Andermann Syndrome

Subjects: Genetics & Heredity
Contributor: Catherine Yang

Andermann syndrome is a disorder that damages the nerves used for muscle movement and sensation (motor and sensory neuropathy). Absence (agenesis) or malformation of the tissue connecting the left and right halves of the brain (corpus callosum) also occurs in most people with this disorder.

Keywords: genetic conditions

1. Introduction

People affected by Andermann syndrome have abnormal or absent reflexes (areflexia) and weak muscle tone (hypotonia). They experience muscle wasting (amyotrophy), severe progressive weakness and loss of sensation in the limbs, and rhythmic shaking (tremors). They typically begin walking between ages 3 and 4 and lose this ability by their teenage years. As they get older, people with this disorder frequently develop joint deformities called contractures, which restrict the movement of certain joints. Most affected individuals also develop abnormal curvature of the spine (scoliosis), which may require surgery.

Andermann syndrome also results in abnormal function of certain cranial nerves, which emerge directly from the brain and extend to various areas of the head and neck. Cranial nerve problems may result in facial muscle weakness, drooping eyelids (ptosis), and difficulty following movements with the eyes (gaze palsy).

Individuals with Andermann syndrome usually have intellectual disability, which may be mild to severe, and some experience seizures. They may also develop psychiatric symptoms such as depression, anxiety, agitation, paranoia, and hallucinations, which usually appear in adolescence.

Some people with Andermann syndrome have atypical physical features such as widely spaced eyes (ocular hypertelorism); a wide, short skull (brachycephaly); a high arch of the hard palate at the roof of the mouth; a big toe that crosses over the other toes; and partial fusion (syndactyly) of the second and third toes.

Andermann syndrome is associated with a shortened life expectancy, but affected individuals typically live into adulthood.

2. Frequency

Andermann syndrome is most often seen in the French-Canadian population of the Saguenay-Lac-St.-Jean and Charlevoix regions of northeastern Quebec. In this population, Andermann syndrome occurs in almost 1 in 2,000 newborns. Only a few individuals with this disorder have been identified in other regions of the world.

3. Causes

Mutations in the *SLC12A6* gene cause Andermann syndrome. The *SLC12A6* gene provides instructions for making a protein called a K-Cl cotransporter. This protein is involved in moving charged atoms (ions) of potassium (K) and chlorine (Cl) across the cell membrane. The positively charged potassium ions and negatively charged chlorine ions are moved together (cotransported), so that the charges inside and outside the cell membrane are unchanged (electroneutral).

Electroneutral cotransport of ions across cell membranes is involved in many functions of the body. While the specific function of the K-Cl cotransporter produced from the *SLC12A6* gene is unknown, it seems to be critical for the development and maintenance of nerve tissue. It may be involved in regulating the amounts of potassium, chlorine, or water in cells and intercellular spaces. The K-Cl cotransporter protein may also help regulate the activity of other proteins that are sensitive to ion concentrations.

Mutations in the *SLC12A6* gene that cause Andermann syndrome disrupt the function of the K-Cl cotransporter protein. The lack of functional protein normally produced from the *SLC12A6* gene is believed to interfere with the development of the corpus callosum and maintenance of the nerves that transmit signals needed for movement and sensation, resulting in the signs and symptoms of Andermann syndrome.

3.1. The gene associated with Andermann syndrome

- SLC12A6

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

- ACCPN
- agenesis of corpus callosum with neuronopathy
- agenesis of corpus callosum with peripheral neuropathy
- agenesis of corpus callosum with polyneuropathy
- Charlevoix disease
- hereditary motor and sensory neuropathy with agenesis of the corpus callosum
- HMSN/ACC

References

1. Dupré N, Bouchard JP, Brais B, Rouleau GA. Hereditary ataxia, spasticparaparesis and neuropathy in the French-Canadian population. Can J Neurol Sci.2006 May;33(2):149-57. Review.
2. Dupré N, Howard HC, Mathieu J, Karpati G, Vanasse M, Bouchard JP, Carpenter S,Rouleau GA. Hereditary motor and sensory neuropathy with agenesis of the corpuscallosum. Ann Neurol. 2003 Jul;54(1):9-18. Review.
3. Gauvreau C, Brisson JD, Dupré N. Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum. 2006 Feb 2 [updated 2020 Sep 17]. In: Adam MP,Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A, editors.GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle;1993-2020. Available from http://www.ncbi.nlm.nih.gov/books/NBK1372/
4. Howard HC, Mount DB, Rochefort D, Byun N, Dupré N, Lu J, Fan X, Song L,Rivière JB, Prévost C, Horst J, Simonati A, Lemcke B, Welch R, England R, ZhanFQ, Mercado A, Siesser WB, George AL Jr, McDonald MP, Bouchard JP, Mathieu J,Delpire E, Rouleau GA. The K-Cl cotransporter KCC3 is mutant in a severeperipheral neuropathy associated with agenesis of the corpus callosum. Nat Genet.2002 Nov;32(3):384-92.
5. Salin-Cantegrel A, Rivière JB, Dupré N, Charron FM, Shekarabi M, Karéméra L,Gaspar C, Horst J, Tekin M, Deda G, Krause A, Lippert MM, Willemsen MA, Jarrar R,Lapointe JY, Rouleau GA. Distal truncation of KCC3 in non-French CanadianHMSN/ACC families. Neurology. 2007 Sep 25;69(13):1350-5.
6. Uyanik G, Elcioglu N, Penzien J, Gross C, Yilmaz Y, Olmez A, Demir E, Wahl D, Scheglmann K, Winner B, Bogdahn U, Topaloglu H, Hehr U, Winkler J. Noveltruncating and missense mutations of the KCC3 gene associated with Andermannsyndrome. Neurology. 2006 Apr 11;66(7):1044-8. Erratum in: Neurology. 2006 Oct24;67(8):1528.
