggesting it could be due to new mutation events, autosomal-recessive inheritance, or even an environmental cause. To date no causative genes have been identified.

At the 59th annual meeting of the American Society of Human Genetics, Drs. Monika Hartig and Holger Prokisch presented data on a cohort of 54 NBIA patients from Poland [45]. They used expression profiling to identify a distinct group of patients with spastic paraparesis, dystonia, psychiatric symptoms, neuropathy, and optic atrophy. A linkage study and subsequent screening of several genes in a region of interest led to the identification of a new NBIA gene harboring four different mutations in 21 patients. It is our understanding that this gene may account for a significant portion of currently idiopathic NBIA and will be of use diagnostically in the near future.

Approach to NBIA

Determining whether a patient has NBIA and diagnosing the specific type can be a challenge. Brain MRI serves as a highly sensitive clinical tool that should help guide clinicians in most cases. In our experience, the phenotype usually evolves to a point where an MRI is ordered, and it is at this time that NBIA is seriously considered. Clinicians should be aware that the imaging findings in NBIA can be subtle, which sometimes leads to the report of normal results for images later found to show evidence of abnormal iron accumulation. Kruer et al. [44] recently submitted a paper that reviews the neuroimaging features of NBIA in detail and includes images from the various forms of NBIA that may help guide diagnostic testing for clinicians. Table 1 from that paper provides guidance to help distinguish forms of NBIA based on clinical and radiographic findings. Once NBIA is suspected and the subtypes are considered, molecular testing is now available either clinically or on a research basis for most of the known genes.

It should be noted that the presentation of INAD is significantly different from other NBIA. Infants with early truncal hypotonia, regression, progression, and later development of spasticity should be considered for *PLA2G6* sequencing. Cerebellar atrophy detected during infancy or early childhood also narrows the differential diagnosis considerably, and INAD should be considered. Woodhouse-Sakati syndrome should also readily distinguish itself with the endocrine abnormalities not observed in other forms of NBIA. Within the late-onset NBIA population, those with aceruloplasminemia should also be distinguishable based on the common findings of diabetes and iron accumulation in the liver. Because neuroferritinopathy is the only known autosomal-dominant form of NBIA, pedigree analysis may help point toward this diagnosis, although family history information is frequently limited. Cystic degeneration in the pallida and putamen, or cavitation, is also unique to neuroferritinopathy.

Treatment

Identification of therapeutic targets that could slow NBIA progression, or even reverse it, remains a goal, and progress has been made over the past year in this area. However, pharmacologic and surgical interventions are still primarily aimed at palliation of symptoms. In our experience, several of the interventions that offer initial improvement of clinical symptoms have a limited period of benefit. Baclofen and trihexyphenidyl remain the most effective drugs for disabling dystonia and spasticity. Botulinum toxin can be useful for individuals whose quality of life is improved significantly by treating a specific area, such as limb, facial, or orobuccolingual muscles. Patients with PKAN do not benefit from levodopa, whereas those with late-onset dystonia-parkinsonism, parkinsonism, or the rare Kufor-Rakeb syndrome are likely to have a dramatic response initially that appears to be short-lived. Those with other forms of NBIA and prominent parkinsonism will sometimes respond to levodopa and may receive more long-term benefit. In recent years tetrabenazine has become more widely available and has been used in this patient population with mixed results, suggesting that it is a reasonable consideration for patients who have exhausted other options.

Placement of an intrathecal baclofen pump may be considered when oral doses are no longer sufficient to control symptoms. An intraventricular technique has been developed and used in at least one PKAN patient with a good short-term outcome [46]; the long-term effects still need to be determined. Deep brain stimulation (DBS) is now more commonly used in NBIA. Six cases of PKAN treated with DBS have been reported in the literature with generally favorable short-term results [47–49]. Although anecdotal evidence and a case report by Krause et al. [49] suggest that benefits decrease over time, DBS can provide relief to patients experiencing extreme dystonia and spasticity.

The chelating agent deferiprone has gained attention since it was reported to remove labile iron from the dentate nuclei and reduce neurologic symptoms in patients with Friedreich's ataxia [50]. In NBIA, it is not clear whether iron accumulation is a primary problem or a downstream effect of the disease process. Anecdotal evidence from a limited number of patients in the United States taking deferiprone suggests it may provide benefit. A small, 6-month trial in PKAN patients was recently completed in Italy (Nardo Nardocci, personal communication). Results have not yet been published, but will speak mainly to safety and short-term effects due to the trial's duration. A larger, multisite, international trial is currently being proposed.

Toward rational therapeutics, the compound pantetheine was recently identified by Rana et al. [51] as a therapeutic target based on work in a *Drosophila* model of PKAN. Further investigation in mice has suggested that oral doses of pantetheine are unlikely to cross the blood–brain barrier in humans. For some time anecdotal evidence has also suggested that oral pantothenate can provide some clinical benefit to individuals with atypical PKAN who likely have some residual enzyme activity.

Conclusions

Significant progress has been made in identifying new NBIA genes and recognizing the expanding phenotypes within this category. Determining how the common pathways among these genes and their proteins intersect, with consideration to lipid, iron, and energy metabolism, will lead to a better understanding of disease pathogenesis and lead us toward new therapeutic targets.

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Table 1

Distinguishing features of the NBIA subtypes

Findings	PKAN	INAD	Atypical 2NAD	Early-onset parkinsonism	FAHN	Kufor-Rakeb	Woodhouse-Sakati	ACP	NFT	SENDA
Neurologic										
Dystonia	+	−	+	Variable	+	+	+	+	+	+
Parkinsonism	Variable	−	Variable	+	−	+	−	−	Variable	+
Psychiatric symptoms	Variable	−	Variable	+	−	+	−	−	+	+
Onset	Child or adult	Infancy	Child	Adult	Child	Adult	Child	Adult	Adult	Child
MRI										
Iron deposition	GP, SN	GP variable	GP, SN	Variable SN & striatum	GP, SN	Variable GP, putamen, caudate lenticular nucleus	GP, SN	All BG	GP, putamen, caudate, dentate, thalamus	GP, SN
White matter involvement	−	Variable	Variable	Variable	+	−	+	+	+	Variable
Cerebellar atrophy	−	+	+	−	+	+	−	+	+	−
Eye-of-the-tiger sign	+	−	−	−	−	−	−		Rarely	−
Gene	*PANK2*	*PLA2G6*	*PLA2G6*	*PLA2G6*	*FA2H*	*ATP13A2*	*C2orf37*	*CP*	*FTL*	Unknown

ACP— aceruloplasminemia; BG— basal ganglia; FAHN— fatty acid hydroxylase-associated neurodegeneration; GP— globus pallidus; INAD—infantile neuroaxonal dystrophy; NAD— neuroaxonal dystrophy; NBIA— neurodegeneration with brain iron accumulation; NFT—neuroferritinopathy; PKAN— pantothenate kinase-associated neurodegeneration; SENDA— static encephalopathy of childhood with neurodegeneration in adulthood; SN— substantia nigra.