Pseudohypoaldosteronism Type 1

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Pseudohypoaldosteronism type 1 (PHA1) is a condition characterized by problems regulating the amount of sodium in the body.

Keywords: genetic conditions

1. Introduction

Sodium regulation, which is important for blood pressure and fluid balance, primarily occurs in the kidneys. However, sodium can also be removed from the body through other tissues, such as the sweat glands and colon. Pseudohypoaldosteronism type 1 is named for its characteristic signs and symptoms, which mimic (pseudo) low levels (hypo) of a hormone called aldosterone that helps regulate sodium levels. However, people with PHA1 have high levels of aldosterone.

There are two types of PHA1 distinguished by their severity, the genes involved, and how they are inherited. One type, called autosomal dominant PHA1 (also known as renal PHA1) is characterized by excessive sodium loss from the kidneys. This form of the condition is relatively mild and often improves in early childhood. The other type, called autosomal recessive PHA1 (also known as generalized or systemic PHA1) is characterized by sodium loss from the kidneys and other organs, including the sweat glands, salivary glands, and colon. This type of PHA1 is more severe and does not improve with age.

The earliest signs of both types of PHA1 are usually the inability to gain weight and grow at the expected rate (failure to thrive) and dehydration, which are typically seen in infants. The characteristic features of both types of PHA1 are excessive amounts of sodium released in the urine (salt wasting), which leads to low levels of sodium in the blood (hyponatremia), and high levels of potassium in the blood (hyperkalemia). Infants with PHA1 can also have high levels of acid in the blood (metabolic acidosis). Hyponatremia, hyperkalemia, or metabolic acidosis can cause nonspecific symptoms such as nausea, vomiting, extreme tiredness (fatigue), and muscle weakness in infants with PHA1.

Infants with autosomal recessive PHA1 can have additional signs and symptoms due to the involvement of multiple organs. Affected individuals may experience episodes of abnormal heartbeat (cardiac arrhythmia) or shock because of the imbalance of salts in the body. They may also have recurrent lung infections or lesions on the skin. Although adults with autosomal recessive PHA1 can have repeated episodes of salt wasting, they do not usually have other signs and symptoms of the condition.

2. Frequency

PHA1 is a rare condition that has been estimated to affect 1 in 80,000 newborns.

3. Causes

Mutations in one of four different genes involved in sodium regulation cause autosomal dominant or autosomal recessive PHA1. Mutations in the *NR3C2* gene cause autosomal dominant PHA1. This gene provides instructions for making the mineralocorticoid receptor protein. Mutations in the *SCNN1A*, *SCNN1B*, or *SCNN1G* genes cause autosomal recessive PHA1. Each of these three genes provides instructions for making one of the pieces (subunits) of a protein complex called the epithelial sodium channel (ENaC).

The mineralocorticoid receptor regulates specialized proteins in the cell membrane that control the transport of sodium or potassium into cells. In response to signals that sodium levels are low, such as the presence of the hormone aldosterone, the mineralocorticoid receptor increases the number and activity of these proteins at the cell membrane of certain kidney

cells. One of these proteins is ENaC, which transports sodium into the cell; another protein simultaneously transports sodium out of the cell and potassium into the cell. These proteins help keep sodium in the body through a process called reabsorption and remove potassium from the body through a process called secretion.

Mutations in the *NR3C2* gene lead to a nonfunctional or abnormally functioning mineralocorticoid receptor protein that cannot properly regulate the specialized proteins that transport sodium and potassium. As a result, sodium reabsorption and potassium secretion are both decreased, causing hyponatremia and hyperkalemia.

Mutations in the *SCNN1A*, *SCNN1B*, and *SCNN1G* genes result in reduced functioning or nonfunctioning ENaC channels. As in autosomal dominant PHA1, the reduction or absence of ENaC function in the kidneys leads to hyponatremia and hyperkalemia. In addition, nonfunctional ENaC channels in other body systems lead to additional signs and symptoms of autosomal recessive PHA1, including lung infections and skin lesions.

The Genes Associated with Pseudohypoaldosteronism Type 1

- NR3C2
- SCNN1A
- SCNN1B
- SCNNIG

4. Inheritance

PHA1 can have different inheritance patterns. When the condition is caused by mutations in the *NR3C2* gene, it is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. When PHA1 is caused by mutations in the *SCNN1A*, *SCNN1B*, or *SCNN1G* genes, it 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

- PHA1
- pseudohypoaldosteronism type I

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