

## Overview of Neurodegeneration with Brain Iron Accumulation (NBIA) Disorders

### **What is NBIA?**

Neurodegeneration with Brain Iron Accumulation is a group of inherited neurological disorders characterized by abnormal accumulation of iron in the basal ganglia. The basal ganglia is a collection of structures deep within the base of the brain that assist in regulating movements.

The exact relationship between iron accumulation and the symptoms of NBIA is not fully understood. Although we all normally have iron in this area, people with NBIA have extra iron that can be seen on MRI (magnetic resonance imaging). Certain MRI views (T2-weighted images) show the iron as dark regions in the brain. High brain iron is most often seen in the part of the basal ganglia called the globus pallidus. It is also often seen in another part called the substantia nigra.

NBIA is progressive and, at this time, there is no cure.

### **Characteristics of the disorders**

The hallmark clinical manifestations of NBIA relate to the body's muscle function and feature a progressive movement disorder. There are several descriptive terms for the neuromuscular symptoms associated with all forms of NBIA.

Dystonia describes involuntary muscle cramping that may force certain body parts into unusual, and sometimes painful, movements and positions.

Choreoathetosis is a condition characterized by involuntary, rapid, jerky movements (chorea) occurring in association with relatively slow, sinuous, writhing motions (athetosis).

In addition, there may be stiffness in the arms and legs because of continuous resistance to muscle relaxing (spasticity) and abnormal tightening of the muscles (muscular rigidity). Spasticity and muscle rigidity usually begin in the legs and later develop in the arms.

Parkinsonism is a condition marked by tremor, slowness, rigidity and poor balance. As affected individuals age, they may eventually lose control of voluntary movements. Muscle spasms combined with decreased bone mass can result in bone fractures not caused by trauma or accident.

Dystonia affects the muscles in the mouth and throat, which may cause poor articulation and slurring (dysarthria), and difficulty swallowing (dysphagia). The progression of dystonia in these muscles can result in loss of speech as well as uncontrollable tongue-biting.

Specific forms of dystonia that may occur in association with NBIA include blepharospasm and torticollis. Blepharospasm is a condition in which the muscles of the eyelids do not function properly, resulting in excessive blinking and involuntary closing of the eyelids. Torticollis is a condition in which there are involuntary contractions of neck muscles resulting in abnormal movements and positions of the head and neck.

Most forms of NBIA involve eye disease. The most common problems are degeneration of the retina and optic atrophy. The retina is a thin membrane that lines the back of the eyeball; it helps the eye perceive an image and send it into the brain. In NBIA, early signs of retinal degeneration may be poor night vision or tunnel vision. It can eventually cause significant loss of vision.

Optic atrophy affects the optic nerve, which sends messages between the retina and the brain. The optic nerve is like a cable with thousands of tiny electrical wires, each carrying some visual information to the brain. When the nerve is damaged or breaks down, vision can become blurry, side vision or color vision may be abnormal, the pupil may not work properly, or there may be decreased lightness in one eye compared to the other. Eventually, optic atrophy can cause blindness.

A general loss of brain cells and tissue also are frequently observed, conditions called cerebral atrophy and cerebellar atrophy.

Some forms of NBIA involve delays in development, mainly pertaining to motor skills (movement). Although cognitive decline occurs in some types of the disorder, more often thinking, perception and other mental processes are relatively spared. Intellectual testing may be hampered by the movement disorder; therefore, newer methods of studying intelligence are necessary to determine if there are cognitive features involved.

Onset of NBIA ranges from infancy to adulthood. Progression can be rapid or slow with long periods of stability. Symptoms may vary greatly from case to case, partly because the genetic cause may differ between families. Also, different changes (mutations) within a gene could lead to a more or a less severe presentation.

The factors that influence disease severity and the rate of progression are still unknown. Usually individuals with NBIA develop increasing disabilities during the course of the disease. As the disease progresses, adjustments commonly need to be made to medications and other treatments. It may take several tries before the best combination is found.

Auxiliary devices could become necessary and may include wheelchairs and devices that help with speech.

Individuals with NBIA also all share a finding in the nerve cells that can only be detected by performing electron microscopy on nerve tissue obtained from a biopsy. Nerve cells have long extensions, called axons that transmit messages from one nerve cell to the next. In NBIA, some axons are found to be swollen with collections of cellular debris or "junk" that should not be there. These swellings are called spheroids, spheroid bodies or axonal spheroids. In most forms of NBIA, spheroids are only located in the nerves of the brain and spinal cord. Therefore, they are usually not detected until an autopsy is performed on someone who has passed away.

In infantile neuroaxonal dystrophy, or INAD, however, spheroids are also found in nerves throughout the body and a biopsy can be done on skin, muscle, or other tissue to look for them. In a few cases of MPAN, spheroids have also been found in peripheral nerves.

## History

Before 2001, NBIA was called Hallervorden-Spatz disease or syndrome. Researchers changed the name to reflect more closely the characteristics of the disorder and to dissociate from the prior name of two unethical Nazi doctors who identified and studied the disorder.

All forms of NBIA were included under the Hallervorden-Spatz name until 2001, when the first NBIA gene was discovered. That gene causes the most common form of NBIA — Pantothenate Kinase-Associated Neurodegeneration, or PKAN.

Over the years, more genes and disorders have since become a part of the NBIA family. In 2006, the *PLA2G6* gene was discovered and another NBIA disorder was identified, now known as PLA2G6-Associated Neurodegeneration, or PLAN.

In 2011, the gene *C19orf12* was identified as being responsible for Mitochondrial-membrane Protein-Associated Neurodegeneration, or MPAN.

Soon after, in 2012 another disorder was put under the NBIA umbrella — Beta-propeller Protein-Associated Neurodegeneration, or BPAN.

These four subtypes of NBIA are considered the most frequent and are identifiable by their varying symptoms and associated gene changes.

Five other rarer disorders are also under the NBIA umbrella, bringing the current total to nine.

All NBIA disorders have separate symptoms and identifying markers but are alike in that they have iron accumulation in the basal ganglia of the brain and are characterized by a progressive movement disorder. Researchers expect this number to continue growing as more genes are discovered.

Affected individuals who have the clinical symptoms of NBIA but no genetic confirmation are considered to have idiopathic NBIA, or NBIA of unknown origin.

## Genetics

Of the nine forms of NBIA currently identified, all but two are recessive. Because most of our genes exist in pairs (one coming from the mother and one coming from the father), we normally carry two working copies of each gene. When one copy of a recessive gene has a change (mutation) in it, the person should still have normal health. That person is called a carrier.

Recessive diseases only occur when both parents are carriers for the same condition and then pass their changed genes on to their child. Statistically, there is a one in four chance that two carriers would have an affected child. There is a two in four chance the parents would have a child who is also a carrier, and there's a one in four chance they would have a child who did not receive the gene mutation.

Neuroferritinopathy is a dominant condition. A person affected with neuroferritinopathy has one working copy and one copy of the gene that is mutated. This single mutation is enough to cause the disease. There is a 50 percent chance that an affected individual will pass the gene change on to any of his or her children. Most affected individuals have one parent who is also affected.

Beta-propeller Protein-Associated Neurodegeneration is thought to occur de novo, meaning there is an alteration in a gene that is new in the affected individual and was not inherited from either parent. This can happen in a germ cell (egg or sperm) from one of the parents or in the fertilized egg itself. In the case of BPAN, the gene sits on the X chromosome, one of the two chromosomes that determine sex.

### **Affected Population**

Overall, NBIA affects males and females in equal numbers (BPAN occurs more frequently in females). The frequency of NBIA in the general population is estimated between one to three people per 1 million individuals.

Because rare disorders like NBIA often go unrecognized, these disorders may be underdiagnosed or misdiagnosed, making it difficult to determine the accuracy of these estimates.

### **Therapies**

Treatment of NBIA is directed towards the specific symptoms that appear in each individual. Research is focusing on a better understanding of the underlying causes of NBIA, which may eventually reveal a more comprehensive treatment.

Treatment may require the coordinated efforts of a team of specialists. Physicians with whom the family may work include the pediatrician or internist, neurologist, pulmonologist, ophthalmologist, orthopedist, gastroenterologist and clinical geneticist.

A team approach to supportive therapy may include physical therapy, exercise physiology, occupational therapy and speech therapy. In addition, many families may benefit from genetic counseling.

One of the most consistent forms of relief from dystonia is baclofen. This medication is first taken orally. A baclofen pump has been used to administer regular doses automatically into the spinal fluid. The pump may be an option for some NBIA individuals, and an evaluation can be done to determine the likelihood that they would respond positively to a pump.

The anti-cholinergic agent trihexyphenidyl (trade name in some countries is Artane) is a second medication that may be taken alone or in combination with baclofen. The combination of baclofen and artane has been found useful for many people with PKAN.

Levodopa/carbidopa (Sinemet) has been helpful for some patients with idiopathic NBIA, although it has not appeared to be helpful for PKAN patients.

Further muscle-relaxing medication include benzodiazepines such as diazepam (trade name in some countries is Valium) and lorazepam (trade name in some countries is Ativan). Efficacy and tolerability may vary from patient to patient.

Individuals experiencing seizures usually benefit from standard anti-convulsive drugs. In addition, standard approaches to pain management are generally recommended where there is no identifiable treatment for the underlying cause of pain.

Many individuals with NBIA have ongoing constipation due to decreased activity, diet and/or medication side-effects. Over-the-counter fiber supplements and stool softeners can often improve the discomfort.

Drugs that reduce the levels of iron in the body (iron chelation) are being studied for effectiveness in treating NBIA. Some studies have shown the drug deferiprone to be helpful for some NBIA individuals. More comprehensive clinical trials for this drug are currently underway and will help assess its effectiveness for use with NBIA disorders.

Injection of botulinum toxin (Botox) into muscles affected by dystonia can also provide relief for several months at a time. This causes temporary weakness of muscles that have involuntary contractions causing pain, twisting, abnormal posture, or changes in person's voice or speech. Because each affected muscle must be injected, this is most practical when an individual has dystonia significantly affecting a specific body area, such as the hand or jaw.

Deep Brain Stimulation (DBS) is another treatment used to control dystonia. It is performed by implanting electrodes into the brain with a programmable device (neurostimulator) under the skin of the chest or abdomen. The neurostimulator sends pulses to targeted areas of the brain thus altering the pathological patterns of activity in the basal ganglia that cause the muscles to move in painful ways. DBS has been tried on several NBIA individuals with some good results, although it is unclear whether there is a long-term benefit.

The benefits and limitations of any of the above treatments should be discussed in detail with a physician.

## **NBIA Disorders**

**PKAN**, or Pantothenic Kinase-Associated Neurodegeneration, is caused by mutations in the *PANK2* gene. This is the most common form of NBIA, making up 35 percent to 50 percent of the NBIA population. This gene provides the instruction for making an enzyme called pantothenate kinase. Current research is investigating how this missing enzyme results in damage to nerve cells in the brain as well as the characteristic iron build-up.

PKAN is generally separated into classic and atypical forms, although some people will have characteristics that place them between these two categories. Individuals with classic disease have a more rapid progression of symptoms. In most cases, atypical disease progresses slowly over several years, and sometimes decades. The symptoms and physical findings vary from case to case.

Children with PKAN typically manifest gait problems around age 3 and later develop progressive dystonia, dysarthria, rigidity, spasticity, hyperreflexia and extensor toe signs. Individuals with later-onset PKAN are likely to present with speech difficulty. Psychiatric symptoms are more frequent in the later onset form.

Retinal degeneration is common, particularly in classic PKAN.

**PLAN**, or PLA2G6-Associated Neurodegeneration, is named for the responsible gene, *PLA2G6*. The group includes INAD, or Infantile Neuroaxonal Dystrophy, NAD, or atypical neuroaxonal dystrophy, which starts a few years later, and an adult form of dystonia-parkinsonism in which onset occurs in the second to third decade in patients with dystonia, neuropsychiatric changes, slowness, poor balance and rigidity.

Classic INAD has early onset and rapid progression. Affected individuals usually develop signs and symptoms of the disease between 6 months and age 3. The first signs are often delays in developing skills, like walking and talking. Children may be floppy or have low muscle tone early on (hypotonia), but this later turns into stiffness (spasticity) as they get older, especially in the arms and legs. Eye disease caused by degeneration of the optic nerve (optic atrophy) is common and can cause poor vision and eventual blindness.

NAD usually starts at a later age than INAD, typically during early childhood, although it can be as late as the second decade. It has a slower progression and a different variety of movement problems than INAD. At the outset, children may have speech delay or features similar to autism. Eventually difficulty with movement develops. Unlike classic INAD, these “atypical” individuals usually have dystonia. They are also more likely to have behavior changes, such as being impulsive, not being able to pay attention for long periods of time or becoming depressed, which may require treatment by a doctor.

**MPAN**, or Mitochondrial-membrane Protein-Associated Neurodegeneration, is caused by the autosomal recessive gene, *C19orf12*. Onset occurs in childhood to early adulthood with dystonia, spasticity, weakness, optic atrophy and neuropsychiatric changes.

**BPAN**, or Beta-propeller Protein-Associated Neurodegeneration, is caused by mutations in the gene *WDR45*, located on the X chromosome. To date, all reported affected individuals have been simplex cases (i.e., a single occurrence in a family). The majority are females, indicating the mutations are new, or de novo, and suggesting that mutations are lethal in most males. Affected individuals have global developmental delay during childhood with slow motor and cognitive gains. However, during adolescence or adulthood, they experience a relatively sudden onset of progressive dystonia-parkinsonism and dementia.

**Aceruloplasminemia** has mainly been studied in Japan, where it occurs in about one per 2 million adults. It is unclear how often it occurs in other populations. The gene responsible is *CP*. It is unusual from other forms of NBIA because iron accumulates not just in the brain, but in other organs, including the liver. The main symptoms are retinal degeneration, diabetes, and neurologic disease related to iron build-up in the basal ganglia. Movement problems include face and neck dystonia, blepharospasm, tremors, and jerky movements.

**FAHN**, or Fatty Acid Hydroxylase-associated Neurodegeneration, is caused by a mutation in the *FA2H* gene. At present, only a few families have been identified with this rare form of NBIA. Onset occurs in childhood featuring leg dystonia, weakness and falling. Affected individuals also experience optic atrophy, profound cerebellar atrophy and white matter changes in the brain, in addition to high brain iron.

**Kufor-Rakeb** is named for the village in Jordan where it was first described in 1994. In 2010, a mutation in the *ATP13A2* gene was deemed responsible. No U.S. families have yet been found to have this form of NBIA, but there are a few in South America, the Middle East, Asian countries and one from Italy. It has been suggested that only a portion of cases may have iron accumulation; it may develop late in disease course, or it may only be associated with more severe mutations. Symptoms include juvenile parkinsonism, dementia, abnormal eye movements and involuntary jerking of facial and finger muscles.

**Neuroferritinopathy** is the only genetically dominant form of NBIA identified so far. It typically starts during adulthood with dystonia, jerky movements (chorea), and mild changes in thinking (cognitive effects). Within 20 years it usually begins to affect movement in all the limbs and causes difficulty speaking and resembles Huntington's disease. Although the prevalence is unknown, only about 100 cases have been found and most of these share the same gene change, suggesting they have descended from a common ancestor. It is caused by mutations in the *FTL* gene, which stands for ferritin light. This refers to one of two protein subunits that make up ferritin, a protein in the body that helps store and detoxify iron. Affected individuals have MRIs that are different from those of other NBIA patients.

**Woodhouse-Sakati Syndrome** is described in 12 Saudi Arabian families. A founder mutation in *DCAF17* accounts for the cases in the Saudi Arabian population. Affected individuals have high brain iron and dystonia in addition to hair loss, diabetes, hearing loss, gonadal dysfunction and mental retardation.

**Idiopathic NBIA** is a type of unknown origin that is suspected to be genetic. It's likely that there are still several additional, less common genes to be found. For many families, the person diagnosed with NBIA is the first and only affected individual, so it is difficult to know whether there is a specific pattern of inheritance. It is thought that most of these cases are probably recessive because there are some families with more than one affected child and because idiopathic NBIA is more common in families where the parents are related, such as distant cousins. This makes it more likely that they share a common recessive gene. The symptoms in this group are more varied because there are probably several different causes of neurodegeneration in this group. As with other forms of NBIA, there are both early-onset and late-onset types.