Hereditary Neuralgic Amyotrophy

Subjects: Genetics & Heredity
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Hereditary neuralgic amyotrophy is a disorder characterized by episodes of severe pain and muscle wasting (amyotrophy) in one or both shoulders and arms. Neuralgic pain is felt along the path of one or more nerves and often has no obvious physical cause. The network of nerves involved in hereditary neuralgic amyotrophy, called the brachial plexus, controls movement and sensation in the shoulders and arms.

Keywords: genetic conditions

1. Introduction

People with hereditary neuralgic amyotrophy usually begin experiencing attacks in their twenties, but episodes have occurred as early as the age of 1 year in some individuals. The attacks may be spontaneous or triggered by stress such as strenuous exercise, childbirth, surgery, exposure to cold, infections, immunizations, or emotional disturbance. While the frequency of the episodes tends to decrease with age, affected individuals are often left with residual problems, such as chronic pain and impaired movement, that accumulate over time.

Typically an attack begins with severe pain on one or both sides of the body; right-sided involvement is most common. The pain may be difficult to control with medication and usually lasts about a month. Within a period of time ranging from a few hours to a couple of weeks, the muscles in the affected area begin to weaken and waste away (atrophy), and movement becomes difficult. Muscle wasting may cause changes in posture or in the appearance of the shoulder, back, and arm. In particular, weak shoulder muscles tend to make the shoulder blades (scapulae) "stick out" from the back, a common sign known as scapular winging. Additional features of hereditary neuralgic amyotrophy may include decreased sensation (hypoesthesia) and abnormal sensations in the skin such as numbness or tingling (paresthesias). Areas other than the shoulder and arm may also be involved.

In a few affected families, individuals with hereditary neuralgic amyotrophy also have unusual physical characteristics including short stature, excess skin folds on the neck and arms, an opening in the roof of the mouth (cleft palate), a split in the soft flap of tissue that hangs from the back of the mouth (bifid uvula), and partially webbed or fused fingers or toes (partial syndactyly). They may also have distinctive facial features including eyes set close together (ocular hypotelorism), a narrow opening of the eyelids (short palpebral fissures) with a skin fold covering the inner corner of the eye (epicanthal fold), a long nasal bridge, a narrow mouth, and differences between one side of the face and the other (facial asymmetry).

2. Frequency

Hereditary neuralgic amyotrophy is a rare disorder, but its specific prevalence is unknown. Approximately 200 families affected by the disorder have been identified worldwide.

3. Causes

Mutations in the *SEPTIN9* gene cause hereditary neuralgic amyotrophy. The *SEPTIN9* gene provides instructions for making a protein called septin-9, which is part of a group of proteins called septins. Septins are involved in a process called cytokinesis, which is the step in cell division when the fluid inside the cell (cytoplasm) divides to form two separate cells.

The *SEPTIN9* gene seems to be turned on (active) in cells throughout the body. Approximately 15 slightly different versions (isoforms) of the septin-9 protein may be produced from this gene. Some types of cells make certain isoforms, while other cell types produce other isoforms. However, the specific distribution of these isoforms in the body's tissues is not well understood. Septin-9 isoforms interact with other septin proteins to perform some of their functions.

Mutations in the *SEPTIN9* gene may change the sequence of protein building blocks (amino acids) in certain septin-9 isoforms in ways that interfere with their function. These mutations may also change the distribution of septin-9 isoforms and their interactions with other septin proteins in some of the body's tissues. This change in the functioning of septin proteins seems to particularly affect the brachial plexus, but the reason for this is unknown.

Because many of the triggers for hereditary neuralgic amyotrophy also affect the immune system, researchers believe that an autoimmune reaction may be involved in this disorder. However, the relation between *SEPTIN9* gene mutations and immune function is unclear. Autoimmune disorders occur when the immune system malfunctions and attacks the body's own tissues and organs. An autoimmune attack on the nerves in the brachial plexus likely results in the signs and symptoms of hereditary neuralgic amyotrophy.

At least 15 percent of families affected by hereditary neuralgic amyotrophy do not have *SEPTIN9* gene mutations. In these cases, the disorder is believed to be caused by mutations in a gene that has not been identified.

3.1. The gene associated with Hereditary neuralgic amyotrophy

- SEPTIN9

4. Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

5. Other Names for This Condition

- Amyotrophic Neuralgia
- Brachial Neuralgia
- Brachial Neuritis
- Brachial Plexus Neuritis
- familial brachial plexus neuritis
- hereditary brachial plexus neuropathy
- heredofamilial neuritis with brachial plexus predilection
- HNA
- NAPB
- Neuralgic Amyotrophy
- neuritis with brachial predilection
- Shoulder Girdle Neuropathy

References

1. Hannibal MC, Ruzzo EK, Miller LR, Betz B, Buchan JG, Knutzen DM, Barnett K,Landsverk ML, Brice A, LeGuern E, Bedford HM, Worrall BB, Lovitt S, Appel SH,Andermann E, Bird TD, Chance PF. SEPT9 gene sequencing analysis reveals recurrentmutations in hereditary neuralgic amyotrophy. Neurology. 2009 May19;72(20):1755-9. doi: 10.1212/WNL.0b013e3181a609e3.
2. Hoque R, Schwendimann RN, Kelley RE, Bien-Willner R, Sivakumar K. Painfulbrachial plexopathies in SEPT9 mutations: adverse outcome related to comorbidstates. J Clin Neuromuscul Dis. 2008 Jun;9(4):379-84. doi:10.1097/CND.0b013e318166ee89.
3. Klein CJ, Wu Y, Cunningham JM, Windebank AJ, Dyck PJ, Friedenberg SM, KleinDM, Dyck PJ. SEPT9 mutations and a conserved 17q25 sequence in sporadic andhereditary brachial plexus neuropathy. Arch Neurol. 2009 Feb;66(2):238-43. doi:10.1001/archneurol.2008.585.

4. Kuhlenbäumer G, Hannibal MC, Nelis E, Schirmacher A, Verpoorten N, Meuleman J,Watts GD, De Vriendt E, Young P, Stögbauer F, Halfter H, Irobi J, Goossens D,Del-Favero J, Betz BG, Hor H, Kurlemann G, Bird TD, Airaksinen E, Mononen T,Serradell AP, Prats JM, Van Broeckhoven C, De Jonghe P, Timmerman V, Ringelstein EB, Chance PF. Mutations in SEPT9 cause hereditary neuralgic amyotrophy. NatGenet. 2005 Oct;37(10):1044-6.
5. Laccone F, Hannibal MC, Neesen J, Grisold W, Chance PF, Rehder H. Dysmorphicsyndrome of hereditary neuralgic amyotrophy associated with a SEPT9 genemutation--a family study. Clin Genet. 2008 Sep;74(3):279-83. doi:10.1111/j.1399-0004.2008.01022.x.
6. Landsverk ML, Ruzzo EK, Mefford HC, Buysse K, Buchan JG, Eichler EE, Petty EM,Peterson EA, Knutzen DM, Barnett K, Farlow MR, Caress J, Parry GJ, Quan D,Gardner KL, Hong M, Simmons Z, Bird TD, Chance PF, Hannibal MC. Duplicationwithin the SEPT9 gene associated with a founder effect in North American familieswith hereditary neuralgic amyotrophy. Hum Mol Genet. 2009 Apr 1;18(7):1200-8.doi: 10.1093/hmg/ddp014.
7. McDade SS, Hall PA, Russell SE. Translational control of SEPT9 isoforms isperturbed in disease. Hum Mol Genet. 2007 Apr 1;16(7):742-52.
8. Sudo K, Ito H, Iwamoto I, Morishita R, Asano T, Nagata K. SEPT9 sequencealternations causing hereditary neuralgic amyotrophy are associated with altered interactions with SEPT4/SEPT11 and resistance to Rho/Rhotekin-signaling. HumMutat. 2007 Oct;28(10):1005-13.
9. van Alfen N, Hannibal MC, Chance PF, van Engelen BGM. Hereditary NeuralgicAmyotrophy – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY. 2008 Feb 27 [updated2012 Dec 6]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, StephensK, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University ofWashington, Seattle; 1993-2020. Available fromhttp://www.ncbi.nlm.nih.gov/books/NBK1395/
10. van Alfen N, van der Werf SP, van Engelen BG. Long-term pain, fatigue, andimpairment in neuralgic amyotrophy. Arch Phys Med Rehabil. 2009 Mar;90(3):435-9. doi: 10.1016/j.apmr.2008.08.216.
11. van Alfen N, van Engelen BG. The clinical spectrum of neuralgic amyotrophy in 246 cases. Brain. 2006 Feb;129(Pt 2):438-50.
