



What is NBIA?

NBIA is a rare, inherited, neurological movement disorder characterized by the progressive degeneration of the nervous system (neurodegenerative disorder). Recently, one of the genetic causes was identified; however, there are probably other causative genes that exist that have not yet been found. Approximately 50% of individuals with a clinical diagnosis of NBIA have gene mutations in *PANK2*, which helps to metabolize vitamin B₅.

The common feature among all individuals with NBIA is iron accumulation in the brain along with a progressive movement disorder. Individuals can plateau for long periods of time and then undergo intervals of rapid deterioration. Symptoms may vary greatly from case to case, partly because the genetic cause may differ between families. There are likely different genes that cause NBIA; and furthermore, different mutations within a gene could lead to a more or less severe presentation. The factors that influence disease severity and the rate of progression are still unknown.

Common features include dystonia (an abnormality in muscle tone), muscular rigidity, and sudden involuntary muscle spasms (spasticity). These features can result in clumsiness, gait (walking) problems, difficulty controlling movement, and speech problems. Another common feature is degeneration of the retina resulting in progressive night blindness and loss of peripheral (side) vision. In general, symptoms are progressive and become worse over time.

Because of concerns about the unethical activities of Dr. Hallervorden (and perhaps also Dr. Spatz) involving euthanasia of mentally ill patients during World War II, the name of this disease has been changed from Hallervorden-Spatz syndrome to Neurodegeneration with Brain Iron Accumulation. NBIA reflects the continuing discoveries about the underlying cause of the disorder. The term NBIA is general enough to cover all conditions previously categorized as Hallervorden-Spatz syndrome. The largest subgroup of NBIA observed so far is PKAN (pantothenate kinase associated neurodegeneration). It is a defect of the gene *PANK2*, which causes a deficiency of the enzyme pantothenate kinase. Until the new name has been fully integrated, one may notice the terms NBIA and PKAN being used interchangeably with HSS.

SYMPTOMS

There are several descriptive terms for the neuromuscular symptoms associated with all forms of NBIA. Dystonia is a group of disorders characterized by involuntary muscle contractions 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. 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 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.

Many of the delays in development pertain to motor skills (movement), although a small subgroup may have intellectual delays. Although intellectual impairment has often been described as a part of the condition in the past, it is unclear if this is a true feature. Intellectual testing may be hampered by the movement disorder; therefore, newer methods of studying intelligence are necessary to determine if there are any cognitive features of this condition.

The symptoms and physical findings associated with PKAN mutations can be distinguished between classical or atypical disease. Individuals with classical disease have a more rapid progression of symptoms. In most cases, atypical disease progresses slowly over several years. The symptoms and physical findings vary from case to case.

Classical PKAN develops in the first ten years of life (average age for developing symptoms is 3 1/2 years). These children may initially be perceived as clumsy and later develop more noticeable problems with walking. Eventually, falling becomes a frequent feature. Because of the limited ability to protect themselves during falls, children may have repeated injury to the face and chin. Many individuals with the classic form of PKAN require a wheelchair by their mid-teens (in some cases earlier). Most lose the ability to move/walk independently between 10-15 years after the beginning of symptoms.

Individuals with classical PKAN are more likely to have specific eye problems. Approximately 2/3 of these patients will have retinal degeneration. This is a progressive degeneration of the nerve-rich membrane lining the eyes (retina), resulting in tunnel vision, night blindness, and loss of peripheral vision. Loss of this

peripheral vision may contribute to the more frequent falls and gait disturbances in the early stages. [For more information on this retinopathy (retinitis pigmentosa), choose "retinitis pigmentosa" as your search term in the Rare Disease Database]. Optic atrophy, a vision impairment caused by gradual degeneration of the nerves of the eyes, is only found in 3% of patients.

The atypical form of PKAN usually occurs after the age of ten years and progresses more slowly. The average age for developing symptoms is 13 years. Loss of independent ambulation (walking) often occurs 15-40 years after the initial development of symptoms. The initial presenting symptoms usually involve speech. Common speech problems are repetition of words or phrases (palilalia), rapid speech (tachylalia), and poor articulation/slurring (dysarthria). Psychiatric symptoms are more commonly observed and include impulsive behavior, violent outbursts, depression, or a tendency to rapid mood swings. While the movement disorder is a very common feature, it usually develops later. In general, atypical disease is less severe and more slowly progressive than early-onset PKAN.

In cases of neurodegeneration with brain iron accumulation (NBIA) that are not caused by PKAN, the movement-related symptoms (such as dystonia) may be very similar. The symptoms in NBIA are more varied because there are probably several different causes of neurodegeneration in this group. There is a subgroup of patients with moderate to severe mental retardation. Also, seizure disorders are more common among non-PKAN individuals.

CAUSES

Individuals with NBIA often have abnormal accumulation of iron in certain areas of the brain. This is especially seen in regions of the basal ganglia called the globus pallidus and the substantia nigra. 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.

GENETICS

PKAN is an autosomal recessive condition. Many other cases of NBIA are presumed to be autosomal recessive as well. In autosomal recessive disorders, a person has received a non-working gene from both parents. Following is a brief review of some of the basic genetic terminology.

A person carries a complete set of genetic material in most cells of their body. The total amount of information is contained on 46 chromosomes. These exist in 23 pairs, where one chromosome from each pair comes from the mother and the other from the father. Chromosomes are like miniature filing cabinets for the thousands of genes that control normal health and development.

Because all of our genes exist in pairs (one coming from the mother and one coming from the father), we normally carry two functioning copies of each gene. When one copy of a recessive gene has an alteration (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 altered

gene on to their child. Statistically, there is a 1 in 4 chance that two carriers would have an affected child, a 2 in 4 chance to have a child who is also a carrier, and a 1 in 4 chance to have a child who did not receive the gene mutation.

PKAN is due to mutations of the *PANK2* gene on chromosome 20. This gene encodes the enzyme pantothenate kinase. Current research is investigating how this missing enzyme results in damage to neurons in the brain as well as the characteristic iron buildup. It is hypothesized that some cysteine-containing chemicals accumulate in high levels causing damage to the neurons in the basal ganglia. No genes have been found for other forms of NBIA.

AFFECTED POPULATION

NBIA affects males and females in equal numbers. The symptoms typically develop during childhood, although occasionally they begin during late adolescence or adulthood.

The frequency of NBIA in the general population is estimated between 1-3/1,000,000 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 STANDARD

Diagnosis

The diagnosis of NBIA is made based upon a detailed patient history, a thorough clinical evaluation, and a variety of specialized tests. The diagnosis can be made by MRI (magnetic resonance imaging). This imaging technique shows the characteristic iron accumulation in certain areas of the brain (globus pallidus and pars reticulata of the substantia nigra). Individuals with PKAN have a characteristic feature called the "eye-of-the-tiger" sign. This is not seen in other forms of NBIA. MRI should be useful in distinguishing PKAN and non-PKAN individuals and may also help to determine which families should have DNA testing for PKAN.

Treatment

There is no specific treatment for individuals with NBIA. Treatment is directed towards the specific symptoms that appear in each individual. Research is focusing on a better understanding of the underlying cause of this disorder, which may eventually help to find a more comprehensive treatment.

Treatment may require the coordinated efforts of a team of specialists. Physicians that the family may work with include the pediatrician or internist, neurologist, ophthalmologist, and geneticist. A team approach to supportive therapy may include physical therapy, exercise physiology, occupation therapy, and speech pathology. In addition, many families may benefit from genetic counseling.

One of the most consistent forms of relief from disabling dystonia is baclofen. This medication has been taken orally, although recently a baclofen pump has been used to administer regular doses automatically into the nervous system.

Levodopa/carbidopa, bromocriptine, and trihexyphenidyl do not appear to help patients with PKAN. These treatments may have a role in the treatment of other causes of NBIA; however, their overall effectiveness is unknown and the responsiveness in individual cases is unpredictable.

Drugs that reduce the levels of iron in the body (iron chelation) have been attempted to treat individuals with NBIA. These agents have proven ineffective.

Pallidotomy and thalamotomy have been investigational attempts at controlling dystonia. These are both surgical techniques which destroy (ablate) very specific regions of the brain, the pallidus and thalamus, respectively. Some families have reported some immediate and temporary relief. However, most patients return to their pre-operative level of dystonia within one year of the operation. Pallidotomy is used for the treatment of disorders that are characterized by changes in muscle tone, postural disturbances, abnormalities in conducting certain voluntary movements, and the development of abnormal involuntary movements (i.e., extrapyramidal disorders). Thalamotomy is usually only used in cases of severe, progressive dystonia that fails to respond to other treatments (intractable).

Deep Brain Stimulation (DBS) is another attempt to control dystonia now being used. It is performed by implanting electrodes into the brain with a programmable device under the skin of the chest or abdomen. It has been tried on several NBIA individuals with some good results, although it is unclear whether there is a long-term benefit.

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.

With the recent discovery of the association between pantothenate kinase and NBIA, there is a new potential therapy that focuses on the underlying chemical defect. Supplemental pantothenate (pantothenic acid, calcium pantothenate) can be taken orally. Pantothenate is another name for vitamin B₅, a water soluble vitamin. Theoretically, this is most likely to assist individuals with very low levels of pantothenate kinase activity. It is hypothesized that classical disease results from complete absence of the enzyme pantothenate kinase, whereas atypical disease results from a severe deficiency, although the individuals still may have some level of enzyme activity. Clinical trials will soon be underway to investigate the effectiveness of this treatment with various forms of NBIA.

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

CURRENT RESEARCH

The National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH) supports research on neurodegenerative movement disorders such as NBIA. The goals of this research are to increase understanding of these disorders, and to find ways to prevent, treat, and cure them.

Researchers at Oregon Health & Science University (OHSU) and University of California, San Francisco (UCSF) are doing research specific to NBIA. They maintain a registry to be used for international research. To be included in the registry and to receive information about possible study participation, please contact:

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