Pantothenate Kinase-Associated Neurodegeneration

Subjects: Genetics & Heredity

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Pantothenate kinase-associated neurodegeneration (formerly called Hallervorden-Spatz syndrome) is a disorder of the nervous system.

genetic conditions

1. Introduction

This condition is characterized by progressive difficulty with movement, typically beginning in childhood. Movement abnormalities include involuntary muscle spasms, rigidity, and trouble with walking that worsens over time. Many people with this condition also develop problems with speech (dysarthria), and some develop vision loss. Additionally, affected individuals may experience a loss of intellectual function (dementia) and psychiatric symptoms such as behavioral problems, personality changes, and depression.

Pantothenate kinase-associated neurodegeneration is characterized by an abnormal buildup of iron in certain areas of the brain. A particular change called the eye-of-the-tiger sign, which indicates an accumulation of iron, is typically seen on magnetic resonance imaging (MRI) scans of the brain in people with this disorder.

Researchers have described classic and atypical forms of pantothenate kinase-associated neurodegeneration. The classic form usually appears in early childhood, causing severe problems with movement that worsen rapidly. Features of the atypical form appear later in childhood or adolescence and progress more slowly. Signs and symptoms vary, but the atypical form is more likely than the classic form to involve speech defects and psychiatric problems.

A condition called HARP (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration), which was historically described as a separate syndrome, is now considered part of pantothenate kinase-associated neurodegeneration. Although HARP is much rarer than classic pantothenate kinase-associated neurodegeneration, both conditions involve problems with movement, dementia, and vision abnormalities.

2. Frequency

The precise incidence of this condition is unknown. It is estimated to affect 1 to 3 per million people worldwide.

3. Causes

Mutations in the *PANK2* gene cause pantothenate kinase-associated neurodegeneration.

The *PANK2* gene provides instructions for making an enzyme called pantothenate kinase 2. This enzyme is active in mitochondria, the energy-producing centers within cells, where it plays a critical role in the formation of a molecule called coenzyme A. Found in all living cells, coenzyme A is essential for the body's production of energy from carbohydrates, fats, and some protein building blocks (amino acids).

Mutations in the *PANK2* gene likely result in the production of an abnormal version of pantothenate kinase 2 or prevent cells from making any of this enzyme. A lack of functional pantothenate kinase 2 disrupts the production of coenzyme A and allows potentially harmful compounds to build up in the brain. This buildup leads to swelling and tissue damage, and allows iron to accumulate abnormally in certain parts of the brain. Researchers have not determined how these changes result in the specific features of pantothenate kinase-associated neurodegeneration. Because pantothenate kinase 2 functions in mitochondria, the signs and symptoms of this condition may be related to impaired energy production.

The Gene Associated with Pantothenate Kinase-Associated Neurodegeneration

- PANK2

4. Inheritance

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

5. Other Names for This Condition

- NBIA1
- neurodegeneration with brain iron accumulation type 1
- PKAN

References

1. Gregory A, Hayflick SJ. Neurodegeneration with brain iron accumulation. Folia Neuropathol. 2005;43(4):286-96. Review.
2. Gregory A, Hayflick SJ. Pantothenate Kinase-Associated Neurodegeneration. 2002Aug 13 [updated 2017 Aug 3]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, BeanLJH, Stephens K,

Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA):University of Washington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1490/

3. Hartig MB, Hörtnagel K, Garavaglia B, Zorzi G, Kmiec T, Klopstock T, RostasyK, Svetel M, Kostic VS, Schuelke M, Botz E, Weindl A, Novakovic I, Nardocci N,Prokisch H, Meitinger T. Genotypic and phenotypic spectrum of PANK2 mutations in patients with neurodegeneration with brain iron accumulation. Ann Neurol. 2006Feb;59(2):248-56.
4. Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, Gitschier J. Genetic, clinical, and radiographic delineation of Hallervorden-Spatzsyndrome. N Engl J Med. 2003 Jan 2;348(1):33-40.
5. Hayflick SJ. Pantothenate kinase-associated neurodegeneration (formerlyHallervorden-Spatz syndrome). J Neurol Sci. 2003 Mar 15;207(1-2):106-7. Review.
6. Hayflick SJ. Unraveling the Hallervorden-Spatz syndrome: pantothenatekinase-associated neurodegeneration is the name. Curr Opin Pediatr. 2003Dec;15(6):572-7. Review.
7. Houlden H, Lincoln S, Farrer M, Cleland PG, Hardy J, Orrell RW. Compoundheterozygous PANK2 mutations confirm HARP and Hallervorden-Spatz syndromes areallelic. Neurology. 2003 Nov 25;61(10):1423-6.
8. Pellecchia MT, Valente EM, Cif L, Salvi S, Albanese A, Scarano V, BonuccelliU, Bentivoglio AR, D'Amico A, Marelli C, Di Giorgio A, Coubes P, Barone P,Dallapiccola B. The diverse phenotype and genotype of pantothenatekinase-associated neurodegeneration. Neurology. 2005 May 24;64(10):1810-2.
9. Shevell M. Hallervorden and history. N Engl J Med. 2003 Jan 2;348(1):3-4.
10. Zhou B, Westaway SK, Levinson B, Johnson MA, Gitschier J, Hayflick SJ. A novelpantothenate kinase gene (PANK2) is defective in Hallervorden-Spatz syndrome. NatGenet. 2001 Aug;28(4):345-9.