Triple A Syndrome

Subjects: Genetics & Heredity
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Keywords: genetic conditions

1. Introduction

Triple A syndrome is an inherited condition characterized by three specific features: achalasia, Addison disease, and alacrima. Achalasia is a disorder that affects the ability to move food through the esophagus, the tube that carries food from the throat to the stomach. It can lead to severe feeding difficulties and low blood sugar (hypoglycemia). Addison disease, also known as primary adrenal insufficiency, is caused by abnormal function of the small hormone-producing glands on top of each kidney (adrenal glands). The main features of Addison disease include fatigue, loss of appetite, weight loss, low blood pressure, and darkening of the skin. The third major feature of triple A syndrome is a reduced or absent ability to secrete tears (alacrima). Most people with triple A syndrome have all three of these features, although some have only two.

Many of the features of triple A syndrome are caused by dysfunction of the autonomic nervous system. This part of the nervous system controls involuntary body processes such as digestion, blood pressure, and body temperature. People with triple A syndrome often experience abnormal sweating, difficulty regulating blood pressure, unequal pupil size (anisocoria), and other signs and symptoms of autonomic nervous system dysfunction (dysautonomia).

People with this condition may have other neurological abnormalities, such as developmental delay, intellectual disability, speech problems (dysarthria), and a small head size (microcephaly). In addition, affected individuals commonly experience muscle weakness, movement problems, and nerve abnormalities in their extremities (peripheral neuropathy). Some develop optic atrophy, which is the degeneration (atrophy) of the nerves that carry information from the eyes to the brain. Many of the neurological symptoms of triple A syndrome worsen over time.

People with triple A syndrome frequently develop a thickening of the outer layer of skin (hyperkeratosis) on the palms of their hands and the soles of their feet. Other skin abnormalities may also be present in people with this condition.

Alacrima is usually the first noticeable sign of triple A syndrome, as it becomes apparent early in life that affected children produce little or no tears while crying. They develop Addison disease and achalasia during childhood or adolescence, and most of the neurologic features of triple A syndrome begin during adulthood. The signs and symptoms of this condition vary among affected individuals, even among members of the same family.

2. Frequency

Triple A syndrome is a rare condition, although its exact prevalence is unknown.

3. Causes

Mutations in the *AAAS* gene cause triple A syndrome. This gene provides instructions for making a protein called ALADIN whose function is not well understood. Within cells, ALADIN is found in the nuclear envelope, the structure that surrounds the nucleus and separates it from the rest of the cell. Based on its location, ALADIN is thought to be involved in the movement of molecules into and out of the nucleus.

Mutations in the *AAAS* gene change the structure of ALADIN in different ways; however, almost all mutations prevent this protein from reaching its proper location in the nuclear envelope. The absence of ALADIN in the nuclear envelope likely disrupts the movement of molecules across this membrane. Researchers suspect that DNA repair proteins may be unable

to enter the nucleus if ALADIN is missing from the nuclear envelope. DNA damage that is not repaired can cause the cell to become unstable and lead to cell death. Although the nervous system is particularly vulnerable to DNA damage, it remains unknown exactly how mutations in the *AAAS* gene lead to the signs and symptoms of triple A syndrome.

Some individuals with triple A syndrome do not have an identified mutation in the *AAAS* gene. The genetic cause of the disorder is unknown in these individuals.

3.1 The gene associated with Triple A syndrome

- AAAS

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

- AAA
- AAA syndrome
- Achalasia-addisonian syndrome
- Achalasia-Addisonianism-Alacrima syndrome
- Achalasia-alacrima syndrome
- Alacrima-achalasia-adrenal insufficiency neurologic disorder
- Allgrove syndrome

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