Hennekam Syndrome

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Hennekam syndrome is an inherited disorder resulting from malformation of the lymphatic system, which is part of both the circulatory system and immune system. The lymphatic system consists of a network of vessels that transport lymph fluid and immune cells throughout the body.

Keywords: genetic conditions

1. Introduction

The characteristic signs and symptoms of Hennekam syndrome are lymphatic vessels that are abnormally expanded (lymphangiectasia), particularly the vessels that transport lymph fluid to and from the intestines; puffiness or swelling caused by a buildup of fluid (lymphedema); and unusual facial features.

Lymphangiectasia often impedes the flow of lymph fluid and can cause the affected vessels to break open (rupture). In the intestines, ruptured vessels can lead to accumulation of lymph fluid, which interferes with the absorption of nutrients, fats, and proteins. Accumulation of lymph fluid in the abdomen can cause swelling (chylous ascites). Lymphangiectasia can also affect the kidneys, thyroid gland, the outer covering of the lungs (the pleura), the membrane covering the heart (pericardium), or the skin.

The lymphedema in Hennekam syndrome is often noticeable at birth and usually affects the face and limbs. Severely affected infants may have extensive swelling caused by fluid accumulation before birth (hydrops fetalis). The lymphedema usually affects one side of the body more severely than the other (asymmetric) and slowly worsens over time.

Facial features of people with Hennekam syndrome may include a flattened appearance to the middle of the face and the bridge of the nose, puffy eyelids, widely spaced eyes (hypertelorism), small ears, and a small mouth with overgrowth of the gums (gingival hypertrophy). Affected individuals may also have an unusually small head (microcephaly) and premature fusion of the skull bones (craniosynostosis).

Individuals with Hennekam syndrome often have intellectual disability that ranges from mild to severe, although most are on the mild end of the range and some have normal intellect. Many individuals with Hennekam syndrome have growth delay, respiratory problems, permanently bent fingers and toes (camptodactyly), or fusion of the skin between the fingers and toes (cutaneous syndactyly).

Abnormalities found in a few individuals with Hennekam syndrome include a moderate to severe shortage of red blood cells (anemia) resulting from an inadequate amount (deficiency) of iron in the bloodstream, multiple spleens (polysplenia), misplaced kidneys, genital anomalies, a soft out-pouching around the belly-button (umbilical hernia), heart abnormalities, hearing loss, excessive body hair growth (hirsutism), a narrow upper chest that may have a sunken appearance (pectus excavatum), an abnormal side-to-side curvature of the spine (scoliosis), and inward- and upward-turning feet (clubfeet).

The signs and symptoms of Hennekam syndrome vary widely among affected individuals, even those within the same family. Life expectancy depends on the severity of the condition and can vary from death in childhood to survival into adulthood.

2. Frequency

At least 50 cases of Hennekam syndrome have been reported worldwide.

3. Causes

Mutations in the *CCBE1* or *FAT4* gene can cause Hennekam syndrome.

The *CCBE1* gene provides instructions for making a protein that is found in the lattice of proteins and other molecules outside the cell (extracellular matrix). The CCBE1 protein is involved in the maturation (differentiation) and movement (migration) of immature cells called lymphangioblasts that will eventually form the lining (epithelium) of lymphatic vessels.

The function of the protein produced from the *FAT4* gene is largely unknown. Research shows that the FAT4 protein may be involved in determining the position of various components within cells (cell polarity).

CCBE1 gene mutations that cause Hennekam syndrome change the three-dimensional shape of the protein and severely decrease its function. The abnormal protein cannot play its role in the formation of the lymphatic vessel epithelium. The resulting malformation of lymphatic vessels leads to lymphangiectasia, lymphedema, and other features of Hennekam syndrome. Since the lymphatic system extends throughout the body, a disruption to the vessels can affect almost any organ. Altered lymphatic development before birth may change the balance of fluids and impair normal development, contributing to many of the other signs of Hennekam syndrome such as unusual facial features.

FAT4 gene mutations that cause Hennekam syndrome result in a FAT4 protein with decreased function. Reduced FAT4 protein activity seems to impair normal development of the lymphatic system, but the mechanism is unknown.

Together, mutations in the *CCBE1* and *FAT4* genes are responsible for approximately half of all Hennekam syndrome cases. The cause of the remaining cases is unknown.

3.1. The genes associated with Hennekam syndrome

- CCBE1
- FAT4

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

- generalized lymphatic dysplasia
- Hennekam lymphangiectasia-lymphedema syndrome
- intestinal lymphagiectasia-lymphedema-mental retardation syndrome
- lymphedema-lymphangiectasia-intellectual disability syndrome

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