

BARTH SYNDROME

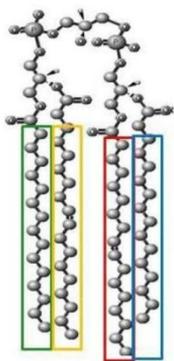
WHAT IS BARTH SYNDROME?

Barth syndrome, TAZ defect or 3-MGA-uria type II is a multisystem disease, with recessive X-linked inheritance, first described by Dr. Peter Barth (1983) in a large Dutch family.

Its prevalence is estimated at 1/300.000- 1/400.000 live births.

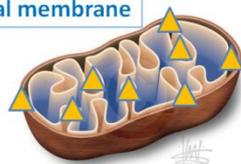
It is caused by mutations in the **TAZ gene** encoding the enzyme protein **tafazzin**.

Cardiolipin



Tafazzin ▲

Internal membrane



External membrane

Membranes are fundamental to the distribution of cell compartments. Mitochondria, namely, have a double membrane, in which anchored proteins and phospholipids can be found.

WHAT IS TFAZZIN?

Tafazzin is an acyltransferase which catalyzes the remodeling of the phospholipid **cardiolipin** located in the inner membrane of the mitochondria.

Cardiolipin is involved in the correct assembly of the ATP synthase complex of the electron transport chain. The electron transport chain is essential for the generation of energy for the cell and is located in the mitochondrial inner membrane.

Altering the remodeling of cardiolipin has been shown to affect the organization and structure of the inner mitochondrial membrane, and is involved in apoptosis (programmed cell death) mitochondrial.

Cardiolipin functions

Optimization of mitochondrial energy production

Stabilization of respiratory chain complexes

Cellular integrity

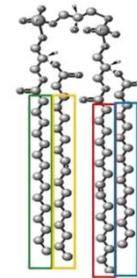
Aging and apoptosis

Mitochondrial protein import

ETC protein control

Vacuolar function

Cellular division



HOW IS BARTH SYNDROME INHERITED?

The **TAZ gene** is located on the X chromosome, so the **inheritance is X-linked**. If the mother is a carrier of a mutation in the **TAZ gene**, may or may not suffer the effects of the enzyme deficiency.

X-linked inheritance



Non-affected father



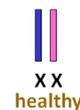
XY



Carrier mother



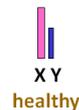
XX



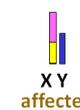
XX healthy



XX carrier



XY healthy



XY affected

If she transmits the mutation to her son, by passing the mutated X chromosome, he will suffer the disease, since he only has one X chromosome and it contains a mutated **TAZ gene**.

If she transmits the mutation to her daughter, who has two X chromosomes, the daughter will become a carrier capable of transmitting the mutated gene. 50% of their daughters will be carriers and 50% of their sons will be affected by **TAZ deficiency**.

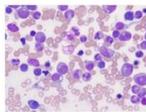
WHAT ARE THE CLINICAL SYMPTOMS OF BARTH SYNDROME?

It occurs between birth and adulthood with cardiomyopathy (heart muscle involvement), neutropenia (decrease in white blood cells), skeletal myopathy (involvement of voluntary muscles), failure to thrive and increased excretion of 3-MGA.

Clinical presentation of Barth syndrome



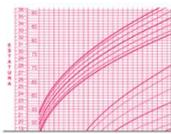
dilated cardiomyopathy



neutropenia



3-MGA-uria



growth failure



myopathy

Cardiomyopathy is one of the main symptoms and is present in 70% of patients already in the first year of life and in the others before 5 years of age. It is generally a dilated cardiomyopathy (dilation and loss of strength of the heart muscle) and can be accompanied by endocardial fibroelastosis (alteration in the structure and composition of the heart muscle that is usually sequel of this and is detected by ultrasound). Progression of cardiomyopathy is variable, and can be stabilized, but overall is progressive and may even require cardiac transplantation.

Neutropenia is a permanent or intermittent finding in 90% of patients. It can be serious, chronic, or cyclical, but overall is intermittent and unpredictable.

Skeletal myopathy is common and many children have motor delay. Muscle weakness is major at the proximal level (near the shoulders and hips) and non-progressive in childhood, so that children can walk but run or play ball with difficulties.

Most patients have **growth failure** probably due to feeding difficulties, diarrhoea, heart disease and recurrent infections.

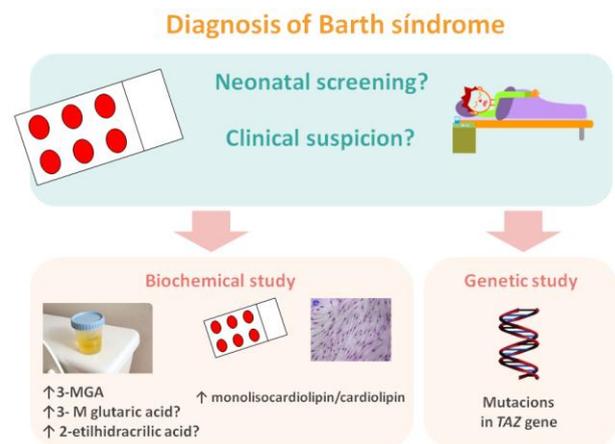
Many children show **dysmorphic features** (broad forehead, round face with prominent chin and cheeks with cherubic appearance, large ears and sunken eyes) more evident in childhood traits. They also have some cognitive difficulties.

No correlation between phenotype (clinical form) and genotype (mutations) and variable phenotypes between males within the same family are observed. Barth syndrome has been described as a cause of recurrent fetal death in males.

HOW IS BARTH SYNDROME DIAGNOSED?

It is diagnosed based on clinical and biochemical data, by the triad of cardiomyopathy, neutropenia and 3-MGA-uria, detectable in the expanded newborn screening.

The excretion of 3-MGA is variable and may be intermittent and not being related to the severity of the clinical course of the disease. Sometimes it is accompanied by 3-methylglutaric and 2-ethylhydracrilic acid. However, patients with normal excretion of 3-MGA have been described.



The presence of lactic acidemia, hypoglycemia (low blood glucose) and hyperammonemia in the neonatal period in infants have been described. Some patients have low levels of total carnitine.

Total cholesterol used to be moderately decreased and also the low density fraction.

Cellular cardiolipin profile is abnormal, showing a significant increase in the monoliscardiolipin/cardiolipin ratio. This altered ratio is perhaps the fastest and most sensitive diagnostic method and can be applied to cells, tissues and even dried blood.

Early diagnosis is very important for prognosis. The TAZ gene mutation study confirms the disease and allows the family genetic counseling and prenatal diagnosis.

HOW IS BARTH SYNDROME TREATED?

The classic treatment of heart failure has included the use of angiotensin-converting enzyme inhibitors, beta blockers, digoxin and diuretics, although there are no published studies analyzing the effectiveness of these therapies. 14% of patients in the Registry of Barth Syndrome Foundation have required a heart transplant.

Most patients, even those which have an adequate nutrition, show a decrease in growth rate during the first two years. Supplements of maize flour (cornstarch) may be used to provide an alternative source of glucose during bedtime and thus limit the degree of muscle loss resulting from an overnight fast.

Symptomatic patients with neutropenia (causing them recurrent infections) are usually treated with a combination of subcutaneous granulocyte stimulating factor and prophylactic antibiotics. Many patients show an evident symptomatic improvement (prevention of aphthous ulcers and sore gums, reducing bacterial infections). Prophylactic antibiotics are often used to reduce the risk of serious infections, especially in children with intermittent neutropenia.

As for the supplements, the value of pantothenic acid has not been proven, and some patients who have been supplemented with L-carnitine have deteriorated soon after its introduction, so that the value of supplementation is not evident.

In addition to medical and surgical intervention, management of patients with Barth syndrome includes supportive care with other specialists such as physiotherapists and occupational therapists, speech therapists, psychologists and special educators. Patients with this complex disease, therefore, are best managed by a multidisciplinary team within specialized units.

However, the prognosis of Barth Syndrome with early diagnosis and proactive treatment has improved considerably in recent times and especially the quality of life of the patients.

Translation

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