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SHORT REPORT

Acute metabolic decompensation and sudden death in Barth syndrome: report of a family and a literature review

Ting-Yu Yen · Wuh-Liang Hwu · Yin-Hsiu Chien · Mei-Hwan Wu · Ming-Tai Lin · Lon-Yen Tsao · Wu-Shiun Hsieh · Ni-Chung Lee

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Abstract Barth syndrome presents in infancy with hypotonia, dilated cardiomyopathy, and neutropenia. We report a patient whose family history included two males who had died suddenly at the age of 15 days and 2 years, respectively. The index case presented with acute metabolic decompensation at 13 days of age. Within 8 h of presenting with metabolic acidosis (pH 7.13), lactic acidemia (18.5 mmol/l), hyperammonemia (375 μg/dl), hypoglycemia (25 mg/dl), and coagulopathy, the patient developed respiratory failure and required intubation. The diagnosis was established by the presence of left ventricular noncompaction and molecular analysis (c.C153G or Y51X mutation of the *TAZ* gene). The gene product, taffazin, is a homologue of the glycerolipid transferases involved in the phospholipid metabolism as tetralinoleoyl-cardiolipin, a component of the mitochondrial inner membrane. In conclusion, mutations in taffazin impair mitochondrial respiratory chain complexes, which may results in the acute metabolic decompensation and sudden death; cardiac transplantation is the only possibility at the present time.

Keywords Barth syndrome · Metabolic decompensation · Lactic acidosis · Left ventricle noncompaction

Abbreviations

DGUOK	deoxyguanosine kinase
LDB3	LIM domain-binging protein
LVNC	left ventricular noncompaction
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
PLOG	polymerase gamma
TAZ	taffazin
TK2	thymidine kinase 2

Introduction

Barth syndrome (OMIM #302060), first described by Barth et al. in 1983, is a rare X-linked disorder characterized by cardioskeletal myopathy, neutropenia, growth retardation, and 3-methylglutaconic aciduria [2]. To date, approximately 100 cases have been reported (personal communication from the Barth Syndrome Foundation). The *TAZ* (*G4.5*, taffazin) gene located in Xq28 has been found to be the causative gene, and the *LDB3* gene also may be involved [14]. The gene product, taffazin, a homologue of the glycerolipid acyltransferases superfamily, is involved in phospholipid metabolism. The *TAZ* gene mutation impairs cardiolipin remodeling and reduces the level of tetralinoleoyl-cardiolipin [9]. Cardiolipin is a component of the mitochondrial inner membrane; a cardiolipin deficiency

T.-Y. Yen · W.-L. Hwu · Y.-H. Chien · M.-H. Wu · M.-T. Lin · W.-S. Hsieh · N.-C. Lee
Department of Pediatrics, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

W.-L. Hwu · Y.-H. Chien · N.-C. Lee
Department of Medical Genetics, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan

L.-Y. Tsao
Department of Pediatrics, Changhua Christian Hospital, Changhua, Taiwan

N.-C. Lee (✉)
Department of Pediatrics, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan
e-mail: ncleentu@ntu.edu.tw

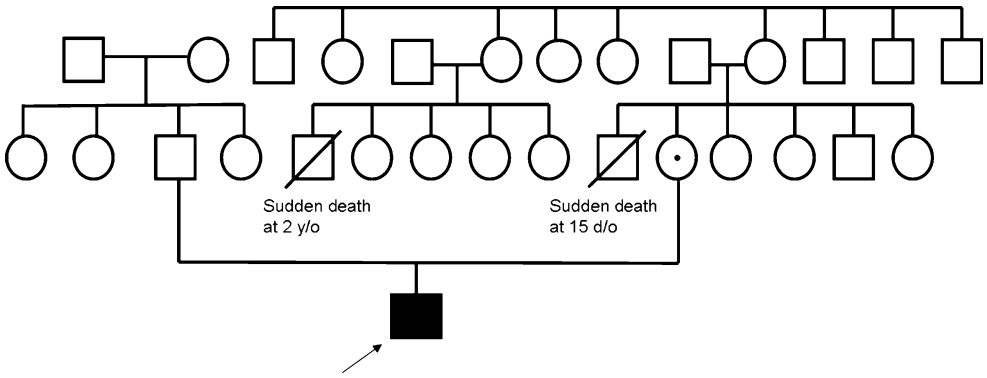

Fig. 1 Pedigree of the patient

changes the mitochondrial lipid milieu and destabilizes transmembrane proteins, mitochondrial respiratory chain complexes, and protein-protein interactions.

Males with Barth syndrome usually present with hypotonia, dilated cardiomyopathy, and neutropenia in infancy. Common causes of death are heart failure and infection; those who survive beyond infancy may have a relatively benign course [2]. Apparently healthy relatives of patients with Barth syndrome have histo- and immuno-pathologic findings similar to those of the patients [12] where cardiac autoantibodies have been evidenced in about 1/3 of the relatives also presenting familial dilated cardiomyopathy [6]. When the family histories of Barth syndrome patients are reviewed, a history of sudden death in infants, sometimes occurring in the early days of life, is occasionally noted. Although a precise diagnosis of the cause of these acute deaths is rarely made, heart problems related to Barth syndrome are usually suspected due to the presence of dilated cardiomyopathy and ventricular non-compaction (LVNC; a cardiomyopathy characterized by numerous excessive trabeculations and deep intertrabecular recesses evidenced on echocardiography) in affected neonates.

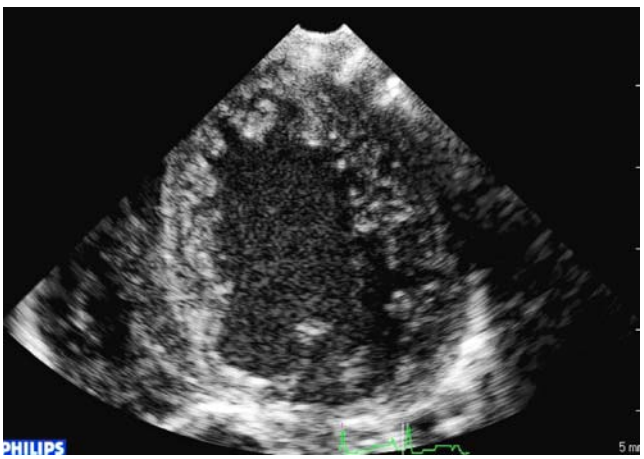

Fig. 2 Echocardiography of this patient showed the typical manifestation of left ventricular noncompaction with the feature of hypertrophic left ventricle with numerous prominent trabeculations and deep intertrabecular recesses

In this paper, we describe a patient who had an acute, life-threatening episode of metabolic decompensation at the age of 13 days. The family history also revealed that two male family members had died acutely at early ages.

Case report

This male patient was the first child of a non-consanguineous, ethnically Chinese couple. He was born after a normal pregnancy and a normal delivery; his birth weight was 3,265 g, and his Apgar score was 9 at 1 min and 9 at 5 min. A review of the family history revealed that one maternal elder brother and one maternal second cousin had died acutely at an early age (15 days and 2 years, respectively) (Fig. 1). The patient was discharged from the nursery at 3 days of age. When he was 13 days old, feeding difficulties, decreased activity, and respiratory distress were noted; the patient was then brought to hospital at midnight. Initial examinations revealed that the patient had no fever, a slightly low blood pressure (65/42 mmHg), tachycardia (heart rate 150–185/min), and tachypnea (respiratory rate 40–75/min). However, laboratory examinations showed a severe metabolic acidosis (pH 7.13, PCO_2 27 mmHg, HCO_3^- 9 mmol/l, base excess −20 mmol/l) with an increased anion gap of 27, hyperammonemia (375 μg/dl, normal <70 μg/dl), lactic acidemia (18.5 mmol/l, normal 0.63–2.44 mmol/l), hypoglycemia (glucose 25 mg/dl, normal 60–100 mg/dl), coagulopathy with prolonged PT/aPTT (31.9/64.6 s, normal 9.5–15.3/35.4–59.8 s), and an elevated D-dimer level (>1,000 ng/dl, normal <300 ng/dl). Liver enzyme levels were normal (ALT/AST 14/58 U/l). The white cell count was 10,100/μl, with an absolute neutrophil count of 5,555/μl. The C-reactive protein level was low (<0.07 mg/dl). The patient's condition deteriorated rapidly; several hours later, the patient required an endotracheal tube and respiratory support, and dopamine was needed to support his blood pressure. With supportive care and empiric antibiotics, his condition improved gradually; he was extubated 3 days later. His septic workup

was negative. Echocardiography revealed cardiomegaly with systolic dysfunction (LVEF 51%). Although severe heart failure can lead to lactic acidosis and metabolic decompensation, his heart function was not that bad. Thus, the patient was transferred to our hospital at 16 days of age.

On arrival at our hospital, the patient's vital signs were stable. However, lactic acid levels were noted to fluctuate; when the patient was agitated, the lactic acid level could reach 11.1 mmol/l. Since LVNC was noted on echocardiography (Fig. 2), Barth syndrome was suspected. A mild elevation of urine 3-methylglutaconic acid was later confirmed. At the age of 1 month, cyclic neutropenia was noted; the leukocyte counts ranged from 2,790 to 8,330/μl, and the absolute neutrophil count varied between 52 to 1,836/μl. The brain MRI was normal. Barth syndrome was confirmed when a c. C153G (Y51X) mutation was identified in his *TAZ* gene. The platelet tetralinoleoyl-cardiolipin level was undetectable. Currently, the patient is 11 months of age. His growth has been poor; his body weight is 6.8 kg (<3rd percentile), and his height is 66.4 cm (<3rd percentile). Aggravation of heart failure occurred when he was 10 months and 27 days old. An emergent mitral valve replacement was done because of the severe mitral insufficiency due to dilation of the cardiac chambers. The patient is currently on the waiting list for cardiac transplantation.

Discussion

Barth syndrome has recently emerged as a unique inborn error that is related to a secondary and generalized disturbance of the mitochondrial electron transfer chain [2, 9]. Among symptoms of Barth syndrome, both cardiomyopathy and skeletal myopathy can be explained by mitochondrial dysfunction; 3-methylglutaconic aciduria is not due to an enzymatic block in leucine metabolism as shown by loading test, but rather reflect overload or more likely mitochondrial leakage. However, the mechanism responsible for neutropenia is not well understood.

Barth syndrome can present at a very early age. Some patients present with cardiac dysfunction as early as the 1st day of life. Earlier studies indicated that there was a high mortality during infancy and childhood; few patients survived beyond 4 years of age [2]. In recent years, increased survival has been observed. Awareness of the diagnosis, as well as early and vigorous treatment of infection and cardiomyopathy, may have contributed to the improvement in the prognosis, but most deaths occur at an early age. Therefore, we suspected that the role that metabolic decompensation can play in the early deaths may have been overlooked. In a recent paper, two cases with clinical findings similar to the current report were described [10]. Both patinets had severe lactic acidemia (10.8 mmol/l and 9.56 mmol/l), profound metabolic acidosis (pH 6.99 in one case), and hypoglycemia (2.2 mmol/l and 1.9 mmol/l). The current patient further had signs of liver failure, including hyperammonemia and coagulopathy. We then reviewed the literature and identified another 21 cases of Barth syndrome in which the clinical courses before 1 month of age were described [2–5, 7, 8, 11, 15–17]. In these reports all patients had cardiomyopathies; few reported the patients' metabolic changes. Therefore, early metabolic changes in Barth syndrome might have been neglected.

Mitochondrial disorders are a heterogeneous group of diseases involving both the mitochondrial DNA and nuclear genes. Recently, the involvement of nuclear genes in mitochondrial diseases is increasingly being recognized. These genes are mostly responsible for the synthesis of mitochondrial DNA (eg. mitochondrial DNA polymerase gamma; *POLG*) or the supply of materials for DNA synthesis (eg. thymidine kinase 2; *TK2* and deoxyguanosine kinase; *DGUOK*) [1]. These nuclear gene-induced mitochondrial syndromes can present as either a myopathic or a hepatocerebral form. In the latter form, lactic acid elevation is prominent, and liver failure often causes early death. It is possible that a disturbance of cardiolipin metabolism may induce frank mitochondrial dysfunction, and death occurs as in other nuclear gene-induced mitochondrial syndromes. In the current case, a delay in treatment of several hours would have resulted in death. The metabolic instability of infants with Barth syndrome is reflected by the increases in blood lactic acid levels that occur when the infant is agitated. A vicious cycle may then become established that ends in death. Therefore, close monitoring of the metabolism of young infants affected by Barth syndrome is needed to better understand the disease's early clinical course. Since cardiac transplantation in Barth syndrome has been successful, and is the only possibility at present time [13], early metabolic stabilization for the young affected infants will be very important.

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