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## Barth Syndrome

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### Definition

Barth syndrome (synonyms: X-linked cardioskeletal myopathy, neutropenia and abnormal mitochondria, 3-methylglutaconic aciduria type II, endocardial fibroelastosis type 2), is a mitochondrial disease (Rezaei et al. 2009; Imai-Okazaki et al. 2018) that presents phenotypic and allelic heterogeneity (Imai-Okazaki et al. 2018). This syndrome is characterized by neutropenia, dilated cardiomyopathy, hypocholesterolemia, aciduria, skeletal myopathy, growth retardation, and cognitive impairment (Rezaei et al. 2009; Imai-Okazaki et al. 2018; Jefferies 2013).

The syndrome was firstly described by Barth et al. in a large Dutch family.

### Introduction

Barth syndrome is an X-linked recessive disease generally caused by mutations in the *TAZ* gene (Rezaei et al. 2009; Imai-Okazaki et al. 2018; Jefferies 2013), which encodes the tafazzin protein. Tafazzin is a phospholipid acyltransferase that is involved in remodeling cardiolipin, which is necessary to maintain mitochondrial structure.

The mutations in *TAZ* gene lead to modifications in cardiolipin composition and to the decline in its total concentration in many tissues and organs, such as granulocytes, fibroblasts, and heart and skeletal muscle (Rezaei et al. 2009).

As cardiolipin is a specific mitochondrial phospholipid, abnormal characteristics of this protein may cause a decrease in mitochondrial respiratory chain complex activity and an oxidative phosphorylation deficiency (Rezaei et al. 2009; Imai-Okazaki et al. 2018).

### Clinical Presentation

Patients with Barth syndrome present clinical disorders associated with the decrease or changes in composition of cardiolipin in many tissues and organs.

The disease is characterized by dilated cardiomyopathy or isolated left ventricular abnormalities, proximal skeletal myopathy, short stature, neutropenia, hypocholesterolemia, cognitive dysfunction, and organic aciduria (Imai-Okazaki et al. 2018; Kang et al. 2016; Steward et al. 2010).

However, this syndrome presents a phenotypic heterogeneity. So clinical manifestations may differ greatly among patients, and they may present variation even in cardiac phenotypes (Imai-Okazaki et al. 2018).


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Various degrees of neutropenia are observed in different patients with Barth syndrome (Rezaei et al. 2009), and it can be associated with bacterial infections and consequently sepsis (Jefferies 2013). The neutropenia may be persistent or intermittent and leads to respiratory and dermatologic infections (Jefferies 2013), besides chronic aphthous stomatitis generally caused by fungus like *Candida* infections (Rezaei et al. 2009).

## Laboratory Findings and Diagnostic Testing

Elevated urinary organic acid excretion in addition to neutropenia and hypocholesterolemia, especially when associated with dilated cardiomyopathy, should lead to suspicion to Barth syndrome (Rezaei et al. 2009; Imai-Okazaki et al. 2018).

Despite Barth syndrome is characterized to present various degrees of neutropenia, the neutrophils seem to have normal function (Rezaei et al. 2009).

Another biochemical abnormality detected in patients with the disease is an elevated monolysocardiolipin/cardiolipin (MLCL/CL) ratio in blood sample. This is a noninvasive test and has been described that the accumulation of MLCL is specific for Barth syndrome and that the MLCL/CL ratio is a better diagnostic marker than the CL (Imai-Okazaki et al. 2018).

Furthermore, the definitive diagnosis may be obtained by genetic analysis. However, because of the allelic heterogeneity, besides direct screening of the *TAZ* gene on the X chromosome, another genetic analysis, such as whole exome sequencing, may be necessary if the *TAZ* gene screening is negative and the patient is clinically suspect. Various mutations have been previously detected in patients with the disease, including frameshift, nonsense, missense, and splice site mutations (Imai-Okazaki et al. 2018).

## Treatment and Prognosis

It is greatly recommended a multidisciplinary approach in the management of patients with Barth syndrome (Reynolds 2015).

Previously, Barth syndrome was considered an early and lethal childhood disease. Even though mortality is still highest in the first 4 years of life, there are patients living until adulthood because of the improvements in the management of neutropenia and infections, skeletal myopathy, and cardiac disease. So, early diagnosis and prompt treatment can improve the prognosis of patients with Barth syndrome (Imai-Okazaki et al. 2018).

Granulocyte colony-stimulating factor (GCSF) may be used in periods of neutropenia to elevate absolute neutrophil numbers, associated with prophylactic antibiotics if clinically necessary (Reynolds 2015).

For short stature, growth hormone (GH) supplementation is not routinely indicated, unless documented central GH deficiency. Despite the decreased levels of GH have been reported in patients less than 15 years old, its levels generally are normal or higher than normal controls at the end of adolescence. As it has been evidenced that arginine depletion may be associated with low growth rates in patients with Barth syndrome, arginine supplementation is a possible treatment in these cases (Reynolds 2015).

The treatment of myocardial dysfunction is essential to prolong life, alleviate symptoms, and provide a better quality of life. The dilated cardiomyopathy can be treated by medical and surgical options, and the treatment must be specific to each cardiac phenotype (Jefferies 2013).

Patients with Barth syndrome also should be benefited by specific dietary interventions (Wintergerst et al. 2017).

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