Eponym

ARTICLE *in* EUROPEAN JOURNAL OF PEDIATRICS · SEPTEMBER 2011

Impact Factor: 1.89 · DOI: 10.1007/s00431-011-1575-6 · Source: PubMed

Eur J Pediatr (2011) 170:1365–1367
DOI 10.1007/s00431-011-1575-6

REVIEW

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Barth syndrome

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Received: 5 September 2011 / Accepted: 7 September 2011 / Published online: 23 September 2011

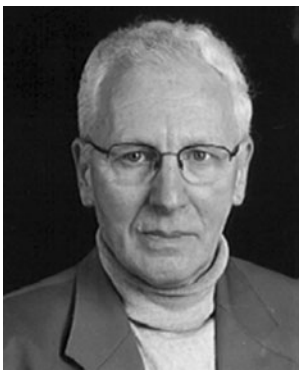

Fig. 1 Dr. Peter G. Barth

Abstract Barth syndrome (OMIM #302060) (BTHS) is an X-linked disorder of lipid metabolism characterized by skeletal myopathy, neutropenia, growth delay, and cardiomyopathy. It is caused by mutations in the tafazzin gene (*TAZ*), which lead to decreased production of an enzyme required to produce cardiolipin, a component of the inner mitochondrial membrane necessary for proper functioning of the electron transport chain. The most common initial presentation of BTHS is significant heart failure due to cardiomyopathy, which is the main cause of death in infancy or childhood. On the other hand, some patients have limited clinical features of BTHS. These patients may be overlooked or misdiagnosed with unclassified congenital myopathy, especially when heart failure is not clinically significant. However, these patients could also develop significant heart failure or life-threatening arrhythmias during or even after childhood. Heart failure in BTHS is often responsive to standard medical therapy, indicating early diagnosis is critical. Diagnostic clues of BTHS in the subclinical stage of heart failure include family histories, findings of lipid storage myopathy in the skeletal muscle biopsy, and elevated plasma brain natriuretic peptide levels. The genetic analysis of *TAZ* is the only confirmatory method for the diagnosis of BTHS. *Conclusion*: physicians should be aware of the possibility of this disease and carry out genetic studies when it is considered.

Keywords Barth syndrome (BTHS) · Lipid storage myopathy · Brain natriuretic peptide (BNP) · Isolated non-compaction of the ventricular myocardium (INVM) · Cardiomyopathy

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Introduction and historical overview of the disorder

In 1983, Dr. Peter G. Barth (Fig. 1), a pediatric neurologist in the Netherlands, first described with his colleagues a large pedigree of X-linked recessive disorder characterized

by skeletal myopathy, neutropenia, growth delay, and cardiomyopathy [3]. The affected patients have high mortality during infancy from severe heart failure or serious bacterial infections owing to neutropenia. Abnormalities of ultrastructure and respiratory chain were observed in their postmortem mitochondria samples. In 1991, Kelley et al. reported seven boys with an X-linked syndrome of dilated cardiomyopathy, growth retardation, neutropenia, and persistently elevated urinary levels of 3-methylglutaconate [15]. Since then, this disorder has been referred to as Barth syndrome (BTHS). In 1996, Bione et al. reported the identification of mutations in Xq28-linked gene, termed G4.5 or *TAZ*, in five families with BTHS [6]. In 1997, Neuwald et al. reported that tafazzin, the protein products of *TAZ*, has a phospholipid acyltransferase function and seems to have an important role in remodeling cardiolipin, a component of the inner mitochondrial membrane necessary for proper functioning of the electron transport chain [4, 18]. So far, over 100 different disease-causing *TAZ* mutations have been reported in all exons.

Clinical presentation

BTHS is associated with a variety of clinical features, including cardiomyopathy, neutropenia, skeletal myopathy, and growth delay (Table 1). These features can change with age and vary significantly between patients.

Heart failure due to cardiomyopathy is the most common initial presentation and the main cause of death in infancy. Survivors beyond infancy could also develop significant heart failure or life-threatening arrhythmias during or even after childhood. Various types of cardiomyopathy have been reported including dilated cardiomyopathy, hypertrophic cardiomyopathy, endocardial fibroelastosis, and isolated noncompaction of the ventricular myocardium (INVM) [21]. Neutropenia may be present at birth and lead to neonatal sepsis, which is the second cause of death in BTHS. However, more common presentation is localized infections of the skin and mucosal membranes [1]. The histology of bone marrow in BTHS often shows a maturation arrest at the myelocyte stage [3].

Table 1 Clinical features in patients with Barth syndrome

Cardiomyopathy (dilated cardiomyopathy, endocardial fibroelastosis, and INVM)
Neutropenia (chronic, cyclic, or intermittent)
Skeletal myopathy (lipid storage myopathy)
Growth delay
3-Methylglutaconic aciduria (normal, <10 μmol/mmol creatinine)

INVM isolated non-compaction of the ventricular myocardium

Patients with BTHS may present with muscular hypotonia due to skeletal myopathy soon after birth and manifest delays in motor development within the first year [5]. However, muscular hypotonia usually improves and does not progress toward respiratory insufficiency or wheelchair dependence. Growth delay is also a common presentation in patients with BTHS, but nearly normal adult height may be achieved in the late teenage years.

Diagnostic clues and workup

Clinical diagnosis of BTHS can be made when there is a combination of clinical features as listed in Table 1. Most patients are diagnosed during infancy after the development of overt heart failure. In contrast, patients in the subclinical stage of heart failure are often overlooked or misdiagnosed even if other features of BTHS are noticed. There are several potential clues to the early diagnosis of BTHS, especially before the development of clinically significant heart failure. A positive family history of BTHS can be the most obvious clue. A family history of early death from cardiomyopathy in males also strongly suggests BTHS [9, 10, 24]. Skeletal muscle biopsy may be another clue to the diagnosis of BTHS; lipid storage myopathy is the characteristic pathological finding of BTHS [3], although the differential diagnoses of lipid storage myopathy alone are extensive [17]. Detection of 3-methylglutaconic aciduria may support the diagnosis of BTHS, although it is not always present.

Additionally, an elevated plasma brain natriuretic peptide level could be one of the most important clues to the early diagnosis of BTHS, especially when it is observed in patients with additional clinical features of BTHS. In such cases, morphological evaluation using echocardiography or cardiac magnetic resonance imaging could be the next step for the diagnosis of BTHS because INVM is the typical finding of BTHS [7, 13].

Thus far, the genetic analysis of *TAZ* is the only confirmatory method for the diagnosis of BTHS [8]. Recently, a tetralinoleoyl cardiolipin high-pressure liquid chromatography–tandem mass spectrometry blood test has become available [16]. Tetralinoleoyl cardiolipin, a metabolite of the acyltransferase that *TAZ* encodes, is significantly reduced in BTHS [12, 19, 20]. In the future, the application of this method to newborn screening will contribute to the early detection of BTHS.

Genetic background

The causative mutations are in *TAZ* [6, 8], which is located at Xq28 and consists of 11 exons. This gene encodes the tafazzin protein, which has a phospholipid acyltransferase

function and seems to play an important role in remodeling cardiolipin, a component of the inner mitochondrial membrane [11]. So far, over 100 different disease-causing *TAZ* mutations including nonsense, frameshift, and missense mutations have been reported in all exons. There was no genotype–phenotype correlation in a study of 14 BTHS pedigrees [14].

Treatment

The treatment strategy depends on the clinical spectrum and severity of the disease. Heart failure in BTHS is mostly responsive to standard medical therapy, such as angiotensin-converting enzyme inhibitors, beta-blockers, and diuretics in a cross-sectional study of the large cohort (age range, 1.2–22.6 years) [21]. Successful heart transplantation was also reported in patients with severe heart failure, although the numbers are limited [2]. Placement of an internal cardiac defibrillator for life-threatening arrhythmias in BTHS was documented to prevent from sudden death [22]. Neutropenia can be usually managed with parenteral antibiotics and administration of granulocyte colony-stimulating factor [23]. Growth hormone therapy is discouraging for growth-retarded children with BTHS. No specific treatment is required for muscle hypotonia because it usually improves spontaneously.

Prognosis and outcome

Infantile BTHS has a high mortality rate from heart failure and severe bacterial infections owing to neutropenia. However, these two manifestations in BTHS are often responsive to standard medical therapy, indicating early diagnosis of BTHS and management of heart failure, and bacterial infections are critical for a better prognosis [7, 21]. Although some patients may have limited clinical features, they could also develop significant heart failure or life-threatening arrhythmias during or even after childhood [21]. Thus, physicians should be aware of the possibility of this disease and carry out genetic studies when it is considered.

Conflict of interest The authors declare that they have no conflict of interest to report.

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