Late diagnosis of Barth syndrome in a 39-year-old patient with non-compaction cardiomyopathy and neutropenia

Andreas Seitz1*, Annely Hinck2, Raffi Bekeredjian1 and Udo Sechtem1

1Department of Cardiology, Robert-Bosch-Krankenhaus, Stuttgart, Germany; 2Department of Medicine–Cardiology, Klinikum Ludwigsburg, Ludwigsburg, Germany

Abstract

Barth syndrome is a rare X-linked recessive disorder characterized by a broad spectrum of clinical features including cardiac and skeletal myopathy, neutropenia, exercise intolerance, and growth delay. Most affected patients are diagnosed during childhood, and mortality is highest in the first years of life. As a consequence, Barth syndrome is often considered a paediatric disease. Here, we report a case where the diagnosis was established in a 39-year-old patient with left ventricular non-compaction and neutropenia. The clinical course of the patient presented here was relatively benign. This suggests that the prevalence of Barth syndrome in adults may be underestimated. Barth syndrome should be considered in the differential diagnosis of male patients with cardiomyopathy and neutropenia.

Keywords Barth syndrome; Cardiomyopathy; Left ventricular non-compaction; Neutropenia; Tafazzin; TAZ

Introduction

Barth syndrome is a rare X-linked recessive disorder characterized by a broad spectrum of clinical features including cardiac and skeletal myopathy, neutropenia, exercise intolerance, and growth delay. The disease is often considered a paediatric disease, because most patients are diagnosed during childhood, and mortality is highest in the first years. Here, we report a case where the diagnosis was established in a 39-year-old patient.

Case description

A 39-year-old male Caucasian patient presented to our outpatient clinic for workup of an unclear cardiomyopathy, which had been known since early childhood. At the current presentation, the patient reported low exercise capacity (NYHA II), pronounced sweating, and an excessive need for sleep (about 10–11 h per night) which had been present since he could remember. The blood pressure was 130/80 mmHg, and proximal muscular hypotrophy was noticed on physical examination. The ECG showed negative T waves in the precordial leads (V4–V6) as well as flattened T waves in the peripheral leads (Figure 1). Blood laboratory testing revealed elevated levels of creatinine kinase (410 U/L [<170 U/L]) and high-sensitive troponin T (45 pg/mL [<14 pg/mL]) and a reduced white blood cell count (2.2 * 10^9 cells/L [3.2 * 10^9–10.5 * 10^9 cells/L]).

The patient’s past medical history included early-onset heart failure and recurrent respiratory tract infections requiring antibiotic treatment. During the first weeks after birth feeding difficulties, fatigue, pronounced sweating, and growth delay (<3rd percentile for weight and height) were noticed leading to hospitalization at the age of 4 months. Physical examination at that time revealed tachypnoea and perioral cyanosis. The ECG showed negative T waves in the precordial leads and cardiomegaly was found on chest X-ray. The LV angiogram demonstrated a reduced LV ejection...
fraction (LVEF) and endomyocardial fibroelastosis. Treatment with digoxin was initiated and continued until the age of 6, when the patient’s condition had stabilized. Neuropediatric assessment at the age of 8, which was performed because of slow motor development and skeletal muscle hypotrophy, revealed floppy muscle tone and positive Gower’s sign. Dystrophic myopathy and polyneuropathy were ruled out by MRI, western blot analysis, and immunohistochemistry. When the patient underwent appendectomy at the age of 10, neutropenia was first noticed, and the diagnosis of intermittent neutropenia was made (latest available neutrophil count 0.7 * 10^9 cells/L). After an episode of acute cardiac decompensation at the age of 12, heart failure therapy was reinitiated including digoxin, spironolactone, and furosemide and continued for a few years before it was stopped again. However, even after heart failure therapy was discontinued, the patient’s condition continuously improved. Thus, he was able to live an almost normal life including graduation from high school followed by a job as a bank clerk. However, he was rapidly exhausted and continued to have an excessive need for sleep. At the time of the current presentation, no medical treatment had been given for at least 15–20 years. The family history included recurrent syncope of the patient’s maternal uncle but was negative for premature heart disease or death from heart failure or infection.

At current presentation, echocardiography showed moderately reduced LVEF as well as hypertrophy and non-compaction of the LV myocardium (Figure 2). For further assessment, cardiac MRI was performed revealing a dilated left ventricle with an LVEF of 41% and hypertrabeculation of the lateral and inferior wall compatible with LV non-compaction (Figure 3). The right ventricle was normal. Late gadolinium enhancement imaging showed diffuse fibrosis of the lateral LV wall. Genetic testing revealed a variant (c.153C>G; p. Tyr51) of the tafazzin (TAZ) gene. Finally, the diagnosis of Barth syndrome was made and heart failure medication was
reinitiated including betablocker and angiotensin-converting-enzyme inhibitor therapy. The condition of the patient remained stable at recent 1-year follow-up.

Discussion

Barth syndrome, which was first described by Peter Barth et al. in 1983, is an X-linked recessive disorder caused by alterations of the TAZ gene, which encodes for tafazzin, a phospholipid transacylase critical for maintaining mitochondrial structure by catalyzing the remodelling of cardiolipin. The clinical manifestation typically involves skeletal and cardiac myopathy, neutropenia, exercise intolerance, feeding problems, and growth delay as well as organic aciduria and lactic acidosis. The type of cardiac involvement varies and comprises features of dilated, hypertrophic, and/or non-compaction cardiomyopathy. Neutropenia can be chronic or intermittent and is associated with recurrent bacterial infections. The incidence of Barth syndrome has been estimated around 1/300 000–400 000 live births in the United States. Estimated prevalence, however, is lower because mortality during childhood is high. In fact, according to the Barth Syndrome Foundation, there were only 151 known living individuals with Barth syndrome in 2012 worldwide. However, adult patients with Barth syndrome have been increasingly reported in recent years suggesting improved survival possibly owing to improvements in diagnosis and treatment. Nevertheless, late diagnosis of Barth syndrome in adult patients remains exceptionally rare. In the present case, the diagnosis was established at the age of 39 although

Figure 2  Echocardiography revealed LV dilatation, hypertrophy, and non-compaction. LV-EF was moderately reduced.
the cardinal characteristics of the syndrome, that is cardiomyopathy, neutropenia, and growth retardation, had been known for many years suggesting that the disease is not well-known among cardiologists. Early diagnosis, however, is important in order to allow early initiation of heart failure treatment and prompt antibiotic treatment in case of bacterial infections. The prognostic implications of an early diagnosis are supported by a comparison of mortality in retrospectively and prospectively identified patients (70% vs. 10%). The underlying mutation can be detected by TAZ sequencing, which is of particular importance in the detection of female carriers or in the setting of antenatal screening. The gene mutation identified in the presented patient has been previously reported. The well-documented course of the disease suggests that childhood might be the most dangerous phase, and adult patients may be oligosymptomatic. Considering this relatively benign course of the disease in our patient, we hypothesize that there could be more unidentified adult patients with Barth syndrome. In the past, one could argue that identifying the underlying genetic pathology in patients with Barth syndrome was not necessary because of the lack of a specific therapy. However, according to the Barth Syndrome Foundation, randomized placebo-controlled trials are currently ongoing or being planned focusing on specific treatments such as bezafibrat or gene replacement therapy. Moreover, positive results have recently been announced for the placebo-controlled, crossover TAZPOWER trial suggesting a potential clinical benefit from elamipretide treatment in patients with Barth syndrome.

Conclusions

Barth syndrome might be underdiagnosed because of a variable spectrum of clinical presentations. We here report a rare case of late diagnosis of Barth syndrome in a 39-year-old patient. The relatively benign course of the disease in this patient corroborates the hypothesis that the prevalence of Barth syndrome in adults may be underestimated. Barth syndrome should be considered in the differential diagnosis of male patients with cardiomyopathy and neutropenia.

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