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BARTH SYNDROME (BTHS)

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ABSTRACT

Barth syndrome (BTHS), also known as 3-Methylglutaconic aciduria type II, is an X-linked genetic disorder. Mutations in the tafazzin gene (TAZ, also called G4.5) are closely associated with Barth syndrome. The gene for Barth syndrome, tafazzin (TAZ, also called G4.5), is located on the long arm of the X chromosome (Xq28). Mutations in the tafazzin gene lead to decreased production of an enzyme required for the synthesis of "cardiolipin," a special lipid that is important in energy metabolism. Other important features of Barth syndrome include bacterial infections because of neutropenia (a reduction in the number of white blood cells called neutrophils), muscle weakness, fatigue, and growth delay. Although most children with Barth syndrome manifest all of these characteristics, some have only one or two of these abnormalities and, as a result, often are given incorrect diagnoses. Barth syndrome occurs in many different ethnic groups and does not appear to be more common in any one group.. There is no specific treatment for Barth syndrome, but each of the individual problems can be successfully controlled, and short stature often resolves after puberty.

Keyword: Barth syndrome, tafazzin gene, cardiolipin, neutropenia, lipid.

DEFINITION

Barth syndrome (BTHS), also known as 3-Methylglutaconic aciduria type II, is an X-linked genetic disorder. Barth syndrome is a rare condition characterized by an enlarged and weakened heart (dilated cardiomyopathy), weakness in muscles used for movement (skeletal myopathy), recurrent infections due to small numbers of white blood cells (neutropenia), and short stature.

INCIDENCE

Barth syndrome is estimated to affect 1 in 300,000 to 400,000 individuals worldwide.

CAUSE

Mutations in the Tafazzin gene (TAZ, also called G4.5) are closely associated with Barth syndrome. The tafazzin gene product functions as an Acyltransferase in complex lipid metabolism. Cardiolipin is intimately connected with the electron transport chain proteins and the membrane structure of the mitochondria which is the energy producing organelle of the cell. The tafazzin gene is located at Xq28 the long arm of the X chromosome. Mutations in tafazzin that cause Barth syndrome span many different categories: missense, nonsense, deletion, frameshift, splicing.

PATHOPHYSIOLOGY

A biochemical marker is any substance, such as an enzyme or small molecule, that is detected in urine or other body fluids and serves as a diagnostic sign of a particular disorder. Researchers have shown that individuals with Barth syndrome have abnormally increased levels of 3-methylglutaconic acid in the urine and in the liquid portion of the blood. According to clinicians, children with Barth syndrome may have

elevated blood levels of 3-methylglutaconic acid from mid-infancy up to about age three. There does not appear to be an association, however, between the increased acid levels and the severity of other symptoms and signs associated with Barth syndrome.

SIGNS & SYMPTOMS

Dilated Endocardial Myopathy typically weakens the heart's pumping action, reducing the volume of blood circulating to the lungs and the rest of the body (heart failure). In young children, for example, heart failure may be manifest as fatigue and shortness of breath (dyspnea) with exertion.

Barth syndrome is also associated with

- abnormally diminished muscle tone (hypotonia),
- muscle weakness (skeletal myopathy),
- Affected infants and children may fail to thrive, and fail to gain weight at the expected rate.
- They may have mild learning disabilities, (although they are usually of normal intelligence), and, in many cases, may be prone to recurrent bacterial infections due to low levels of circulating neutrophils in the blood. Neutropenia, and growth retardation, patients with Barth syndrome have a specific biochemical marker that has been recognized for many years as a primary indicator of Barth syndrome.
- High blood and urine levels of lactic acid (a by-product of intense muscular activity) and low carnitine levels. Carnitine plays a role in the movement of chemicals, especially fatty acids, across the cell membrane.

DIAGNOSIS

- Clinical evaluation, identification of characteristic physical findings, a complete patient and family history, and a variety of specialized tests.
- Low levels of circulating neutrophils (neutropenia); elevated urinary levels of 3-methylglutaconic acid (aciduria); abnormal mitochondria within heart muscle; and/or muscle abnormalities (myopathy) of unknown cause that occur in association with growth retardation.
- For infants and children with signs of cardiomyopathy, Metabolic screening tests should be conducted, including studies to measure levels of 3-methylglutaconic acid and other organic acids in the urine and blood. An elevated urinary level of 3-methylglutaconic acid (3-methylglutaconic aciduria) has been recognized as a biochemical marker that may function as a diagnostic sign of Barth syndrome.

TREATMENT

Many infants and children with Barth syndrome require therapy with diuretic and digitalis medications to treat heart failure. For affected individuals with confirmed neutropenia, complications due to bacterial infection are often preventable by ongoing monitoring and early therapy of suspected infections with antibiotics. Genetic counseling will also benefit affected individuals and their families. Other treatment for this disorder is symptomatic and supportive.

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