

Barth syndrome

Author: Doctor Pascale de Lonlay¹

Creation Date: February 2003

Scientific Editor: Professor Paola Melacini

¹Unité Pédiatrie-Métabolisme Département de pédiatrie, Hôpital Necker - Enfants Malades, 149 Rue de Sèvres, 75743 Paris Cedex 15, France. pascale.delonlay@nck.ap-hop-paris.fr

[Abstract](#)

[Keywords](#)

[Disease name and synonyms](#)

[Definition](#)

[Main symptoms](#)

[Frequency](#)

[Biological findings](#)

[Diagnostic methods](#)

[Etiology](#)

[Management](#)

[References](#)

Abstract

Barth syndrome is a metabolic disorder characterized by a cardiomyopathy of the dilated type, more rarely of the hypertrophic type, neutropenia, skeletal myopathy, diminished statural growth and 3-methylglutaconicaciduria. However the clinical presentation can be of variable expression. Presentation can be slowly progressive or sudden. In most cases, the disease is manifest in infancy. The most common initial presentation is cardiac failure. Barth syndrome seems to be very rare, however it seems to occur in all ethnic groups. After clinical and biochemical characterization of Barth syndrome, the causative gene was mapped to Xq28 by positional cloning and the G4,5 gene (also called TAZ - tafazzin - gene) was identified by mutational analysis. More than 20 mutations have been identified. Treatment is essentially supportive and follow-up should be multidisciplinary, i.e. done by both cardiologists and hematologists.

Keywords

Metabolic disorder, cardiomyopathy, neutropenia, myopathy, xq28 locus, *taffazin* gene

Disease name and synonyms

- Barth syndrome
- X-linked cardioskeletal myopathy and neutropenia

Definition

Barth syndrome is a rare metabolic disorder characterized by a cardiomyopathy of the dilated type, more rarely of the hypertrophic type, neutropenia, skeletal myopathy, statural growth retardation and 3-methylglutaconicaciduria. However the clinical presentation can be of variable expression.

Main symptoms

Presentation can be slowly progressive or sudden. In most cases, the disease is manifest in infancy. Cardiomyopathy is symptomatic before one year of age and the most common initial presentation is cardiac failure. Neutropenia can be permanent or mostly transitory during infections (cyclic neutropenia) and bone marrow findings reveal a maturation defect with a vacuolation in immature neutrophils. The consequences of neutropenia may be severe (septicemia in newborns) or less dramatic with bacterial skin infections and oral aphthous lesions. Hypotonia and muscular weakness can be severe or ascribed to general failure to thrive.

Frequency

Barth syndrome seems to be very rare, however it seems to occur in all ethnic groups.

Biological findings

Metabolic screening by gas chromatography-mass spectrometry shows elevated excretion of several organic acids, especially 3-methylglutaconic acid but also 3-methylglutaric acid and 2-ethylhydracrylic acid, in addition to a low cholesterol level.

Diagnostic methods

Cardiolipin (CL) is a unique phospholipid with a dimeric structure (diphosphatidylglycerol) that contains four acyl groups and carries two negative charges. CL is found almost exclusively in the mitochondrial inner membrane and plays a central role in mitochondrial oxidative phosphorylation because several respiratory chain complexes depend on CL. Tetralinoleoyl-cardiolipin (L4-CL) is a cardiolipin in which all four acyl positions are substituted by linoleic acid. L4-CL has been shown to be a single mitochondrial phospholipid species which was lacking in the skeletal muscle, heart and platelets of patients with Barth syndrome.

The formation of L4-CL is thought to involve specific acyltransferase activity. Inhibition of this process has been suggested by decreased linoleic acid incorporation into CL in cultured skin fibroblasts of patients with Barth syndrome. This test can be used to diagnose Barth syndrome. Other cardiolipin species are accumulated due to inhibition of the remodelling pathway leading to L4-CL, suggesting one other test to diagnose Barth syndrome. However gene mutation analysis may be needed to complete the diagnosis.

Etiology

After clinical and biochemical characterization of Barth syndrome, the causative gene was mapped to Xq28 by positional cloning and the *G4,5* gene (also called *TAZ* - *tafazzin* - gene) was identified by mutational analysis. The *G4,5* gene has 11 exons and 5 different messenger RNAs dependent on alternate splicing of exons 5, 6 and 7 and 2 transcription initiation sites on exons 1 and 3. More than 20 mutations have been identified.

A skewed X inactivation has been shown in female carriers. In these patients, only some cells contain the mutated gene on the active X chromosome. They therefore do not show any symptom.

The function of the protein encoded by the *G4,5* gene remained unknown for a long time.

Mitochondrial dysfunction has been suspected as abnormal mitochondria were found in myocardial specimens. Variable lactic aciduria and excess excretion of citric acid cycle intermediates were observed, and mitochondrial respiratory chain studies indicated involvement of more than a single complex in muscle biopsy specimens.

Homologues of the *G4,5* gene are conserved in many species. They show sequence homology with a superfamily of acyltransferases. Then the product of the mutated *G4,5* gene has been shown to be homologous to phospholipid acyltransferases. This led to the speculation that the product of the *G4,5* gene is involved in the synthesis or turnover of one or more complex lipids. This could explain the low cholesterol level observed in patients. Membrane structure of the mitochondria, especially the inner membrane that carries the respiratory complexes, may be altered by an abnormal lipid structure. These findings support the notion that Barth syndrome is caused by alteration of mitochondrial lipids.

Management

Treatment is essentially supportive and should be multidisciplinary, that is patients should be followed-up by both cardiologists and hematologists.

References

- Barth PG**, Wanders RJ, Vreken P. X-linked cardioskeletal myopathy and neutropenia (Barth syndrome)-MIM 302060. *J pediatr* 1999; 135:273-276.
- Valianpour F**, Wanders RJ, Barth PG, Overmars H, van Gennip AH. Quantitative and compositional study of cardiolipin in platelets by electrospray ionisation mass spectrometry: application for the identification of Barth syndrome patients. *Clin Chemistry* 2002; 48:1390-1397.
- Barth PG**, Wanders RJ, Vreken P, Janssen EAM, Lam J, Baas F. X-linked cardioskeletal myopathy and neutropenia (Barth syndrome) (MIM 302060). *J Inher Metab Dis* 1999; 22:555-567.
- Schlame M**, Towbin JA, Heerdt PM, Jehle R, DiMauro S, Blanck TJ. Deficiency of tetralinoleoyl-cardiolipin in Barth syndrome. *Ann Neurol* 2002; 51:634-637.
- Vreken P**, Valianpour F, Nijtmans LG, Grivell LA, Plecko B, Wanders RJ, Barth PG. Defective remodelling of cardiolipin and phosphatidylglycerol in Barth syndrome. *Bioch Biophys Res Com* 2000; 279:378-382.