Congenital Generalized Lipodystrophy

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Congenital generalized lipodystrophy (also called Berardinelli-Seip congenital lipodystrophy) is a rare condition characterized by an almost total lack of fatty (adipose) tissue in the body and a very muscular appearance.

Keywords: genetic conditions

1. Introduction

Adipose tissue is found in many parts of the body, including beneath the skin and surrounding the internal organs. It stores fat for energy and also provides cushioning. Congenital generalized lipodystrophy is part of a group of related disorders known as lipodystrophies, which are all characterized by a loss of adipose tissue. A shortage of adipose tissue leads to the storage of fat elsewhere in the body, such as in the liver and muscles, which causes serious health problems.

The signs and symptoms of congenital generalized lipodystrophy are usually apparent from birth or early childhood. One of the most common features is insulin resistance, a condition in which the body's tissues are unable to recognize insulin, a hormone that normally helps to regulate blood sugar levels. Insulin resistance may develop into a more serious disease called diabetes mellitus. Most affected individuals also have high levels of fats called triglycerides circulating in the bloodstream (hypertriglyceridemia), which can lead to the development of small yellow deposits of fat under the skin called eruptive xanthomas and inflammation of the pancreas (pancreatitis). Additionally, congenital generalized lipodystrophy causes an abnormal buildup of fats in the liver (hepatic steatosis), which can result in an enlarged liver (hepatomegaly) and liver failure. Some affected individuals develop a form of heart disease called hypertrophic cardiomyopathy, which can lead to heart failure and an abnormal heart rhythm (arrhythmia) that can cause sudden death.

People with congenital generalized lipodystrophy have a distinctive physical appearance. They appear very muscular because they have an almost complete absence of adipose tissue and an overgrowth of muscle tissue. A lack of adipose tissue under the skin also makes the veins appear prominent. Affected individuals tend to have prominent bones above the eyes (orbital ridges), large hands and feet, and a prominent belly button (umbilicus). Affected females may have an enlarged clitoris (clitoromegaly), an increased amount of body hair (hirsutism), irregular menstrual periods, and multiple cysts on the ovaries, which may be related to hormonal changes. Many people with this disorder develop acanthosis nigricans, a skin condition related to high levels of insulin in the bloodstream. Acanthosis nigricans causes the skin in body folds and creases to become thick, dark, and velvety.

Researchers have described four types of congenital generalized lipodystrophy, which are distinguished by their genetic cause. The types also have some differences in their typical signs and symptoms. For example, in addition to the features described above, some people with congenital generalized lipodystrophy type 1 develop cysts in the long bones of the arms and legs after puberty. Type 2 can be associated with intellectual disability, which is usually mild to moderate. Type 3 appears to cause poor growth and short stature, along with other health problems. Type 4 is associated with muscle weakness, delayed development, joint abnormalities, a narrowing of the lower part of the stomach (pyloric stenosis), and severe arrhythmia that can lead to sudden death.

2. Frequency

Congenital generalized lipodystrophy has an estimated prevalence of 1 in 10 million people worldwide. Between 300 and 500 people with the condition have been described in the medical literature. Although this condition has been reported in populations around the world, it appears to be more common in certain regions of Lebanon and Brazil.

3. Causes

Mutations in the *AGPAT2*, *BSCL2*, *CAV1*, and *CAVIN1* genes cause congenital generalized lipodystrophy types 1 through 4, respectively. The proteins produced from these genes play important roles in the development and function of adipocytes, which are the fat-storing cells in adipose tissue. Mutations in any of these genes reduce or eliminate the function of their respective proteins, which impairs the development, structure, or function of adipocytes and makes the body unable to store and use fats properly. These abnormalities of adipose tissue disrupt hormones and affect many of the body's organs, resulting in the varied signs and symptoms of congenital generalized lipodystrophy.

Some of the genes associated with congenital generalized lipodystrophy also play roles in other cells and tissues. For example, the protein produced from the *BSCL2* gene is also present in the brain, although its function is unknown. A loss of this protein in the brain may help explain why congenital generalized lipodystrophy type 2 is sometimes associated with intellectual disability.

In some people with congenital generalized lipodystrophy, no mutations have been found in any of the genes listed above. Researchers are looking for additional genetic changes associated with this disorder.

3.1. The Genes Associated with Congenital Generalized Lipodystrophy

- AGPAT2
- BSCL2
- CAV1
- CAVIN1

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

- Berardinelli-Seip congenital lipodystrophy
- Berardinelli-Seip syndrome
- Brunzell syndrome (with bone cysts)
- BSCL
- generalized lipodystrophy
- lipodystrophy, congenital generalized
- Seip syndrome
- total lipodystrophy

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