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Barth syndrome: A life-threatening disorder caused by abnormal cardiolipin remodeling

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ABSTRACT

Barth syndrome (BTHS) is a rare X-linked genetic disorder characterized by cardiomyopathy, skeletal myopathy, neutropenia, and organic aciduria. The presence and severity of clinical manifestations are highly variable in BTHS, even among patients with identical gene mutations. Currently, less than 200 patients are diagnosed worldwide, but it is estimated that the disorder may be substantially under-diagnosed due to the variable spectrum of clinical manifestations. BTHS is caused by mutations in the gene tafazzin (*TAZ*), resulting in defective remodeling of cardiolipin (CL), the signature phospholipid of the mitochondrial membranes. Many of the clinical sequela associated with BTHS can be directly attributed to mitochondria defects. In 2008, a definitive biochemical test was described based on detection of the abnormal CL profile characteristic of BTHS. This mini-review provides an overview of the etiology of BTHS, as well as a description of common clinical phenotypes associated with the disorder.

Introduction

Barth syndrome (BTHS) is a rare X-linked genetic disorder associated with a wide array of clinical manifestations, including cardiomyopathy, skeletal myopathy, neutropenia, 3-methylglutaconic aciduria, and hypercholesterolemia[1-3]. The gene locus was mapped to Xq28[4], with mutations identified in G4.5, now referred to as the tafazzin (*TAZ*) gene[4-5]. Tafazzin is a mitochondrial acyltransferase involved in remodeling cardiolipin (CL), the signature phospholipid of the inner mitochondrial membrane[4,6]. Mutations in the *TAZ* gene resulting in either the complete loss of tafazzin or the expression of truncated tafazzin lead to BTHS, and a number of point mutations have also been identified in BTHS patients[4,7]. Interestingly, there is no clear correlation between individual *TAZ* gene mutations and the severity of clinical abnormalities observed in BTHS. Furthermore, clinical manifestations vary from severely incapacitating to nearly asymptomatic, even among patients with the identical *TAZ* gene mutations[8]. The high degree of variation in the clinical symptoms observed in BTHS patients with the same *TAZ* gene mutation suggests that additional physiological factors influence the CL remodeling and clinical outcomes in BTHS. To date, there are no published reports on the identification of other genetic loci that influence the clinical symptoms observed in BTHS. However, studies in yeast have identified genetic loci that exacerbate the phenotypes observed in CL deficient yeast cells. Specifically, it was observed that genetic ablation of pathways involved in acetyl-CoA synthesis,

Fe-S biogenesis, mitochondrial protein import, and supercomplex formation are lethal in CL deficient yeast[9]. Thus, it is tempting to speculate that genetic factors that influence these pathways may contribute to the variability of symptoms in BTHS patients.

CL is a unique phospholipid consisting of four acyl chains, and CL synthesis pathways are highly conserved from prokaryotes to humans[10]. Importantly, newly synthesized CL contains primarily saturated fatty acids, and undergoes remodeling to form CL containing predominately unsaturated fatty acids. CL remodeling involves two steps: (i) enzymatic hydrolysis of a single acyl chain to form a monolysocardiolipin (MLCL) intermediate and (ii) tafazzin-dependent acylation of MLCL. The link between CL and BTHS was first reported by Peter Vreken and colleagues, who demonstrated that fibroblast cultures from BTHS patients contain less CL than control cultures[11]. Furthermore, BTHS cells displayed decreased incorporation of the unsaturated fatty acid, linoleic acid, into both phosphatidylglycerol (PG) and CL. Similar to CL, PG is remodeled in a process that involves the activity of a lysoPG acyltransferase[12]. Previous studies suggest that tafazzin deficiency may be the cause of defective remodeling of both PG and CL in BTHS[11]. However, the clinical significance of defective PG remodeling has not been established in BTHS. Subsequent analysis confirmed that BTHS patient cells have decreased CL content and an accumulation of MLCL species[13]. BTHS patient tissues were found to be completely devoid of tetralinoleoyl CL (L4CL), the predominant CL species found in normal cardiac and skeletal muscle[14].

The availability of BTHS model systems has greatly improved our understanding of the cellular and subcellular consequences of tafazzin deficiencies. The mitochondria of BTHS patient lymphoblast grown in culture exhibit decreased mitochondrial membrane potential, abnormal energy metabolism, and mitochondrial hyperproliferation[15]. These abnormalities are consistent with findings from studies of tafazzin deficient yeast[16] and may be due to increased adhesion of opposing inner mitochondrial membranes leading to altered mitochondrial crista formation[17]. These findings suggest that tafazzin deficiency leads to perturbations in mitochondrial physical structure, which may contribute to the observed bioenergetic defects fundamental to BTHS.

Clinical phenotypes

The most widely characterized clinical phenotypes of BTHS are cardiomyopathy, skeletal myopathy, neutropenia, growth retardation and 3-methylglutaconic aciduria[18]. Studies involving large cohorts of BTHS patients conducted in 2006 and 2012 provide information about additional clinical manifestations observed in BTHS, including cardiac emboli, septicemia, hypocholesterolemia, hypoglycemia, lactic acidosis, osteopenia, fetal hydrops, and miscarriage and stillbirth of male fetuses[19,20]. The predominant clinical phenotypes observed in BTHS patients are further described as follows.

Cardiomyopathy

The major clinical manifestation observed with high prevalence during the early stages of life in BTHS is cardiomyopathy. Data from the BSF registry indicate that when a diagnosis of BTHS is made before six months of age, nearly 70% of patients present with cardiomyopathy; however, other BTHS patients developed cardiomyopathy within the first five years of life[20]. Importantly, while most affected patients present with some form of cardiomyopathy, a small subset of BTHS patients do not present initially with cardiomyopathy, but may develop cardiomyopathy later in life. Thus, initial absence of cardiomyopathy does not preclude a patient from being diagnosed with BTHS. The exact percentage of BTHS patients that do not develop cardiomyopathy is not known. Currently less than 200 patients have been diagnosed with BTHS and nearly all of them have developed cardiomyopathy at some point. There is currently insufficient clinical data to identify any specific compensatory mechanisms. However, compensatory mechanisms likely contribute to the variability in cardiomyopathy severity. The characteristic features of cardiomyopathy in BTHS include dilated cardiomyopathy (DCM) with variable hypertrophy, left ventricular non-compaction (LVNC), and endocardial fibroelastosis. The cardiac manifestations in BTHS often change over time (undulating cardiomyopathy) and can lead to arrhythmia, congestive heart failure and sudden cardiac death[19,21-23]. Unfortunately, cardiomyopathy in BTHS can mimic viral myocarditis and is often diagnosed late or misdiagnosed as a viral infection[19,24] leading to cardiac failure in BTHS. While the link between altered CL remodeling and disturbed cardiac ontogenesis has not been clearly elucidated, loss of CL perturbs cross-communication between mitochondria and endoplasmic reticulum, which may affect calcium handling and contribute to the cardiac phenotype observed in BTHS[25]. A retrospective study of 22 BTHS patients conducted in 2013 found the five-year survival rate to be 51%, with the risk for early mortality peaking in the first few years of life[26]. The study also found that BTHS patients born before 2000 had a five-year survival rate of 22%, compared to 70% in those born in or after 2000. This finding is likely related to improved management of these patients in more recent years.

Skeletal myopathy

Most patients diagnosed with BTHS are widely recognized by pronounced skeletal myopathy, low muscle mass, delayed gross motor development, exercise intolerance, and muscle weakness[19,27]. The loss of muscle mass results in a much lower than expected weight-for-

height, which can be misdiagnosed as failure to thrive. Specific growth curves for boys with Barth syndrome have been published[20], which indicate that between the ages of six to 36 months the 50th percentile for weight of boys with Barth syndrome is roughly equivalent to the third percentile in the standard curve. With age, BTHS patients are unable to conduct normal physical activity, and increased creatine phosphokinase levels have been documented, consistent with debilitating myopathy. Skeletal myopathy leads to easy fatigability, which is exaggerated by the cardiovascular complications associated with BTHS[28,29].

Neutropenia

One clinical phenotype of BTHS that makes the management of these patients particularly challenging is neutropenia, which can be chronic, intermittent, cyclic, or not present. As with cardiac manifestations, neutropenia in BTHS is extremely variable, even among patients with the identical *TAZ* gene mutations. Intermittent or persistent forms of neutropenia are diagnosed in 90% of BTHS patients, putting them at increased risk of life-threatening bacterial infection[7,30]. In fact, more than half of the BTHS patients first diagnosed by Dr. Peter Barth died due to bacterial infection[30]. Often, neutrophil counts partially rebound during an acute infection, which can delay the diagnosis of neutropenia and worsen outcomes associated with common infections, including mouth ulcers, respiratory tract infection due to bacteria, and dermatitis[18]. While granulocyte colony stimulating factor (G-CSF) is routinely used in the management of BTHS, the intermittent and cyclic nature of the neutropenia in these patients complicates the chronic use of G-CSF. Dosing can be challenging because of innate variations in patient neutrophil counts[31]. The molecular mechanism underlying neutropenia in BTHS is currently unknown, thereby limiting the development of effective treatment strategies[20]. Studies by van Raam et al. (2009) suggest that neutropenia results from increased reactive oxygen species within mitochondria triggering the clearance of neutrophils by tissue macrophages[32]. Recent studies have implicated the dissipation of mitochondrial membrane potential, activation of caspase-3, and release of cytochrome C in the accelerated apoptosis of myeloid progenitor cells leading to neutropenia in BTHS[33,34].

Growth delay

BTHS patients often exhibit growth delay, which is likely the result of other underlying complications, including diarrhea, poor nutrition, cardiomyopathy, and recurrent infection[20,35]. However, not all BTHS patients display poor growth. Spencer et al. (2006) reported that 58% of patients less than 18 years of age fall below the 5th percentile for weight and height[19]. The early growth delay is often followed by accelerated growth in mid to late puberty, which may be accompanied by worsening cardiac function.

Metabolic aspects

BTHS patients present with complex metabolic abnormalities, including 3-methylglutaconic aciduria and 2-ethylhydracrylic aciduria. Organic acids present in the urine are often more than 20-fold higher than normal[18]. While 3-methylglutaconic aciduria is an important biochemical marker of BTHS, the variability of urine 3-methylglutaconic acid levels in BTHS patients and the existence of other syndromes in which 3-methylglutaconic aciduria manifests, limits its diagnostic specificity[36]. Other metabolic abnormalities reported in BTHS patients include decreased low density lipoprotein (LDL) cholesterol, reduced plasma carnitine and pre-albumin levels, hypocholesterolemia, hypoglycemia, lactic acidosis, elevated creatine kinase and serum transaminases, and mild hyperammonemia[18,19,37]. Lactic acidosis and hypoglycemia are commonly observed during neonatal and infant life, and are exaggerated during exercise[37,38]. The metabolic phenotype in BTHS is most likely a direct result of defective mitochondrial oxidative metabolism, which ultimately contribute to the aforementioned clinical manifestations.

Inheritance

As BTHS is an X-linked genetic disorder, transmission occurs from mother to son. Women who are heterozygous carriers of a *TAZ* gene mutation do not exhibit symptoms because they have one normal gene[31]. Boys born to a female carrier have a 50% chance of having BTHS, and girls born to a carrier have a 50% likelihood of being carriers themselves. Improved diagnosis and treatment of BTHS has resulted in affected patients reaching sexual maturity. All daughters of males with BTHS are carriers; however, sons of males with BTHS will not inherit the mutated allele. To date, one female BTHS patient was diagnosed and found to be a hemizygote for the mutated allele of the *TAZ* gene[39].

Diagnosis

The initial diagnostic triad used to identify BTHS relied on male patients presenting with a combination of cardiomyopathy, 3-methylglutaconic aciduria, and neutropenia. This, however, proved to be insufficient, as many BTHS patients did not present with either neutropenia or 3-methylglutaconic aciduria. Currently, a straightforward diagnosis of BTHS is made by assaying the ratio of MLCL:L4-CL[13,40,41]. This diagnostic assay is highly sensitive and specific for BTHS[40-42]. A recent study employing targeted next-generation sequencing of children diagnosed with primary cardiomyopathy provides evidence for a high rate of newly identified TAZ mutations[43]. This suggests that the incidence of BTHS is larger than originally estimated based on confirmed cases. Accordingly, a diagnosis of BTHS should be considered in cases of male children who present with any combination of the following: cardiomyopathy,

neutropenia, skeletal myopathy, growth delay, or a family history consistent with X-linked inheritance, including pregnancy loss involving male fetuses. Furthermore, the measurement of the MLCL: L4-CL ratio should also be considered in such cases.

Treatment

Standard treatments to manage heart failure include beta blockers, angiotensin converting enzyme (ACE) inhibitors, diuretics, and digoxin, but no published studies have directly evaluated the efficacy of these therapies in BTHS. Commonly, BTHS patients require cardiac transplantation[29]. The combination of prophylactic antibiotics and G-CSF are used to treat symptomatic neutropenia. To date, no food or drug supplement has been shown to be conclusively beneficial for the management of cardiomyopathy or neutropenia[44]. However, preventing hypoglycemia (e.g. during overnight fasting) may reduce muscle atrophy. In addition to traditional surgical and medical intervention, specialized care in the form of occupational, physical, language, and speech therapy plays a significant role in the management of BTHS.

Conclusion

BTHS is a complex disorder arising from an inborn error in CL remodeling. Since its first description, BTHS was presumed to be an extremely rare disorder and only patients presenting with a combination of cardiomyopathy, neutropenia, and 3-methylglutaconic aciduria were diagnosed. However, the estimated frequency of this disease is much higher than previously suspected, as many clinicians are unaware of the disease, its clinical features, or diagnostic tests. It is highly recommended that a diagnosis of BTHS be ruled out in male babies and young boys presenting with unexplained ventricular arrhythmia or sudden death, cardiomyopathy, LVNC, bacterial sepsis, or unexplained feeding problems. Ongoing research endeavors using BTHS model systems and BTHS patient tissues will continue to expand our understanding of the pathophysiology underlying BTHS and provide new treatment avenues. All interested scientists and clinicians should refer to the Barth Syndrome Foundation website (www.barthsyndrome.org) where a routinely updated archive of all BTHS-related research publications, case studies, as well as diagnostic and treatment recommendations are published.

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