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REVIEW

Barth syndrome: mechanisms and management

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Objectives: Barth syndrome is an ultra-rare, infantile-onset, X-linked recessive mitochondrial disorder, primarily affecting males, due to variants in *TAZ* encoding for the cardiolipin transacylase tafazzin. This review aimed to summarize and discuss recent and earlier findings concerning the etiology, pathogenesis, clinical presentation, diagnosis, treatment, and outcome of Barth syndrome.
Method: A literature review was undertaken through a MEDLINE search.
Results: The phenotype of Barth syndrome is highly variable but most frequently patients present with hypertrophic/dilated/non-compaction cardiomyopathy, fibroelastosis, arrhythmias, neutropenia, mitochondrial myopathy, growth retardation, dysmorphism, cognitive impairment, and other, rarer features. Lactic acid and creatine kinase, and blood and urine organic acids, particularly 3-methylglutaconic acid and monolysocardiolipin, are often elevated. Cardiolipin is decreased. Biochemical investigations may show decreased activity of various respiratory chain complexes. The diagnosis is confirmed by documentation of a causative *TAZ* variant. Treatment is symptomatic and directed toward treating heart failure, arrhythmias, neutropenia, and mitochondrial myopathy.
Conclusions: Although Barth syndrome is still an orphan disease, with fewer than 200 cases described so far, there is extensive ongoing research with regard to its pathomechanism and new therapeutic approaches. Although most of these approaches are still experimental, it can be expected that causative strategies will be developed in the near future.
Keywords: Barth syndrome, tafazzin, TAZ, cardiomyopathy, non-compaction, X-linked

Introduction

Barth syndrome (Online Mendelian Inheritance in Man [OMIM] 302060) is an ultra-rare, infantile-onset, X-linked recessive mitochondrial disorder (MID), primarily affecting males, due to variants in a nuclear DNA-located gene encoding for the cardiolipin transacylase tafazzin (TAZ),[1] which has been initially termed G4.5.[2] Biochemically, *TAZ* variants result in a decrease in total cardiolipin with a specific decrease in tetralinoleoyl cardiolipin and an increase in monolysocardiolipin.[1] Barth syndrome was first described in 1983 by Barth et al, and is phenotypically characterized by the triad of mitochondrial myopathy, neutropenia, and dilated cardiomyopathy.[3] Additional phenotypic features of the initial description include exercise intolerance, lactic acidosis, abnormal lipid composition of mitochondrial membranes, low serum and muscle carnitine, and increased organic acids in the serum or urine.[3,4] This review aims to summarize and discuss recent and earlier findings concerning the etiology, pathogenesis, clinical presentation, diagnosis, treatment, and outcome of patients with Barth syndrome.

Methods

Data for this review were identified by searches of MEDLINE for references of relevant articles. Search terms used were "Barth syndrome", "tafazzin", "TAZ",

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"G4.5", and "cardiolipin", combined with "noncompaction", "non-compaction", "cardiomyopathy", "mitochondria", "neutropenia", "3-methylglutaconic acid", "left ventricular hypertrabeculation", and "therapy". Results of the search were screened for potentially relevant studies by the application of inclusion and exclusion criteria for full texts of relevant studies. Included were randomized controlled trials, observational studies with controls, case series, and case reports. Only original articles about humans and published between 2000 and 2019 were included. Excluded were reviews, editorials, letters, and articles in languages other than English, French, Spanish, or German. Reference lists of retrieved studies were checked for reports of additional studies. Three websites were checked for additional, particularly genetic, information: Genetic Home Reference: https://ghr.nlm.nih.gov/condition/barth-syndrome; GeneReviews Bookshells NCBI: https://www.ncbi.nlm.nih.gov/books/NBK195853/; and Neuromuscular Disease Center: https://neuromuscular.wustl.edu/

Results

History

Barth syndrome was first described by Barth et al in 1983.[3] The title of the original article was "An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes".[3] Elevated levels of organic acids, particularly 3-methylglutaconic acid (3-MGA), in the serum and urine were first reported in 1996 by Christodoulou et al.[5] The protein that is mutated in Barth syndrome, tafazzin, was first identified in 1996 by Bione et al.[2] The first causative *TAZ* variant was also detected by Bione et al in 1996.[2] Identification of tafazzin functions started in 1999.[6] The first mouse model of Barth syndrome was introduced by Acehan et al in 2011.[7]

Etiology

Barth syndrome is due to variants in *TAZ* on chromosome Xq28. About 45% of the genomic sequence of *TAZ* is represented by interspersed repeat sequences (LINES, SINES) and 75% of them are Alu sequences.[8] The gene produces four major mRNA splice variants.[9] Point mutations (substitutions, truncations), deletions,[10] and duplications have been identified so far as being causative. In more than 90% of cases, point mutations are responsible for the disease.[11] No variants in other genes have been reported to cause Barth syndrome. Rarely, Barth syndrome may be due to microdeletions of the X-chromosome.[12] As a result of alternative splicing, various different mRNAs are produced (eg, canonical/reference sequence, deletion of exon 5 or 7, or both).[2,13] *TAZ* variants lead to loss of function of tafazzin.[14] Almost exclusively, hemizygous males are affected.[15] Affected males express complete penetrance but with variable expressivity. There is no ethnic or racial predilection, as Barth syndrome occurs worldwide. Since *TAZ* is located on the X-chromosome, transmission of the disease follows an X-linked trait of inheritance. Only in a single case has compound hemizygosity been reported.[16] Mild clinical manifestations in patients with *TAZ* missense mutations are attributed to the minimal inhibitory effect of these variants on the enzyme function.[17]

Pathogenesis

Tafazzin

TAZ encodes a membrane-associated transacylase involved in phospholipid biosynthesis, also called tafazzin, which is responsible for remodeling the inner mitochondrial membrane phospholipid, cardiolipin.[18,19] Tafazzin contains 292 amino acids and has a molecular weight of 33.5 kDa. Tafazzin contains a transmembrane domain and a phosphate, acyltransferase domain. Tafazzin shuttles acyl groups between phospholipids or, more specifically, transfers unsaturated fatty acids with acyl chains from phospholipids to monolysocardiolipin, and regulates the remodeling and maturation of cardiolipin.[20,21] The reason why general ablation of tafazzin leads to cardiomyopathy is the impaired formation of respiratory chain super-complexes, specifically in myocardial tissue, and the cardio-specific loss of succinate dehydrogenase.[22] In mouse embryonic fibroblasts, doxycycline-induced knockdown of taz impaired oxidative phosphorylation, and caused severe oxidative stress and defective mitophagosome biogenesis.[23]

Cardiolipin

Cardiolipin is synthesized de novo from phosphatidic acid via the cytidine-5′-diphosphate-1,2-diacyl-sn-glycerol pathway and is deacylated to monolysocardiolipin to be remodeled into the form that is observed in mitochondrial membranes.[24] This resynthesis of deacylated cardiolipin from monolysocardiolipin occurs via tafazzin and acyl-lysocardiolipin acyltransferase-1, monolysocardiolipin acyltransferase-1, and the alpha-subunit of trifunctional protein.[24] Mature cardiolipin is essential in the mitochondrial membrane for mitochondrial morphology and function, particularly in tissues with high energy demand.[7] Cardiolipins are

crucial for correct mitochondrial structure and function. In addition to their contribution to basic mitochondrial functions of ATP production, cardiolipins play essential roles in cardiac function, apoptosis, autophagy, cell cycle regulation, and Fe-S cluster biosynthesis.[20] Unlike most phospholipids, which carry two fatty acyl chains, cardiolipin has four acyl chains, resulting in unique biophysical characteristics that affect several biological processes, including membrane fission and fusion.[21] *TAZ* variants lead to compositional alterations of cardiolipin molecular species, causing respiratory chain dysfunction, extensive mitochondrial aberrations, and ultrastructural muscle damage.[25] Mitochondrial dysfunction is particularly characterized by reduced mitochondrial membrane potential and by reduced activity of complex V of the respiratory chain.[26] There is specific destabilization of higher order oxidative phosphorylation super-complexes, as well as changes in complexes involved in cristae organization and cardiolipin trafficking.[27] In addition, the key metabolic complexes 2-oxo-glutarate dehydrogenase and branched-chain ketoacid dehydrogenase are profoundly destabilized in fibroblasts of patients with Barth syndrome.[27] Recent studies on cell cultures revealed that phosphorylation of phosphor proteins (phosphokinome profile) is impaired in lymphoblasts from Barth syndrome patients.[1] Pathway analysis of abnormal metabolites may generally show involvement of mitochondrial and extramitochondrial biochemical pathways, including insulin regulation of fatty acid metabolism, lipid metabolism, biogenic amine metabolism, amino acid metabolism, endothelial nitric oxide synthase signaling, and tRNA biosynthesis.[28] Which of these pathways is most severely affected in Barth syndrome remains speculative. There are indications that cardiolipin is uniquely protected from normal lipid turnover by its association with mitochondrial membrane proteins. This particular association is compromised in Barth syndrome and leads to an unstable cardiolipin.[29]

Phenotype

The phenotype is generally quite variable.[30,31] According to the original description, Barth syndrome most frequently manifests with infantile-onset cardiomyopathy, myopathy, and neutropenia.[3] Additional, typical phenotypic features, including prepubertal growth retardation, failure to thrive, chronic fatigue, dysmorphism, most evident in early infancy, and cognitive impairment, have later been identified.[11] Which of them are the most prevalent features has not been investigated so far.

Cardiac disease

Cardiomyopathy. Cardiomyopathy is most frequently of the dilated type and almost always presents before the age of 5 years.[32] Dilated cardiomyopathy may go along with or without left ventricular hypertrabeculation (LVHT), also known as left ventricular non-compaction, and with or without endocardial fibroelastosis or subendocardial vacuolization of myocytes.[33] LVHT can be found in about half of the patients with Barth syndrome.[34] In a study of 11 patients with Barth syndrome, LVHT was detected in seven of them (63%).[35] In a study of 79 patients with LVHT, two were detected who carried *TAZ* variants.[36] More rarely than dilated cardiomyopathy, hypertrophic cardiomyopathy can be found in Barth syndrome.[37] Cardiomyopathy may change from the hypertrophic type to the dilated type and vice versa.[11] In some cases, cardiomyopathy may improve over time or may remain stable throughout the disease course.[11] LVHT can be complicated by heart failure, cardioembolism, ventricular arrhythmias, and sudden cardiac death (SCD).[16,31,38,39] Cardiac abnormalities may be more prevalent if LVHT is present. Only rarely, cardiomyopathy may develop late in the disease course[40] or patients may not develop cardiomyopathy at all.[25] Cardioembolism may be complicated by embolic stroke or occlusion of peripheral arteries.

Arrhythmias and conduction defects. Patients with Barth syndrome carry an increased risk of developing conduction defects or supraventricular or ventricular arrhythmias, potentially leading to SCD.[38,41] Arrhythmias and conduction defects may occur in children and adolescents, but also in adults.[11] In a study of five patients with ventricular arrhythmias leading to cardiac arrest or implantation of an implantable cardioverter defibrillator, all five had a history of vagovasal manifestations, including postural dizziness, nausea, and pallor.[41] Four patients presented with only mild dilatation and normal or mildly decreased systolic function, and only one manifested with severely reduced systolic function.[41] In three of these patients, electrophysiological stimulation induced ventricular arrhythmias.[41] In two of these patients, the family history was positive for SCD.[41] Holter recordings were normal in two patients.[41]

Neutropenia

Neutropenia in Barth syndrome may be mild (1,000–1,500 cells/μL), moderate (500–1,000 cells/μL), or severe (<500 cells/μL).[42] Neutropenia may be chronic (persisting) or cyclic.[19] Neutropenia is independent of age.[11] In a study of

22 patients, neutropenia was found in 16 of them (72%).[35] According to a study of 73 patients, neutropenia occurred in almost 70% of them.[43] Neutropenia may be complicated by infections, as reported in the initial description of the disease.[1] In this study, three of seven patients died from infections.[1] According to the study by Roberts et al, 60% of affected males had mouth ulcers, 20% pneumonia, and 10% bacteriemia.[43] Overall, the frequency of infections is, despite neutropenia, lower than initially believed. A reason for the relatively low frequency of infections in Barth syndrome could be a compensatory upregulation of monocytes.[44] In the study by Rigaud et al, the median number of monocytes was 1,100 cells/μL.[35] In a study of 28 patients, the mean number of monocytes was 894 cells/μL.[45] In a 2019 study of 88 patients, 84% presented with neutropenia below 1.5×10/L in at least one cell count and 44% had severe, chronic neutropenia.[46]

Mitochondrial myopathy

Myopathy in Barth syndrome predominantly affects proximal limb muscles and is clinically characterized by mild weakness, wasting, exercise intolerance, and hypotonia.[47] Myopathy in Barth syndrome is frequently non-progressive or only minimally progressive during childhood.[32] Muscle weakness may be associated with delayed motor milestones, manifesting as a delay in sitting up (66%) or a delay in learning to walk (72%).[48] In a study of 22 patients, the median age of walking was 19 months.[35] Exercise intolerance in Barth syndrome may be attributable not only to myopathy but also to cardiac involvement or impaired oxygen utilization by the muscle.[48] In a study of 33 patients, the motion reaction time, functional exercise capacity, knee extension strength, physical activity, and balance were reduced.[49] In a cell model using C2C12 myoblasts, differentiation of these cells was reduced.[50] Reduced bioenergetics of the skeletal muscle is reflected by the peak oxygen uptake on phosphorus magnetic resonance spectroscopy.[51]

Prepubertal growth deficiency

Young patients with Barth syndrome typically present with growth retardation.[43] Proportionate growth retardation not only may be evident in infancy but also has been reported in post-pubertal patients.[34] However, postpubertal patients may experience a delayed growth spurt with remarkable "catch-up" growth.[33] In patients younger than 18 years of age, weight and height are typically below average,[11] and the body mass index is typically reduced in almost half of the patients.[11] In patients older than 18 years of age, weight and height gradually become normal. Growth retardation may partly be due to feeding problems, which occur in 50–70% of patients.[52]

Dysmorphism

Dysmorphism may be evident not only in the face but also in the feet. Young patients usually present with a characteristic facial appearance characterized by a tall and broad forehead, round face, full cheeks, prominent pointed chin, large ears, or deep-set eyes.[11] This appearance persists throughout childhood and regresses during puberty. Only the ears remain prominently large and low set.[11] Some of the patients may present with talipes equinovarus, suggesting a prenatal onset of myopathy.[48,53] After puberty the most striking dysmorphic feature becomes gynoid fat distribution.[54]

Cognitive impairment

Intellectual abilities are frequently mildly reduced in Barth syndrome.[11,55] Vocabulary and reading skills are age appropriate but performance in mathematics and selective visuospatial skills are below average.[56] There is also delay in first words or putting words together.[43] In about half of the patients older than 7 years, learning difficulties are evident.[43] In a study of *TAZ* knockdown mice, significant memory deficits were detected on the novel object recognition test.[57] Brains of *TAZ* knockdown mice exhibited reduced *TAZ* expression, reduced total cardiolipin levels, and a marked accumulation of monolysocardiolipin.[57]

Other features

Other features reported in patients with Barth syndrome include a strong gag reflex,[58] delayed bone age,[43] reduced bone mineral density,[47] and scoliosis.[43] Many patients have preferences for salty, spicy, fried, or cheesy foods, and avoid vegetables and fruits (food selectivity), together with a restricted repertoire of foods[58,59] and food refusal.[52] Although suggested,[52] altered food preference in Barth syndrome (preferring salty and fried food and avoiding vegetables and fruits) cannot be attributed to altered olfactory perception.[59] There is also an increased prevalence of male fetal loss, stillbirth, severe neonatal illness, and neonatal death.[16,60] Some patients may present with reduced birth weight or reduced intrauterine weight gain.[35,43]

Blood/urine chemical findings

Blood tests may show acute metabolic acidosis due to lactic acid elevation,[61] elevation of liver enzymes,[61] hypoglycemia,[61] hypoalbuminemia,[62] low carnitine,[62] or

hyperammonemia.[61] Metabolic dysfunction may occur even in patients with preserved cardiac functions.[38,60] Urine 3-MGA and 3-methyl-glutaric acid levels are frequently elevated on gas chromatography.[10] Lactic acidosis may not be present in all patients, but only in a proportion of the affected subjects. Conversely, there may be severe lactic acidosis without 3-MGA-uria.[26] Amino acids may be reduced or elevated in patients with Barth syndrome. In a study of 22 patients, reduced serum arginine levels were found.[35] In a study of 28 patients, arginine levels were reduced but proline levels were increased.[45] Another feature of the phenotype may be hypocholesterolemia. In a study of 25 patients, six had hypocholesterolemia.[34] Other studies, however, found only a minor proportion of patients with hypocholesterolemia.[45] Occasionally, patients with Barth syndrome may present with hypoglycemia.[5,35,44] Hypoglycemia may be explained by an increased glucose uptake in cells.[63] As with most mitochondrial myopathies, creatine kinase can be mildly elevated.[34] Several patients with relative monocytosis have been reported.[58]

Pathological findings

Muscle biopsy may give non-specific and quite variable results. In the initial study by Barth et al, muscle biopsy showed type I muscle fiber predominance, increased number of lipid droplets, and morphological abnormalities of mitochondria.[3] These findings were confirmed by later studies.[44,64] Muscle biopsy of patients with Barth syndrome may occasionally show features of lipid storage myopathy.[64] In a myoblast model of Barth syndrome, it has been demonstrated that differentiation of C2C12 cells (tafazzin knockout myoblasts) is reduced.[50] Biochemical investigations of fibroblasts may show reduced activity of complex III, complex IV, or complex V of the respiratory chain.[65] Levels of mature cardiolipin are reduced in muscle.[27]

Age and manifestations at onset

Age at onset is most frequently in early infancy or childhood.[35,45,47] Manifestations at onset reported in the literature include cardiomyopathy, LVHT, infection, and hypoglycemia.[35,61] In a study of 73 patients, cardiomyopathy was the most frequent manifestation at onset.[43] In a study of 22 patients, hypoglycemia was the initial manifestation.[35] Some patients may present at onset with isolated LVHT without other clinical manifestations.[26] In a report on two patients, manifestations at onset were growth retardation and mild myopathy.[66] Other hallmarks of Barth syndrome were missing in these two patients.[66]

Female carriers

Females carrying *TAZ* variants are usually asymptomatic carriers of the disease without revealing any clinical or biochemical abnormalities.[45,67] However, owing to the Lion hypothesis, the inactivation of one X-chromosome in females is skewed, resulting theoretically in a wide phenotypic spectrum from asymptomatic carriers to clinical presentations similar to those of males. Because of the recessive transmission, a normal XX-karyotype is not associated with disease. Nonetheless, a single manifesting carrier has been reported.[37] This female presented with severe heart failure at 1 month of age.[37] Echocardiography revealed dilated and hypertrophic cardiomyopathy together with LVHT.[37] She also had neutropenia. Genotypically, the patient carried an X-ring chromosome in a mosaic distribution. A second female with Barth syndrome has also been reported.[68] Barth syndrome in this second female was due to the point mutation c.253insC in exon 3 of *TAZ*.[68] The female manifested clinically with LVHT and hypotonia.[68]

Frequency

Fewer than 200 individuals worldwide are estimated to be affected by Barth syndrome.[59] The incidence of Barth syndrome was estimated by Kelley et al in 1991 as 1:300,000–1:400,000.[44] In a 2013 study by Clarke et al in South West England and Wales, the incidence of Barth syndrome was calculated as 1:140,000.[32] In the study by Rigaud et al, the incidence was estimated as 1.5 per million births.[35] The true frequency of Barth syndrome is regarded as being higher as patients with mild manifestations may go undiagnosed and some patients die prematurely, before being correctly diagnosed.

Diagnosis

Barth syndrome should be suspected in the case of a male child with dilated cardiomyopathy with or without fibroelastosis, LVHT, or hypertrophic cardiomyopathy, together with neutropenia (<1,500 cells/μL), myopathy, prepubertal growth delay, dysmorphism, or a family history positive for an X-linked disorder, including recurrent pregnancy loss of male fetuses. Investigations to confirm the suspicion should include an extensive individual and family history, a clinical neurological and cardiological examination, and instrumental investigations, such as blood and urine tests, electromyography, standard and long-term

electrocardiograms (ECGs), echocardiography, cardiac and cerebral magnetic resonance imaging, neuropsychological testing, and genetic work-up. Laboratory investigations to confirm the suspicion should include determination of plasma and urine organic acids, particularly determination of 3-MGA and 3-methyl-glutaric acid, which are increased, by means of high-performance liquid chromatography (HPLC).[69] Urine organic acids may not be elevated in all patients. Also useful is the determination of monolysocardiolipin by HPLC–mass spectrometry of monolysocardiolipin, which is increased, and of cardiolipin, which is decreased. The ratio of these last two parameters is usually increased in Barth syndrome.[70] Measuring this ratio seems to be more sensitive than determining cardiolipin alone.[71] These tests can be also carried out with fibroblasts.[70] Highly suggestive of Barth syndrome is the association of lactic acidosis and 3-MGA-uria.[45] Urinary excretion of 3-MGA is increased not only in Barth syndrome but also in a number of other conditions. In case of palpitations, syncopes, or ECG abnormalities, electrophysiological investigations should be considered.[41] Lipid analysis of leukocytes by means of matrix-assisted laser desorption/ionization–time of flight mass spectrometry has been proposed as a screening tool to identify patients in an early stage.[72] The diagnosis should be confirmed by genetic testing and documentation of a point mutation or deletion/duplication in *TAZ* by means of sequence analysis or deletion/duplication analysis.[73] Sequence analysis is usually carried out before deletion/duplication analysis. If analysis of *TAZ* is negative, next-generation sequencing by means of panel investigations or exome sequencing should be considered. There is an average delay of 3 years between first presentation and diagnosis of the condition.[11]

Differential diagnoses

To confirm the diagnosis, exclusion of all possible differential diagnoses is essential. Differential diagnoses that have to be excluded before diagnosing Barth syndrome include disorders in which 3-MGA is also increased, such as primary and secondary 3-MGA-uria, Costeff syndrome (*OPA3* variant), MEGDEL syndrome, MID due to *TMEM70* variants, or *DNAJC19*, 3-methylglutaconyl-CoA hydratase deficiency, in dilated cardiomyopathy with ataxia (DCMA) syndrome, and NOS-3-MGA-uria. All disorders associated with LVHT have to be excluded before considering Barth syndrome. The broad spectrum of differential diagnoses for neutropenia and for mitochondrial myopathy also has to be excluded.

Treatment

There is no curative therapy for Barth syndrome available. However, a number of symptomatic measures can be offered.

Cardiac

Patients developing heart failure require appropriate treatment with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, or diuretics. In cases of severe heart failure or atrial fibrillation and a CHADSVASc (congestive heart failure, hypertension, age, diabetes mellitus, stroke/transient ischemic attack, vascular disease, and sex) score >1, oral anticoagulation should be considered. The response to this standard therapy is usually favorable. In a study of 30 patients with dilated cardiomyopathy, 16 recovered to normal systolic function.[34] In a number of patients, however, heart failure therapy may be ineffective, and these patients require other approaches, including heart transplantation.[43,74–76] The interval until heart transplantation becomes feasible may be bridged by mechanical circulatory support.[77] In the case of right ventricular failure, administration of prostaglandin E_1 may be beneficial.[55]

Neutropenia

Neutropenia can be treated by regular administration of granulocyte–colony-stimulating factor (G-CSF).[11] To prevent infections, prophylactic administration of antibiotics may be necessary. All prophylactic measures available should be taken to avoid recurrent infections. Despite administration of G-CSF and normalization of the granulocyte count, however, patients may develop severe infections.[35]

Myopathy

In cases of muscle weakness, patients may benefit from foot or ankle orthoses, walkers, or wheelchairs.[48] In a study on nine patients, progressive exercise resistance training (ERT) during 12 weeks was demonstrated to improve muscle strength.[47] Endurance training has also been shown to be beneficial, at least in four adult patients with Barth syndrome.[78] If respiratory muscles become affected, invasive or non-invasive ventilatory support may be necessary. It has been demonstrated that exercise training in a mouse model of Barth syndrome ameliorated complex III deficiency in these animals.[79]

Other

Supplemental feeding via a gastrostomy tube or nasogastric tube may be necessary in one-third of patients.[43] Since patients with Barth syndrome experience reduced quality of life,[80] they may benefit from monitoring by a school psychologist or contact with a school counselor.[11] Prophylactic use of antibiotics may be useful during conditions with a high risk of infection.[35] Because of the propensity to hypoglycemia, prolonged fasting should be avoided.[81] As patients with Barth syndrome carry an increased risk of abnormal serum potassium levels, this parameter should be carefully monitored.[82] Patients with Barth syndrome also carry an increased risk of developing malignant hyperthermia-like conditions, and therefore elective general anesthesia should be designed, as in patients with malignant hyperthermia susceptibility. There is no evidence for any benefit from the application of coenzyme Q, panthotenic acid, L-carnitine, or L-arginine.

Experimental findings

Beneficial effects. In *TAZ* knockdown mice, bezafibrate attenuated cardiac dysfunction and improved exercise intolerance.[83,84] Expression of monolysocardiolipin acyltransferase-1 in lymphoblasts from Barth syndrome patients improved mitochondrial respiratory functions.[85] In a yeast model of Barth syndrome, overexpression of the mitochondrial oxodicarboxylate carrier (ODC1) preserved oxidative phosphorylation.[86] Exogenous application of cardiolipin in myeloid progenitor cells prevented apoptosis of these cells induced by *TAZ* knockdown.[87] In a mouse model of Barth syndrome, replacement of the *TAZ* gene by an AAV9 vector improved the expression profile of cardiac proteins.[88] In a similar study with the same experimental setting, gene therapy restored mitochondrial and cytoskeletal functions.[89]

Ineffective approaches. Administration of exogenous cardiolipin in nanodisk delivery particles failed to show a beneficial effect in *TAZ* knockdown mice.[90] Whether resolution of mitochondrial oxidative stress may be sufficient to prevent cardiomyopathy and myopathy in Barth syndrome remains speculative. In a crossing of mice that overexpressed catalase in mitochondria and mice that were *TAZ* deficient (TAZKD mice), resolution of oxidative stress was not sufficient to suppress the development of cardioskeletal myopathy, despite decreased mitochondrial H_2O_2 emission and decreased lipid peroxidation in these animals.[91] Of interest for future gene therapy studies is a study of 42 Barth syndrome patients showing that there are genotypes with a less severe metabolic and clinical profile.[92]

Pregnancy

Since pregnancy with a child known to have Barth syndrome can be complicated by intrauterine growth restriction, oligohydramnion stillbirth, hydrops fetalis, fetal loss, left ventricular dysfunction neonatal illness, or neonatal death,[60,93] such pregnancies should be supervised by a high-risk maternal fetal obstetrician.

Genetic counseling

Genetic counseling will be offered to affected adults, adult female carriers, and those at risk of being a carrier. In pregnant females at risk of carrying a *TAZ* variant, prenatal diagnosis is possible. It is also possible to diagnose the disease before implantation in the process of in vitro fertilization. Owing to the X-linked recessive transmission of the disease, a female carrying a *TAZ* variant has a 50% risk of giving birth to an affected child. A male carrying a variant will be affected. Females carrying a *TAZ* variant will be unaffected carriers. An affected male will transmit the mutation to all his daughters but not to his sons. The mother of an affected male is an obligate carrier if other family members also have the disease. If a mother has more than one affected ^{son} but no other family members are affected, and if the variant cannot be detected in her blood, she has germline mosaicism, as has been reported in a few cases.[35,94,95] If a mother has only a single affected son, she may carry the variant or it may have occurred de novo, as has been occasionally reported.[9] The risk of a sibling of the sole patient in a family becoming affected is increased because of the possibility of germline mosaicism in their mother. Owing to the random X-inactivation, the carrier status of a female may not always become evident by conventional means, and X-chromosome inactivation studies may be necessary. The genetic risk of transmission should be preferentially assessed before a woman becomes pregnant.

Outcome

One of the most frequent causes of death in Barth syndrome is intractable heart failure.[30] Heart failure is thus a significant cause not only of morbidity but also of mortality. Cardiac function usually steadily decreases with disease progression, as has been shown in a study of 73 males.[43] In a study of 22 males, 54 hospitalizations were due to heart failure.[35] In this

cohort, nine patients died from heart failure and two patients from sepsis.[35] Median age at death in this cohort was 5.1 months.[35] In cases where intractable heart failure requires management by heart transplantation, there is the risk that patients will develop malignancy from chronic immunosuppression.[96] The prognosis of cardiac involvement significantly improves if patients survive the first 5 years of life.[74] In a study of 27 patients, most of them had recovered near normal cardiac function when assessed by conventional echocardiography.[74] However, when analyzing strain, abnormal myocardial deformation and abnormal rotational mechanics were still evident.[74] Another factor determining the outcome of Barth syndrome patients is neutropenia. Since neutropenia is associated with an increased risk of infectious disease, affected patients also have an increased risk of dying from an intractable infection or sepsis. Factors identified as influencing survival include severe neutropenia at diagnosis and birth before or after the year 2000.[34] Patients with a leukocyte count of <500 cells/μL have a 1-year survival rate of only 25% compared to 68% among those with a leukocyte count of >500 cells//μL.[35] The 5-year survival rate among 22 patients was 50%, with no death of a patient older than 3 years.[35] In general, life expectancy is reduced in patients with Barth syndrome but single patients exceptionally survive into their forties, fifties, or even sixties.[31]

Discussion

Barth syndrome is an X-linked inborn error of metabolism, which almost exclusively affects males. The main phenotypic manifestations are cardiomyopathy, mitochondrial myopathy, growth delay, intermittent neutropenia, and 3-MGA-uria. The underlying cause has been traced to variants in the *TAZ* gene on chromosome Xq28.[4] *TAZ* encodes a phospholipid transacylase that promotes cardiolipin acyl-chain remodeling.[4] Absence of tafazzin results in heterogeneity of cardiolipin molecular species, increased levels of monolysocardiolipin, and low cardiolipin abundance. Dysfunction of cardiolipin perturbs the inner mitochondrial membrane, and impairs respiratory chain functions and thus aerobic respiration.[4] Decreased electron flow from fuel metabolism via complex-I activity leads to accumulation of NADH and product inhibition of key tricarboxylic acid (TCA) cycle enzymes.[4] Reduction of TCA cycle activity results in the diversion of pyruvate, generated by glycolysis, to lactic acid.[4] As a consequence, lactic acid (Cori) cycle activity increases to supply muscle with glucose for continued ATP production.[4] Acetyl-coenzyme A, which is unable to enter the TCA cycle, is diverted to organic acid waste products that are excreted in urine.[4] Diagnosis of the condition is confirmed by mutational analysis of the *TAZ* gene and documentation of an increased ratio of monolysocardiolipin to tetralinoleoyl-cardiolipin.[11]

This review covered the etiology, pathogenesis, clinical presentation, diagnosis, therapy, and outcome of Barth syndrome. All sections include a discussion of the current knowledge, but some issues will have a stronger impact on diagnostic procedures, treatment guidelines, economics, and drug application than others. These include the etiology and pathogenesis of the condition, and the treatment options that are applicable and those in the pipeline.[83–89] Concerning the etiology, there is increasing evidence that only variants in *TAZ* cause Barth syndrome.[1] Thus, no other genes have to be screened when there is clinical suspicion. A quick diagnosis may be prevented in case of clinical presentations which do not include the canonical features of the phenotype but include only some or one of the typical features. Knowing that Barth syndrome is a monogenic disease allows implementation of the most relevant diagnostic tests in the routine genetic work-up with a high sensitivity and specificity. Diagnostic difficulties may arise in certain conditions, such as the presence of an X-ring chromosome or the presence of microdeletions of the X-chromosome covering the *TAZ* gene.[37] Confirmation of inheritance from a female carrier may be difficult in cases of germline mosaicism.[94]

Besides the advances in the clarification of the genetic background, advances have been made in unraveling the pathogenesis of the disease. There is increasing knowledge about the function of tafazzin and increasing insight into the peculiarities of cardiolipins and their role in maintaining the inner mitochondrial membrane.[97] Lack of cardiolipin impairs not only the morphology of mitochondria but also their functions, in particular energy production, compensation of oxidative stress, and apoptosis. Loss of cardiolipin is often accompanied by increased levels of lysocardiolipins and impairs mitochondrial inner membrane organization.[97] Only extreme remodeling of cardiolipin acyl chains influences mitochondrial membrane properties.[97]

Improvements have also been achieved on the therapeutic side. At least in animal models of the disease and cell cultures, it is now possible to beneficially influence disrupted pathways and to improve impaired mitochondrial functions. In *TAZ* knockdown mice, bezafibrate attenuated cardiac dysfunction and improved exercise intolerance.[83,84] In a mouse model of Barth syndrome, replacement of *TAZ*

by an AAV9 vector improved the expression profile of cardiac proteins[88] and restored mitochondrial and cytoskeletal functions.[89] In cell models of the disease, expression of monolysocardiolipin acyltransferase-1 improved mitochondrial respiratory functions.[85] Application of cardiolipin to *TAZ*-deficient myeloid progenitor cells prevented apoptosis.[87] In a yeast model of the disease, overexpression of the mitochondrial oxodicarboxylate carrier (ODC1) preserved oxidative phosphorylation.[86]

Limitations preventing further achievements are the lack of animal models that entirely mimic human disease and the lack of complete understanding of the mechanisms that lead to impaired functioning of cardiolipins. Despite these shortcomings, there is hope that these limitations will be overcome with future research, and there are indications that first steps in this direction have been successfully made.[89,98] Areas of research that need to be covered in this respect are epidemiological studies about the distribution and frequency of the disease, the development of an effective, widely available, affordable, and safe gene therapy, the provision of more effective drugs for heart failure, and more effective means to treat neutropenia and concomitant infections. Another focus of research should be directed toward appropriate nutrition and the handling of mitochondrial myopathy. Since Barth syndrome represents an MID[99] and since the prevalence of these conditions is increasing, it is important to elucidate all uncovered issues as a model for this group of inherited metabolic diseases. It is quite likely that within the next 5 or 10 years, these goals will be achieved and that in the near future more effective diagnostic means and therapeutic measures will be available to improve the management and outcome of these patients. Until then, we need to accept the challenge to manage these patients with the currently available compounds by a multi-professional approach.

Disclosure

The author reports no conflicts of interest in this work.

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