Neurodegeneration with Brain Iron Accumulation

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Abstract
Neurodegeneration with brain iron accumulation (NBIA, formerly Hallervorden-Spatz syndrome) encompasses a group of rare neurodegenerative disorders transmitted in an autosomal recessive fashion. An estimated prevalence of 1-3/1,000,000 has been suggested based on observed cases in a population. Since the recent discovery of the major genetic defect causing NBIA, this heterogeneous group of disorders can now be differentiated by clinical, radiographic, and molecular features. The hallmark features of NBIA include progressive extrapyramidal dysfunction (dystonia, rigidity, choreoathetosis) and iron accumulation in the brain, primarily in the basal ganglia. Brain MRI is standard in the diagnostic evaluation of all forms of NBIA. Approximately half of the patients given a clinical diagnosis of NBIA are found to have identifiable mutations in the PANK2 gene, which causes pantothenate kinase-associated neurodegeneration, or PKAN. At this time most treatments for NBIA are palliative. Research is currently underway to identify additional NBIA genes and improve treatment possibilities by characterizing the underlying causes of these disorders.

Key-words
Dystonia, basal ganglia, pantothenate kinase-associated neurodegeneration, PKAN, Hallervorden-Spatz syndrome, neurodegeneration with brain iron accumulation, NBIA

Disease Name/Synonyms

- Neurodegeneration with brain iron accumulation (NBIA)
- Hallervorden-Spatz syndrome
- Pantothenate kinase-associated neurodegeneration (PKAN)

NBIA encompasses a group of progressive extrapyramidal disorders characterized by radiographic evidence of iron accumulation in the brain, usually in the basal ganglia (Hayflick *et al.,* 2003). The term NBIA is already in use in the medical literature (Arawaka *et al.*, 1998; Bruscoli *et al*., 1998; Galvin *et al*., 2000;

Neumann *et al*., 2000; Swaiman 2001; Zhou *et al*., 2001) and is sufficiently broad to cover the spectrum of disorders previously called Hallervorden-Spatz syndrome and additional disorders of high brain iron, including neuroferritinopathy and aceruloplasminemia. The major form of NBIA is pantothenate kinase-associated neurodegeneration, or PKAN, caused by mutations in the *PANK2* gene (Zhou *et al*., 2001).
The original eponym for this group of disorders acknowledges the work of neuropathologists Julius Hallervorden and Hugo Spatz (Hallervorden *et al.*, 1922). The new term NBIA is now favored in light of the unethical activities of Hallervorden and Spatz before and during World War II (Shevell 1992).

Definition/Diagnostic criteria
The category of NBIA consists of disorders in which there is progressive extrapyramidal disease with brain iron accumulation, usually in the basal ganglia. The subgroups of NBIA include PKAN, HARP syndrome, aceruloplasminemia, neuroferritinopathy, and, by exclusion, NBIA of unknown cause. This review will mainly focus on PKAN, which accounts for the majority of NBIA cases.

PKAN
Suspicion of PKAN often arises when characteristic radiographic MRI changes are demonstrated in a patient with suggestive clinical features. Following the discovery of the *PANK2* gene, Hayflick *et al* (Hayflick *et al*., 2003) delineated two clinical forms of PKAN, the classic form and an atypical form, based on age at onset and rate of disease progression. The diagnostic criteria continue to evolve to reflect the distinctions between PKAN and other forms of NBIA.

Hallmark features of PKAN
Extrapyramidal dysfunction, including one or more of the following:

- Dystonia
- Rigidity
- Choreoathetosis

Onset

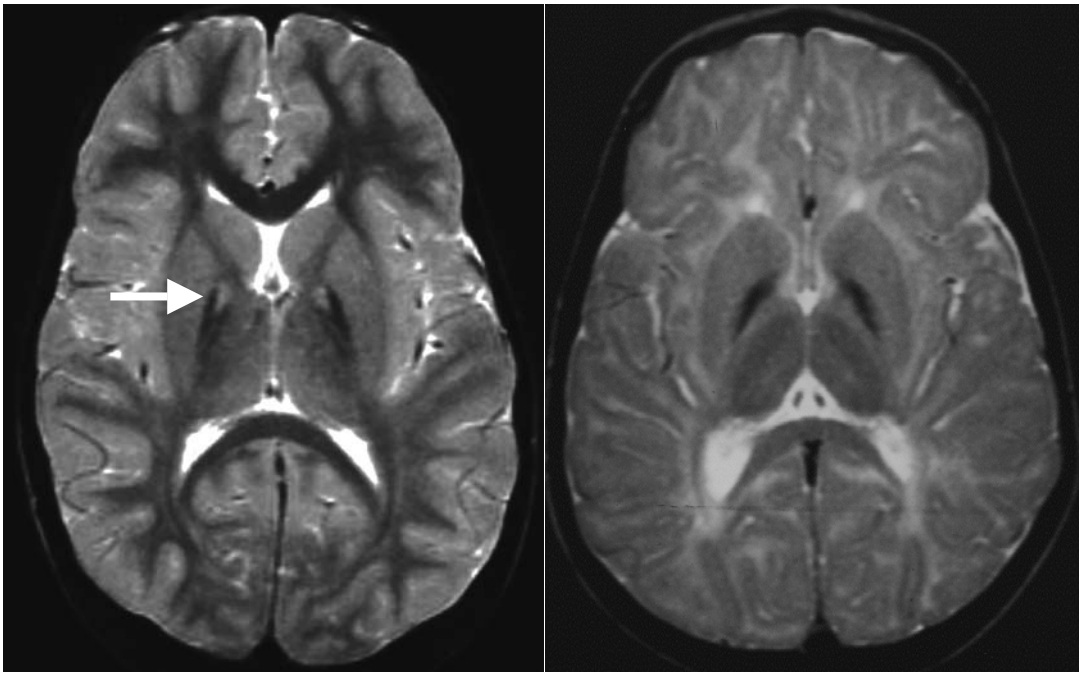
- Classic form usually presents in first decade of life;
- Atypical form presents more commonly in the second or third decade of life.

Loss of ambulation

- Classic form: often occurring within 10-15 years of onset
- Atypical form: often occurring within 15-40 years of onset

'Eye of the tiger' sign on T2-weighted magnetic resonance imaging (1.5 Tesla or greater). To date this has been observed in all patients with one or two *PANK2* mutations (Hayflick *et al*., 2003) (**Figure 1**).

Figure 1. Brain MRI of the globus pallidi: Left image shows the 'eye of the tiger' change characteristic of PKAN, whereas the image on the right shows only globus pallidus hypointensities, consistent with iron deposition and supporting a diagnosis of NBIA.



Corroborative features

- Corticospinal tract involvement
    - Spasticity
    - Extensor toe signs

- Retinal degeneration or optic atrophy. In early-onset, rapidly progressive (classic) PKAN, two-thirds of affected individuals demonstrate pigmentary retinopathy (Hayflick *et al.*, 2003), a much higher fraction than was previously reported (Roth *et al*., 1971; Newell *et al*., 1979; Luckenbach *et al*., 1983). Although this feature occurs early in disease, retinopathy is not often recognized until a full diagnostic evaluation, including electroretinogram (ERG) and visual field testing, is performed.
- Red blood cell acanthocytosis. Red blood cell (RBC) acanthocytes have been reported in a subset of individuals with PKAN (Roth *et al*., 1971; Swisher *et al.*, 1972; Luckenbach *et al*., 1983; Higgins *et al*., 1992; Tripathi *et al*., 1992). Confirmation of erythrocyte morphology by scanning electron microscopy may be helpful if available.
- Low or absent plasma pre-beta lipoprotein fraction (see HARP syndrome).
- Family history consistent with autosomal recessive inheritance (may include consanguinity).

NBIA Exclusionary features

- Abnormalities of copper metabolism or other evidence of Wilson disease
- Evidence of neuronal ceroid lipofuscinosis by electron microscopy, enzymatic assay or the presence of a DNA mutation in any of the six genes associated with this condition.
- Family history of Huntington disease or other dominantly inherited movement disorder
- Caudate atrophy
- ß-hexosaminidase A deficiency or GM1-galactosidase deficiency

NBIA Pathological Diagnosis

Before the availability of MRI, NBIA was a post-mortem diagnosis. The neuropathologic literature is limited by the heterogeneity of conditions grouped under this diagnosis(Halliday 1995). Hallervorden-Spatz syndrome was initially characterized by the appearance of rust-brown pigmentation in the globus pallidus and the reticular zone of the substantia nigra. Iron is the major component of this pigment (Hallervorden 1924). In PKAN, the accumulation of iron is specific to the globus pallidus and substantia nigra. These areas contain approximately three times the normal amount of iron. Systemic iron metabolism is normal (Kornyey 1964; Volkl *et al*., 1972; Dooling *et al*., 1974; Vakili *et al*., 1977) and a global increase in brain iron is not seen (Spatz 1922). In regions of iron accumulation, spheroid bodies are also seen (Koeppen *et al*., 2001). Axonal spheroids are thought to represent swollen axons, possibly secondary to defects in axonal transport. They are not limited to those portions of brain in which iron accumulates.

Differential Diagnosis

PKAN can be distinguished from the other cases of NBIA by the changes on brain MRI. In most patients with non-PKAN NBIA, the globus pallidus is uniformly hypodense on T2-weighted images (see **Figure 1**). This change indicates high iron content; however, it is distinct from the 'eye of the tiger' sign and is not seen in association with *PANK2* mutations. Iron deposition in the red nucleus and dentate nucleus in conjunction with cerebellar atrophy are common in the non-PKAN NBIA group. Seizures are also more prominent in these individuals but rarely occur in PKAN. Sea blue histiocytes in bone marrow, historically a feature of Hallervorden-Spatz syndrome, do not occur in PKAN, but may be observed in other forms of NBIA.

A distinct sub-group of individuals with non-PKAN NBIA have early developmental delay with moderate-to-severe mental retardation diagnosed in early childhood. They may have spasticity and often are diagnosed with cerebral palsy. Their disease is static until late childhood or, more commonly, adolescence or early adulthood. With no clear inciting event, these individuals experience a sudden and rapid deterioration usually marked by prominent dystonia. At this later stage, brain MRI changes associated with NBIA may be seen. The gene causing this form of NBIA has not yet been identified.

Patients with aceruloplasminemia have additional iron accumulation in the visceral organs and develop diabetes relatively early in disease progression. They have retinal degeneration with characteristic yellow opacities in the retinal pigment epithelium.

Neuroferritinopathy typically presents with involuntary movements in the fourth to fifth decade of life and does not exhibit the marked dysarthria observed in PKAN.

The presence of impulsivity and other behavioral changes without dysarthria could point towards a primary psychiatric illness. For all of the disorders in this category, T2-weighted MRI would distinguish NBIA.
Other disorders to consider are:

- Neuronal ceroid lipofuscinosis
- Childhood-onset hereditary ataxias (especially SCA3 and SCA7)
- Dystonias such as DYT1 and Leigh syndrome
- Neuroacanthocytosis syndromes
- Juvenile Huntington disease
- Choreoacanthocytosis
- Infantile neuroaxonal dystrophy
- Lesch-Nyhan syndrome
- Wilson disease
- Recessive hereditary spastic paraplegia
- Juvenile-onset neuroaxonal dystrophy
- Tourette syndrome

Etiology

Most known forms of NBIA are inherited in an autosomal recessive fashion. Because NBIA is rare, consanguinity is not uncommon in the families of affected individuals.
PKAN is attributed to a deficiency or absence of pantothenate kinase 2, which is encoded by *PANK2* on chromosome 20p13-p12.3, one of four human pantothenate kinase genes. Pantothenate kinase is an essential regulatory enzyme in CoA biosynthesis, catalyzing the cytosolic phosphorylation of pantothenate (vitamin B5), N-pantothenoyl-cysteine, and pantetheine. Pantothenate kinase deficiency is thought to cause accumulation of N-pantothenoyl-cysteine and pantetheine, which may cause cell toxicity directly or via free radical damage as chelators of iron (Yang *et al*., 2000; Yoon *et al.*, 2000). Deficient pantothenate kinase 2 is also predicted to result in CoA depletion and defective membrane biosynthesis in those tissues in which this is the major pantothenate kinase or in tissues with the greatest CoA demand. Rod photoreceptors continually generate membranous discs; therefore, the retinopathy frequently observed in classic PKAN may be secondary to this deficit. The biochemical perturbations leading to clinical sequelae are still not completely understood and require further investigation.
HARP syndrome is now considered to represent part of the PKAN disease spectrum. Mutations in the *PANK2* gene have been identified in the only two families reported with HARP syndrome (Ching *et al.*, 2002; Houlden *et al*., 2003).
Aceruloplasminemia is caused by mutations in the gene encoding ceruloplasmin (Gitlin 1998).
Neuroferritinopathy is caused by mutations in the *ferritin light chain* gene (Curtis *et al*., 2001).
The remaining fraction of NBIA is assumed to be caused by one or more genes that remain to be discovered. Studies are currently underway to identify the next NBIA gene.

Diagnostic Methods

Brain MRI is standard in the diagnostic evaluation of all forms of NBIA (Tanfani *et al.*, 1987; Mutoh *et al*., 1988; Sethi *et al*., 1988). MRI was the first clinical test to enable pre-mortem diagnosis of NBIA. The radiographic changes that have been associated with NBIA are high iron in the basal ganglia, seen as hypointense lesions in the globus pallidus and substantia nigra pars reticulata on T-2 weighted images (see Figure 1) (Drayer 1987) (Tanfani *et al*., 1987; Mutoh *et al*., 1988; Sethi *et al*., 1988).
MRI can distinguish changes that are more specifically recognized as indicative of PKAN with the 'eye of the tiger' sign. This is a characteristic radiographic sign defined on coronal or transverse T-2 weighted images of the globus pallidus as a central region of hyperintensity surrounded by a rim of hypointensity (Sethi *et al*., 1988). This specific change is highly correlated with the presence of a *PANK2* mutation in both classic and atypical disease (Hayflick *et al*., 2001). Brain MRI is sensitive and specific and can be used in clinical care to identify those patients in whom *PANK2* molecular genetic testing is indicated. It has also accurately predicted PKAN in presymptomatic siblings of patients (Hayflick *et al.*, 2001). In atypical PKAN, the same brain MRI changes are seen as in classic, early-onset PKAN. These changes usually are evident early in disease. Patients diagnosed with HARP syndrome also have the 'eye of the tiger' sign.
Molecular testing for PKAN focuses on identifying mutations within the *PANK2* coding sequence (Westaway *et al*., 2002). The *PANK2* gene comprises seven exons, and deleterious mutations have been found in all of them. Several splice site mutations have also been identified. Two specific sequence variations account for one-third of patient mutations: G411R and T418M. Of the remaining mutations, none occurs in more than 3% of patients, with the majority being unique to each individual family.
Approximately 50% of individuals with clinical evidence of NBIA are predicted to have mutations of the *PANK2* gene (International Registry of PKAN and Related Disorders, Hayflick). To date at least one *PANK2* mutation has been identified in all patients who have a true 'eye of the tiger' sign. A single identified *PANK2* mutation in the presence of the 'eye of the tiger' sign should be considered confirmatory of PKAN. Approximately 23% of families with PKAN have known or suspected consanguinity

and 33% of families with PKAN demonstrate homozygous *PANK2* mutations. Preliminary evidence suggests that large intragenic deletions may account for some of the mutations missed by sequencing; however, these alleles have not yet been fully characterized.
Aceruloplasminemia is a disorder of iron metabolism caused by lack of ceruloplasmin ferroxidase activity resulting from mutations in the *CP* gene that encodes ceruloplasmin. The diagnosis of aceruloplasminemia in a symptomatic individual relies upon the absence of serum ceruloplasmin and some combination of the following: low serum copper concentration, low serum iron concentration, high serum ferritin concentration, and increased hepatic iron concentration. The diagnosis is supported by characteristic MRI findings of abnormal low intensities reflecting iron accumulation in the brain (striatum, thalamus, dentate nucleus) and liver on both T1- and T2-weighted images. Molecular genetic testing of the *CP* gene (chromosomal locus 3q23-q24) is available on a research basis.
Neuroferritinopathy is caused by mutations in the ferritin light chain (*FTL*) located on chromosome 19q13.3-q13.4 (Curtis *et al*., 2001). Molecular genetic testing is available on a research basis.

Epidemiology
No reliable prevalence data have been collected on this rare disorder. An estimate of 1-3/1,000,000 has been suggested based on observed cases in a population, assuming a small number of misdiagnoses and missed cases. This figure would imply a general population carrier frequency of one in 275-500. At this time, a discernable increased incidence has not been identified in any specific ethnic group.

Clinical Description
Classic PKAN
The neurologic signs and symptoms of early-onset, rapidly progressive (classic) PKAN are primarily extrapyramidal and include dystonia, dysarthria, and rigidity. Dystonia is always present and usually is an early manifestation. Cranial and limb dystonia are frequent and may lead, respectively, to recurrent trauma to the tongue, in some cases requiring full mouth dental extraction, or atraumatic long bone fracture from the combination of extreme bone stress and osteopenia. Corticospinal tract involvement is common and includes spasticity, hyperreflexia, and extensor toe signs. Seizures are rare. Intellectual impairment may or may not be a major feature of PKAN. Pigmentary retinal degeneration occurs in two-thirds of affected individuals with classic PKAN. The retinal degeneration follows a typical clinical course, with nyctalopia (night blindness) followed by progressive loss of peripheral visual fields and sometimes eventual blindness. Optic atrophy is occasionally seen in PKAN.
The clinical features of classic PKAN are remarkably homogeneous. It presents in early childhood, usually before six years of age (mean age 3.4 years). The most common presenting symptom is impaired gait due to a combination of lower extremity rigidity, dystonia, and spasticity, as well as restricted visual fields in those children with retinopathy. Some children have developmental delay, which is primarily motor but occasionally global. Visual symptoms may bring children with PKAN to medical attention. Toe-walking and upper extremity dystonia are less common presenting signs.
PKAN is a progressive disorder and the rate of progression correlates with age at onset; those with early symptoms decline more rapidly. As the disease advances, dystonia and spasticity compromise the child's ability to ambulate, and most of those with early-onset disease are wheelchair-bound by mid-teens. For some, this occurs much earlier. PKAN progresses at a non-uniform rate. Affected individuals experience episodes of rapid deterioration, often lasting one to two months, interspersed with longer periods of stability. Common causes of stress and catabolism do not seem to correlate with periods of decline, a phenomenon for which no cause has been found. Lost skills usually are not regained.
Premature death does occur; however, lifespan is variable. With improvements in medical care, a greater number of affected individuals are living into adulthood. Orofacial dystonia can result in the secondary effects of swallowing difficulty and poor nutrition. Premature death is more likely related to these secondary effects (e.g. nutrition-related immunodeficiency, aspiration pneumonia) rather than the primary neurodegenerative process.

Atypical PKAN
The clinical features of late-onset, slowly progressive PKAN are more varied than those of early-onset disease. By definition, onset is later, progression is slower and presenting features are distinct, usually involving speech as either the sole presenting feature or part of the constellation of problems. Onset is in the first three decades (mean age 13.6 years). The speech defects include palilalia (repetition of words or phrases), tachylalia/tachylogia (rapid speech of words and/or phrases), and dysarthria (poor articulation, slurring) (Benke *et al*., 2000; Benke *et al*., 2001). Psychiatric symptoms, including personality changes with impulsivity and violent outbursts, depression, and emotional

lability are common in late-onset disease (Szanto *et al*., 1966; Williamson *et al*., 1982; Morphy *et al*., 1989). Patients may also exhibit motor and verbal tics. As with early-onset disease, cognitive impairment may be part of the late-onset PKAN phenotype, but additional investigations are needed. Motor involvement is usually a later feature, although individuals with motor involvement often have been described as clumsy in childhood and adolescence. Spasticity, hyperreflexia, and other signs of corticospinal tract involvement are common and eventually limit ambulation. Conspicuously reminiscent of Parkinson disease, some individuals demonstrate "freezing" during ambulation, especially when turning corners or encountering surface variations (Guimarães *et al*., 1999). Retinopathy is rare in late-onset disease (Coppeto *et al*., 1990), and optic atrophy has not been associated with atypical disease.

HARP syndrome

Hypoprebetalipoproteinemia, acanthocytosis, retinopathy, and pallidal degeneration (HARP) refers to a disorder now known to fall within the phenotypic spectrum of PKAN. The two HARP families reported in the literature have been shown to have *PANK2* mutations (Ching *et al.*, 2002; Houlden *et al*., 2003).

NBIA

NBIA includes patients who meet the diagnostic criteria for PKAN, with the exception of the 'eye of the tiger' sign and mutations in the *PANK2* gene or the other two genes known to cause NBIA (*CP, FTL*). Despite the known heterogeneity in this group, there are certain characteristics that distinguish these patients from those with PKAN, including brain MRI imaging. In NBIA, the globus pallidus is uniformly hypointense on T2-weighted images. This change indicates high iron, but is distinct from the 'eye of the tiger' sign. Iron deposition in the dentate nucleus and red nucleus is observed only in NBIA. Functional and radiographic abnormalities in other regions of the brain, particularly cerebellar atrophy, are common in NBIA and rare in PKAN. Finally, seizures are a prominent finding in patients with NBIA but rarely occur in those with PKAN.

Neuroferritinopathy

Neuroferritinopathy is an autosomal dominant, late-onset basal ganglia disease. It presents with extrapyramidal features similar to Huntington disease, including choreoathetosis, dystonia, spasticity, and rigidity (Curtis *et al*., 2001). It is not associated with significant cognitive decline or cerebellar involvement.

Aceruloplasminemia

Aceruloplasminemia is an autosomal recessive condition characterized by iron accumulation in the brain and visceral organs. A classic triad of retinal degeneration, diabetes mellitus, and neurological disease distinguishes it from other NBIA disorders (Miyajima *et al*., 1987; Logan *et al*., 1994; Morita *et al*., 1995; Miyajima *et al.*, 1996). Onset usually occurs between 25 and 60 years.

Genetic Counseling

Mode of Inheritance

Pantothenate kinase-associated neurodegeneration (PKAN) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

The parents of an affected child are obligate heterozygotes (carriers), and, therefore, carry one mutant allele.

Heterozygotes have no symptoms.

To date, no *de novo* mutations or cases of germline mosaicism have been documented.

Sibs of a proband

At conception, sibs of a proband have a 25% chance of being affected, a 50% chance of being an unaffected carrier, and a 25% chance of being unaffected and not a carrier.

Once an at-risk sib is known to be unaffected (*i.e*., an at-risk sib who is asymptomatic beyond the typical age of onset), the risk of his/her being a carrier is 2/3.

Offspring of a proband

To date, reproduction among probands is rare.

The offspring of an individual with PKAN are obligate heterozygotes (carriers).

The offspring are at risk to be affected only if the proband's reproductive partner is a carrier for a disease-causing mutation.

Other family members

Sibs of the proband's parents are at 50% risk of also being carriers.

Carrier detection

Carrier testing for at-risk family members is available on a clinical basis once the mutation(s) have been identified in the proband.

Research opportunities for families

Efforts have been made to expand biochemical, clinical, and pathologic research for this condition. The NBIA Disorders Association has information about coordinating donations to brain banks in memory of deceased patients to enable more detailed brain studies in the future. The

NBIA Disorders Association may have additional information about other research interests in which families may choose to participate.

Antenatal Diagnosis

Prenatal diagnosis for pregnancies at 25% risk for NBIA is possible when at least one mutation has been identified in the proband. DNA is extracted from fetal cells obtained by amniocentesis usually performed at about 15-20 weeks' gestation or chorionic villus sampling (CVS) at about 10-13 weeks' gestation.

Management/Treatment

Therapies that have been tried to manage the dystonia in some affected individuals with varying success include intramuscular Botulinum toxin and intrathecal baclofen (Albright *et al*., 1996). Ablative pallidotomy or thalmotomy have resulted in transient benefit for some people, although the dystonia does return, usually about one year following surgery (Tsukamoto *et al.*, 1992; Justesen *et al*., 1999). Deep brain stimulation has been used on a very limited basis with possible benefit. Studies are currently underway to determine the effects of deep brain stimulation. Oral medications that seem to provide the most relief include baclofen and trihexyphenidyl. Iron chelating agents have been tried without clear benefit (Dooling *et al.*, 1974; Albright *et al.*, 1996). Trials have been limited by the development of systemic iron deficiency before any clinical neurological benefits were evident. Therapies that may have a role in other forms of NBIA but generally do not help individuals with PKAN include levodopa/carbidopa and bromocriptine.

Affected individuals with recurrent tongue-biting from severe orobuccolingual dystonia often come to full mouth dental extraction as the only effective intervention; bite-blocks and other more conservative measures usually fail. Assurance of adequate nutrition through swallowing evaluation and regular dietary assessments is important. Placement of gastrostomy tube may be necessary once the patient can no longer maintain an adequate diet orally.

As the disease progresses, episodes of extreme distress may last for days or weeks. It is especially important during these episodes to evaluate for treatable causes of pain. These may include occult GI bleeding, urinary tract infections, and bone fractures. The combination of osteopenia in a non-ambulatory patient with marked stress on long bones from dystonia makes people with NBIA at especially high risk of fractures without apparent trauma.

The existence of residual enzyme activity in some affected individuals with PKAN raises the possibility of treatment using high dose pantothenate, the *PANK2* enzyme substrate. Pantothenate has no known toxicity in humans; high oral doses of panthothenic acid or calcium pantothenate (up to ten grams per day for several weeks) do not appear to be toxic to humans. The efficacy of pantothenate supplementation in ameliorating symptoms is currently unknown. Based on the role of coenzyme A (CoA) in the synthesis and degradation of fatty acids, the importance of docosahexanoic acid (DHA) as a major component of rod photoreceptor disc membranes, and the observation of retinal degeneration in a large portion of individuals with PKAN, there may be a role for DHA in preventing this complication, although no studies have yet been performed. The compound may be provided as an oral nutritional supplement in the form of omega-3-fats (fish oil) and is without known toxicity.

Unresolved questions

Several questions related to NBIA remain to be answered. Although PKAN accounts for approximately 50% of cases of NBIA, the causative gene or genes for the remainder have not yet been identified. Much is now understood about PKAN and the role of pantothenate kinase 2 in the CoA pathway, but the underlying cause of this disorder has not yet been characterized. As progress is made in this area, better treatments will emerge.

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