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Barth Syndrome – A Review

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ABSTRACT:
Barth syndrome is an X-linked recessive mitochondrial illness (MID) with infantile onset that is incredibly rare and mostly affects men. G4.5 is most likely the genetic locus associated with Barth syndrome. It is caused by a mutation in the highly conserved acyltransferase gene TAZ (previously known as tafazzin), which is located at Xq28. Clinically, skeletal muscle myopathy (BTHS) is a common sign. Because the primary defect in the pathophysiology of BTHS is the alteration of cardiolipin, a phospholipid found in mitochondrial membranes, it is unique among human diseases. There are two phases of CL remodeling. An increase in the monolysocardiolipin to cardiolipin ratio (MLCL/CL ratio) is the primary metabolite measurement utilized for diagnosis in BTHS.The effects of bezafibrate, an agonist of the peroxisome proliferator-activated receptor (PPAR), and elamipretide, a drug that targets the cardiolipin, were studied.

KEY WORDS: Barth syndrome, Cardiolipin, Tafazzin, Acyltransferase, Elamipretide, Bezafibrate, Monolysocardiolipin.

I. INTRODUCTION

Due to variants in a nuclear DNA-located gene encoding for the cardiolipin trans-acylase tafazzin (TAZ), originally known as G4.5.2, Barth syndrome (Online Mendelian Inheritance in Man [OMIM] 302060) is an extremely rare, infantile-onset, X-linked recessive mitochondrial disorder (MID), primarily affecting males. Biochemically, TAZ variants cause a decrease in total cardiolipin with a specific decrease in tetralinoleoyl cardiolipin and an increase in monolysocardiolipin. (1)

Barth syndrome is also known as 3-methylglutaconic aciduria type 2 (BTHS), skeletal myopathy with aberrant mitochondria and neutropenia, DNAJC19 deficiency, MGA type 2, and MGA type II, 3 type II “.

The original G4.5 transcript can be transcribed into different mRNAs by alternative splicing, which results in the production of new proteins with distinct N termini and core regions. Most of the putative proteins—which we refer to as "tafazzins"—have their translation interrupted by stop codons introduced by the mutations in the open reading frame. Based on our findings, the genetic locus linked to Barth syndrome is likely G4.5. (2).

G4.5 mutations were found to be the cause of BTHS. When Bione et al. cloned this gene, they called the G4.5 encoded protein TAFAZZIN (TAZ), after the masochistic television character "Tafazzi," who was well-liked in Italy. It was discovered that skeletal and cardiac muscle had high levels of TAZ expression. Although the rates of biosynthesis of CL and its processor, phosphatidylglycerol (PG), were normal, Vreken et al. reported that the CL levels were significantly decreased in cultured skin fibroblasts derived from BTHS patients, in accordance with the bioinformatic prediction that TAZ belongs to a superfamily consisting of acyltransferases involved in phospholipid biosynthesis and/or remodelling. (3).

The highly conserved acyltransferase gene TAZ (formerly known as tafazzin), which is located at Xq28, is mutated to cause it. A wide range of conditions can be seen in the clinical symptoms, such as ventricular arrhythmia, sudden cardiac death, endocardial fibroelastosis (EFE), hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and prolonged QTc interval. Delayed motor milestones, proximal myopathy, fatigue and lethargy, neutropenia (absent to severe; persistent, intermittent, or perfectly cyclical), growth and pubertal delay, hypoglycaemia, lactic acidosis, feeding issues, failure to thrive, episodic diarrhoea, distinctive facies, and X-linked family history are some of the conditions that may be present. (4)

Low blood cholesterol, increased urinary excretion of 3-methylglutaconic acid, 3-methylglutaric acid, and 2-ethylhydracrylic acid, and fluctuating lactic acidaemia and lactic aciduria (Barth et al., 1983) are among the clinical biochemical characteristics. The illness was attributed to distal Xq28 by linkage analysis. The conditions of X-Linked cardioskeletal myopathy and neutropenia.(5)

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Skeletal muscle myopathy (BTHS) is a prominent clinical symptom marked by hypotonia, exercise intolerance, and muscular weakening and atrophy. Not only does skeletal myopathy impair muscle function during exercise, but it can also make it difficult to carry out daily tasks and eventually lead to the need for ambulatory support. There is currently a knowledge vacuum that hinders the development of effective treatments for people with BTHS because the processes linking skeletal myopathy to TAFAZZIN mutations are poorly understood.(6).

Although some people may not experience neutropenia, it varies for each individual over time and within the population. Furthermore, major bacterial infections and even death can result from neutropenia in BTHS patients [Barth et al., 2004]. A common early characteristic of the condition is skeletal muscle weakness, which is proximal in nature and causes motor deficits. (7).

II. MATERIALS AND METHODS

Information sources

Potential studies were identified through a systematic search of online databases, including PubMed, Embase, CENTRAL, ClinicalTrials.gov, Scopus, and preprint servers (medRxiv, bioRxiv, and SSRN). No time or language filters were applied.

Search

In general, the following search keywords were used: “Barth Syndrome”, “Taffazins”, “Cardiolipin”, “Skeletal myopathy”, “Methylglutaconic aciduria”, “Neutropenia”, “X-linked recessive mitochondrial disorder”, “Remodelling”, “MLCL/CL ratio”, “Elamipretide”, “Bezafibrate”, and “CARDIOMAN”.

PATHOGENESIS:

The pathophysiology of BTHS is distinct since it is the only human disease that is known to have modification of cardiolipin, a phospholipidpresentin mitochondrial membranes, as its main abnormality. Given that the disease affects numerous body systems from prenatal development to adulthood, obstetricians, geneticists, general pediatricians, cardiologists, and neurologists should be aware of it. This is especially true now that rapid, conclusive biochemical testing is readily available. (8).

Even if the pathophysiology of BTHS is still unclear, phospholipid side chain remodelling gone wrong is a significant effect of this enzyme shortage (Vreken et al., 2000). This leads in lack of cardiolipin (CL) with four linoleic acid side chains and relative excess of monolysocardiolipin (MLCL, with just three side chains), and therefore to a severely aberrant MLCL/CL ratio (Valianpour et al., 2005; Schlame, 2007).(9)

Cardiolipin, also known as bis-(1,2-diacyl-sn-glycero-3-phospho)-1′,3′-sn-glycerol, is an essential phospholipid found in the mitochondrial membrane. It is made up of two phosphatidyl moieties that are linked to glycerol. In higher mammals, the four acyl chains are typically composed of mono- and di-unsaturated fatty acids. Cardiolipin remodelling determines the ultimate, unique acyl composition of the molecule through deacylation and subsequent reacylations. Mammals only contain CL in the inner membrane of their mitochondria; nonetheless, it is typically concentrated at the places where the inner and outer membranes of the mitochondria meet.(10)

Two stages are involved in CL remodelling: (i) tafazzin-dependent acylation of MLCL, which is formed by the enzymatic hydrolysis of a single acyl chain to generate an intermediate monolysocardiolipin (MLCL). Peter Vreken et al. initially documented the association between CL and BTHS by showing that fibroblast cultures from patients with BTHS had lower levels of CL than control cultures11. In addition, it was observed that BTHS cells incorporated less linoleic acid, an unsaturated fatty acid, into phosphatidylglycerol (PG) and CL. LysoPG acyltransferase12 is involved in the remodelling of PG, same like it is in CL. Tafazzin deficiency may be the root cause of BTHS11's faulty remodeling of both PG and CL, according to earlier research. On the other hand, in BTHS, the clinical implications of faulty PG remodeling, isyet unknown.(11)

Tafazzin, the only remodelling enzyme found in the three distinct CL remodeling pathways described in mammals, is an MLCL transacylase that transfers an acyl chain from another phospholipid—PC or PE, preferably—to MLCL, regenerating CL in its fully mature form (Xu et al., 2003, 2006). Mammalian CL remodeling involves two more enzymes. The MLCL acyltransferase 1 (MLCLAT1) in pig liver mitochondria demonstrates a selectivity for linoleate and sits on the inner leaflet of the IMM(Taylor et al., 2012). It's interesting to note that BTHS patient lymphoblasts with overexpressed MLCLAT1 incorporated more linoleic acid into CL.(12)

Ten differently sized introns and eleven short exons make up the human TAZ gene. There

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are currently 105 known TAZ gene mutations, 94 of which have been linked to BS. But in BS, there hasn't been any evidence of a relationship between the genotype and the severity of the illness or the cardiac characteristics.(13)

Tetralineoyl-CL was absent and monolyso-CL accumulated in heart muscle as a result of TAZ deficiency. Moreover, there were modifications to the mitochondrial morphology of skeletal and cardiac muscle. The cristae of the mitochondria in skeletal muscle were disturbed, and the mitochondria in the heart were noticeably enlarged and moved neighbouring myofibrils.(14)

DIAGNOSIS

The main metabolite measurement used for diagnosis in BTHS is an increase in the monolysocardiolipin to cardiolipin ratio (MLCL/CL ratio). In blood spots, the diagnostic sensitivity and specificity of this ratio are 100%. Increased plasma and urine concentrations of 3-methylglutaconic acid (3MGC) are among the other biochemical anomalies commonly observed in BTHS. Sequencing the TAZ gene can molecularly confirm a diagnosis of BTHS; pathogenic variations, including missense, nonsense, splice, minor in/dels, and big deletions, have been identified in all exons except exon 5. (15)

An unambiguous screening test for BTHS is HPLC-tandem mass spectrometry analysis of dried bloodspots, which has the potential to screen newborns suspected of having BTHS quickly. This allows for distant and retrospective diagnosis for a condition that is most likely underdiagnosed. (16)

TREATMENT

The multisystem illness known as Barth syndrome may have been initially recognized by a variety of experts or generalists. Although Barth syndrome does not yet have a treatment, it is often able to manage its clinical symptoms. (16)

Treatment now focuses on managing particular clinical characteristics rather than correcting the underlying metabolic abnormality. Two recent clinical trials, however, have focused on the mitochondrial pathology of this illness. Elamipretide, a medication that targets the cardiolipin, and bezafibrate, an agonist of the peroxisome proliferator-activated receptor (PPAR), were investigated for their effects. Enzyme and gene therapies are among the treatments being developed to specifically target the malfunctioning TAFAZZIN pathway.(17)

Lipid replacement therapy, peroxisome proliferator-activated receptor agonists, tafazzin gene replacement therapy, induced pluripotent stem cells, mitochondria-targeted antioxidants and peptides, and the polyphenolic compound resveratrol are among the most recent and promising therapeutic options for this uncommon mitochondrial disease.(18). Due to a critical role in energy metabolism and mitochondrial bioenergetics, peroxisome proliferator-activated receptors (PPARs) may be viable therapeutic targets for metabolic focused therapy to improve cardiac dysfunction resulting by Taz shortage.(19)

Bezafibrate's effectiveness in treating individuals with Barth syndrome was examined in the UK single-center, double-blinded, randomized, placebo-controlled CARDIOMAN (Cardiolipin Manipulation) research. The course of treatment was divided into two 15-week periods, with at least one month of washout time in between each phase. In addition to evaluating bezafibrate's potential as a treatment for the disease and expanding our understanding of the mechanisms behind Barth syndrome, the feasibility of the CARDIOMAN project will contribute to the conduct of future randomized controlled trials in populations affected by rare diseases.(20)

Elamipretide has been proven in trials to date to stabilize the inner mitochondrial membrane and aid in normalizing these processes, hence improving ATP production in BTHS, where cardiolipin is dysfunctional. In addition to having positive effects on cellular functions like normal gene and protein expression, the increase in ATP synthesis aids in meeting demand. In order to restore the health of the heart's muscle cells, or cardiomyocytes, normal genes and proteins facilitate mitochondrial repair and permit normal pathway communication.(21)

III. CONCLUSION

There are many different phenotypic variations in BTHS, an uncommon genetic condition. Our work offers important new perspectives on the effects of BTHS's psychosocial and mental health components. Over time, quality of life underwent substantial changes in a number of areas, both positively and negatively. Significant changes in anxiety and depression ratings were observed in a large number of persons. These findings help us understand the clinical pathway that is available for the BTHS population's essential and suitable care.(22)

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