



Barth Syndrome
Foundation

Description of Barth Syndrome Barth Syndrome - X-linked Cardiomyopathy and Neutropenia

Richard I. Kelley, MD, PhD
Division of Metabolism, Kennedy Krieger Institute
Department of Pediatrics, Johns Hopkins Medical Institutions

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History and Overview

In 1983, Barth et al. [Barth et al, 1983] described an extended pedigree with an unusual pediatric neuromuscular disease having principal features of dilated cardiomyopathy, skeletal myopathy, growth retardation, and neutropenia. The disorder segregated as an apparent X-linked recessive trait and had a high rate of mortality during infancy and early childhood from congestive cardiomyopathy or overwhelming bacterial infections. Histologic examination of the heart in some patients showed swollen fibers, partial loss of cross striations, central granular material, and bizarre mitochondria with stacked or whorled layers of cristae. The skeletal muscle also had a number of mostly non-specific histological changes, such as mildly increased fat vacuolization of type I fibers and increased subsarcolemmal spaces without ragged red changes. Bone marrow aspirates to evaluate the neutropenia showed maturational arrest of the neutrophil line at the myelocyte level with dilated, relatively empty-appearing mitochondria and clear cytoplasmic vacuoles that appeared to arise from the golgi system. By enzymatic assay, multiple respiratory chain complexes had moderately diminished activities, but a specific mitochondrial lesion could not be identified. Lactic acidosis with exercise was common, and some children had mildly to moderately decreased plasma levels of carnitine. The neutropenia was severe and variable but not truly cyclical.

Prior to the publication of the original Barth syndrome family in 1983, only one family with a similar, possibly X-linked disorder had been described in the medical literature [Neustein et al, 1979]. However, in the 10 years following the 1983 report, at least 25 additional cases with the same triad of cardioskeletal myopathy, neutropenia, and growth retardation were described [Bolhuis et al, 1991; Gibson et al, 1991; Kelley et al, 1991; Ades et al, 1993; Christodoulou et al, 1994]. In 1991, Kelley et al [Kelley et al, 1991] described an important biochemical marker for the syndrome, 3-methylglutaconic aciduria, which is now recognized as the fourth major criterion for the diagnosis. The level of 3-methylglutaconic acid is increased at any age, but especially high (up to 200X normal) between the ages of six months and three years (R. Kelley, unpublished). However, the level of 3-methylglutaconic acid appears to be largely independent of the severity of other features of the disorder. Interestingly, although 3-methylglutaconic acid is known as an intermediate in the catabolism of the amino acid L-leucine, the excess 3-methylglutaconic acid in Barth syndrome appears to arise independent of the metabolism of leucine. Instead, the 3-methylglutaconic acid in Barth syndrome may derive largely

from the polyisoprenoid/cholesterol biosynthetic pathway via the "mevalonate shunt" [Edmond and Popjak, 1974; Hughes-Fulford et al, 1986] or from longer chain isoprenoids [Schroepfer, 1982]. Furthermore, the incorporation of labeled acetate into urinary 3-methylglutaconic acid in humans also underscores the non-leucine-dependent origin of 3-methylglutaconic acid [Steen and Ransnas, 1983]. The finding of low blood cholesterol levels in most Barth syndrome patients [Kelley et al, 1991] also suggests that there may be a primary or secondary disturbance of sterol/polyisoprenoid biosynthesis in Barth syndrome, although the complexity of lipoprotein metabolism offers many other ways in which blood cholesterol levels could be depressed in Barth syndrome.

Another defining characteristic of Barth syndrome is its sex-linked pattern of inheritance. By pedigree analysis, classic X-linked recessive inheritance is observed. Although, theoretically, clinically affected unfavorably Lyonized females could occur, no clinically affected heterozygote females have been yet reported, nor have carriers of the Barth gene been found to have increased plasma or urinary levels of 3—methylglutaconic acid (Kelley, unpublished data). This appears to be because of an extremely skewed X-inactivation pattern (>95:5) in obligate carriers [Orstavik et al, 1998]. Guided by X-chromosome marker analysis, which had earlier localized the Barth gene to gene-rich Xq28 [Bolhuis et al, 1991; Ades et al, 1993; Christodoulou et al, 1994], Bione et al [Bione et al, 1996] identified apparently disabling mutations in a previously anonymous Xq28-linked gene, G4.5, in 5 families, including the original family reported by Barth et al [Barth et al, 1983]. The multiple putative protein products arising from variable splicings of G4.5 mRNA were named "tafazzins." The proposed causative role for G4.5 or "TAZ," mutations in Barth syndrome was further supported by the finding of disabling mutations of TAZ in 14 additional Barth syndrome families [Johnston et al, 1997]. The recognition of homology of TAZ with a family of acyltransferases involved in complex lipid metabolism [Neuwald, 1997] and evidence that defects in cardiolipin biosynthesis can lead to mitochondrial dysfunction [Ohtsuka et al, 1993] led Vreken et al [Vreken et al, 2000] to hypothesize and then show experimentally that tetralinoleoyl cardiolipin biosynthesis in Barth syndrome is abnormal. A defect in Barth syndrome in the synthesis of tetralinoleoyl cardiolipin, the principal phospholipid of the mitochondrial inner membrane, provides an attractive model for explaining some of the mitochondrial abnormalities found in Barth syndrome. However, some severely affected Barth patients have no biochemical or histological evidence of mitochondrial dysfunction, and certain features of the syndrome, such as growth retardation and cyclic neutropenia, are not easily explained by the relatively mild degree of mitochondrial impairment in Barth syndrome. These two observations suggest that the Barth protein may have also a role in the transacylation of non-mitochondrial glycerophospholipid species. Such a proposal is now supported by the discovery of a different phospholipid abnormality in a rare autosomal recessive form of Barth-like syndrome (R. Kelley, unpublished).

Clinical Manifestations

The majority of children with Barth syndrome are hypotonic at birth and have clinical signs of cardiomyopathy within the newborn period or the first few months of life [Barth et al, 1983; Kelley et al, 1991; Christodoulou et al, 1994; Barth et al, 1999]. Occasionally, a patient will present with only neutropenia in the first year or even later, and a number of clinically symptomatic but affected boys have been identified when the diagnosis of Barth syndrome is made in a more severely affected sibling. In one extended pedigree, an adult with a *TAZ* mutation and typical biochemical features of the disease had a history of only moderate growth retardation and hypotonia during early childhood [Kelley et al, 1991]. Birth weight is normal or only slightly reduced (most likely from muscle hypoplasia), but most affected children experience a marked deceleration in growth in the first year even when they are thriving and adequately nourished. By two years of age, the typical child with Barth syndrome is four standard deviations below normal for height with a proportionately equal or even much lower weight but normal head circumference. Height and weight remain below but parallel to the third percentile until the pubertal years when growth may accelerate and a normal or low-normal adult height is achieved in the late teenage years. Endocrine studies of growth retardation in Barth patients, including detailed analysis of growth hormone release and metabolism in some, have been normal [Katsushima et al, 2002]. Interestingly, one growth retarded boy (-5 SD) was treated with growth hormone for one year but showed no change in his growth velocity.

Almost all children with Barth syndrome have clinically significant muscular hypotonia and weakness. Delayed gross motor milestones, myopathic facies, a waddling gait, and a positive Gower sign are common but not universal. Muscle mass in most children is markedly reduced, which contributes to the appearance of failure-to-thrive. Except for muscle weakness and its consequences, such as decreased stretch reflexes or strabismus, the general neurological examination is normal. Although affected children usually have normal intelligence, a high proportion have mild to moderate learning disabilities, especially in the areas of visual-spatial and arithmetic reasoning [Mazzocco and Kelley, 2001]. Other common neurological problems include rapid fatigue with moderate physical activity or even sustained fine motor activities, such as handwriting.

Cardiac disease in Barth syndrome typically presents as a dilated cardiomyopathy, often with a degree of left myocardial thickening and, sometimes, endocardial fibroelastosis. The cardiac disease is most often identified at birth or in the first few months of life. However, one patient with a diagnosis of neutropenia first developed signs of cardiomyopathy at age eight years only to have the heart disease resolve two years later [Kelley et al, 1991]. Although Barth syndrome often is listed in medical texts as a form of endocardial fibroelastosis, there are other, more common causes of endocardial fibroelastosis, and echocardiographically visible endocardial fibroelastosis occurs in only a relatively small proportion of Barth patients. Another abnormality reported in some Barth syndrome hearts is "isolated" non-compaction of the left ventricle [Bleyl et al, 1997b; Ichida et al, 2001]. However, like endocardial fibroelastosis, non-compaction of the left ventricle also is a non-specific abnormality [Chin et al, 1990; Ichida et al, 2001], and,

although some hypertrabeculation may not be rare in Barth syndrome, a major degree of non-compaction clearly is uncommon. Many children require digitalization, diuretics, and afterload reduction with ACE inhibitors as infants and toddlers, but not infrequently they can be weaned from most or all cardiac medications before age ten years. In almost all Barth patients who have been followed through puberty, the cardiac disease either resolves or improves substantially after the end of the pubertal growth spurt, but may worsen somewhat and require remedication during puberty (R. Kelley, unpublished). With improved pharmacologic treatment of heart failure in the last 20 years, progressive cardiac disease in Barth syndrome is now very uncommon. However, several children in recent years have had progressive cardiac failure ending in cardiac transplantation [Adwani et al, 1997; Bleyl et al, 1997a; Ronghe et al, 2001]. Two patients have died following transplant, but neither had evidence of recurrent Barth-type cardiac disease. Another life-threatening complication is sudden cardiac arrest, presumably from arrhythmia, which has occurred in three otherwise healthy Barth children [Barth et al, 1999] [Kelley, unpublished]. Systematic electrophysiological studies to determine intrinsic susceptibility to arrhythmia in Barth syndrome have yet to be reported.

For some Barth children, neutropenia can be as serious and life-threatening as the cardiac disease. Indeed, almost half of the patients studied by Barth et al. [Barth et al, 1983] died of infections rather than heart disease, although such a high death rate from infection has not been found in other larger series of patients [Kelley et al, 1991; Christodoulou et al, 1994; Cantlay et al, 1999]. The neutropenia of Barth syndrome, while not always cyclical, often follows a predictable 3 to 5-week cycle. Some patients may pass through many cycles for years without clinical evidence of neutropenia, while others can have aphthous ulcers with every monthly nadir in the neutrophil count. The absolute neutrophil count typically is lower than 500 and sometimes zero, even when the children are clinically well. There is also usually a moderate monocytosis, which may explain why most children with Barth syndrome have relatively few bacterial infections compared to other disorders with equally severe neutropenia. The histology of the bone marrow in Barth syndrome shows normal cell lineages apart from the myeloid series, which often appears to be arrested at the myelocyte stage [Barth et al, 1983]. However, the incomplete nature of the block in myelopoiesis is clear from the observations that, once a systemic bacterial infection develops, children with Barth syndrome often develop a marked neutrophilia and that they respond quite well to granulocyte colony-stimulating factor (G-CSF) (R. Kelley, G. Cox, unpublished). Leukocyte migration and killing tests have usually been normal when autologous serum is removed.

Genetic and Molecular Pathology

The causative role of mutations in the G4.5 tafazzin (TAZ) gene in Barth syndrome is now clearly established [Bione et al, 1996; Johnston et al, 1997; Cantlay et al, 1999]. The TAZ gene is located at Xq28 and consists of 11 exons, the first two of which are non-coding. The predicted protein sequence encompasses 292 amino acids and has strong homology with a highly conserved superclass of acyltransferases [Neuwald, 1997]. The TAZ mRNA is most abundantly expressed in skeletal and cardiac muscle, but also well-expressed in essentially all tissues [Bione

et al, 1996]. Bione et al [Bione et al, 1996] have also shown that the many different mRNAs that arise from multiple alternative mRNA splicings are differentially expressed in various tissues. Theoretically, such tissue specificity of mRNA distributions could be associated with TAZ mutations that yield different effects in different tissues. However, in a detailed study of 14 Barth syndrome families, there was no evident phenotype-genotype correlation [Johnston et al, 1997]. To date, more than 50 different mutations in the TAZ gene have been found, of which 60% are frame-shift, stop, or splice-site mutations predicted to disrupt completely the function of the Barth proteins. Another 30% lead to a change in the charge of the protein. A substantial fraction of the mutations are de novo mutations, in a proportion not inconsistent with the one-third new mutation rate predicted for X-linked recessive diseases (Haldane fraction) (I. Gonzales, R. Kelley, unpublished).

Evidence for a direct role of the Barth protein in cardiolipin biosynthesis is strong if still circumstantial. Cardiolipin is a glycerophospholipid with four fatty acyl groups, which in the mitochondrial inner membrane are all linoleic acid (tetralinoleoyl cardiolipin). The structure of the predicted Barth protein suggests that it may have a role in the maturation of nascent di- or trilinoleoyl cardiolipin into tetralinoleoyl cardiolipin, a proposal supported by the finding of very low levels of tetralinoleoyl cardiolipin, but normal levels of other cardiolipins, in cultured fibroblasts from Barth syndrome patients [Vreken et al, 2000]. As the principal glycerophospholipid of the inner mitochondrial membrane, tetralinoleoyl cardiolipin is intimately associated with the electron transport chain and is essential for normal function of numerous mitochondrial substrate transporters. Surprisingly, however, in one yeast mutant deficient in cardiolipin biosynthesis, mitochondrial function appears to be normal until the ambient temperature is raised above the physiologic range [Jiang et al, 1999]. Also it is unknown whether or not other species of cardiolipin not deficient in Barth syndrome can substitute for tetralinoleoyl cardiolipin in mammalian mitochondria since, in some species, tetralinoleoyl cardiolipin is not the dominant cardiolipin in mitochondria. The dependence of many mitochondrial substrate transporters on cardiolipin may also explain the abnormal organic aciduria of Barth syndrome, which, in addition to 3-methylglutaconic acid, often includes increased amounts of several dicarboxylates of the citric acid cycle, such as aconitate, succinate, and 2-ketoglutarate (Kelley, 1991 #37).

As noted above, a primary abnormality of mitochondrial metabolism has long been suspected in Barth syndrome because of its myopathy, exercise-induced lactic acidosis, and structurally abnormal mitochondria. However, a number of biopsy specimens of severely abnormal Barth syndrome hearts have contained normal-appearing mitochondria, and some patients have had no systemic or biochemical evidence of abnormal mitochondrial function [Johnston et al, 1997][Kelley, unpublished]. Although a degree of mitochondrial dysfunction may indeed contribute to the myopathy and cardiomyopathy of some patients with Barth syndrome, the primary defect must have fundamental importance not only for muscle function but also myelopoiesis and body growth. The characteristic severe growth retardation of Barth syndrome is not mimicked by other mitochondrial disease of equal or even much greater biochemical severity.

Epidemiology

Barth syndrome occurs in many different ethnic groups and does not appear to be common in any one group. Unfortunately, there are no good studies of the population or birth incidence of Barth syndrome. However, probably fewer than 10 new Barth infants are identified each year in the United States, which suggests an incidence of only 1 in 300 — 400,000 births and a true birth incidence of probably no more than 1 in 200,000 birth (R. Kelley, I Gonzales, unpublished observations). Because a metabolic evaluation of a pediatric cardiomyopathy, including urinary organic acid analysis, has become routine in many pediatric centers, ascertainment is improving. Nevertheless, the incidence of Barth syndrome is almost certainly underestimated because infants and children who die acutely with a dilated cardiomyopathy are often assumed to have a viral myocarditis and may not always have a full metabolic evaluation. Furthermore, because the diagnostically important organic aciduria of Barth syndrome often is quantitatively relatively mild compared to that of many classical organic acidurias, diagnostic laboratories do not always recognize the importance of the Barth syndrome organic acid profile. Another reason for missed diagnoses of Barth syndrome is that not all autopsies for cardiomyopathy include electron microscopy of heart muscle. However, even when electron microscopy is performed, the mitochondrial abnormalities that might suggest the diagnosis of Barth syndrome are not always present.

Differential Diagnosis

The metabolic differential for a dilated cardiomyopathy in children includes defects of fatty acid beta-oxidation and various other disorders of mitochondrial oxidative metabolism, such as mitochondrially inherited DNA point mutations. However many of these more characteristically have a hypertrophic rather than dilated cardiomyopathy and are not associated with chronic or cyclic neutropenia. Furthermore, whereas certain mitochondrial disorders, such as ATP synthase deficiency [Holme et al, 1992] and Pearson syndrome [Gibson et al, 1992a], also can have 3-methylglutaconic aciduria, in most of these the clinical picture and other associated biochemical abnormalities are very different from Barth syndrome. Although forms of 3-methylglutaconic aciduria without heart disease are common, most are associated with either biochemical evidence of defective leucine metabolism, as in 3-methylglutaconyl-CoA hydratase deficiency [Narisawa et al, 1986; Gibson et al, 1992b] or have serious central nervous system abnormalities [Greter et al, 1978; Hagberg et al, 1983; Gibson et al, 1988; Gibson et al, 1992b], unlike patients with Barth syndrome. Because a secondary 3—methylglutaconic aciduria can develop whenever cholesterol is acutely depleted, as in sepsis or shock (R. Kelley, unpublished), patients suffering from acute viral cardiomyopathy might be found to have a transient 3—methylglutaconic aciduria. However, the 3-methylglutaconic aciduria resolves when the cholesterol level returns to normal.

There are a number of genetic causes of dilated cardiomyopathy other than Barth syndrome [Ferlini et al, 1999; Mestroni et al, 1999; Arbustini et al, 2000]. X-linked dilated cardiomyopathy has been reported in adults in several pedigrees, but none with associated 3-methylglutaconic

aciduria or neutropenia. Mutations of the Duchenne-related dystrophin gene have been found in some of these pedigrees [Muntoni et al, 1993], whereas in others the molecular defect remains unknown [Berko and Swift, 1987]. It is likely that some reported cases of X-linked endocardial fibroelastosis [Lindenbaum et al, 1973; Westwood et al, 1975; Hodgson et al, 1987] represent cases of Barth syndrome.

Diagnostic Evaluation

The diagnosis of Barth syndrome should be considered for any male child who presents with dilated cardiomyopathy, neutropenia, endocardial fibroelastosis, abnormal mitochondria in cardiac muscle, 3-methylglutaconic aciduria, or idiopathic myopathy with growth retardation. In all cases, a complete family history should be obtained, looking for possible cases of cardiac disease, failure-to-thrive, unexplained infantile deaths, and unexplained sudden deaths. In addition, urinary organic acids should be analyzed and the level of 3-methylglutaconic acid in urine and blood should be measured quantitatively [Kelley, 1993]. With the availability of a definitive molecular test for Barth syndrome, unless there is a true medical urgency, a cardiac or skeletal muscle biopsy in a candidate Barth syndrome patient before completion of the TAZ mutation analysis may be contraindicated because of attendant anesthetic risks. As noted above, histological abnormalities of the muscle are not always present and, when they are, they are rarely sufficiently specific to be considered diagnostic of Barth syndrome. In clinical situations where a 3—methylglutaconic aciduria could be a transient phenomenon, there may be no alternative except to repeat quantification of 3—methylglutaconic acid in several weeks.

Prognosis and Complications

Today the prognosis for Barth syndrome appears to be much more favorable than suggested by the original family of Barth et al. [Barth et al, 1983]. Recent experience suggests that, with good cardiac management, at least 75% of patients will show gradual improvement and even normalization of their cardiac function. However, it is also possible that differences in intrinsic severity among pedigrees may make significant morbidity and mortality more common in some families [Barth et al, 1983; Ades et al, 1993] and rare in others [Kelley et al, 1991; Christodoulou et al, 1994]. In the past 20 years in the United States, only 10% of Barth syndrome patients have died once the diagnosis has been made, whereas 70% of their older siblings had died before the diagnosis of Barth syndrome in the family was recognized. Similarly, once neutropenia is recognized, its complications are largely preventable by close monitoring of the patients and prompt use of antibiotics. In some children who have frequent infections and neutrophil counts persistently below 500, a good response to granulocyte/macrophage colony stimulating factors has been achieved. However, many other patients with severe neutropenia do not have recurrent infections, possibly because of a chronic, substantial monocytosis. As discussed above, despite growth retardation as severe as -6 SD during childhood, almost all adult Barth patients have normal heights. One child who for many years grew at only -4 SD until puberty reached an adult height of 74 inches. Because of growth retardation that behaves like an endogenous nutrient deficiency syndrome, children with Barth syndrome have lower than normal caloric

requirements, which must be respected. Attempts to induce growth by overfeeding have led both to chronic diarrhea and to worsening metabolic acidosis. There also appears to be a greater than normal incidence of chronic or frequent diarrhea in Barth children, a problem that often is blamed for the growth retardation. In addition, like any child with marked muscle hypoplasia, a child with Barth syndrome can rapidly become potassium-depleted during a gastrointestinal illness. Conversely, in lacking a normal muscle "reservoir" for potassium, Barth children given intravenous fluids containing potassium can rapidly develop hyperkalemia, which has been the apparent cause of death in several Barth children (Kelley, unpublished).

Management

The management of Barth syndrome is essentially supportive. Both cardiology and hematology specialists should be available for consultation or direct management, as indicated. Although cardiac disease usually commands the greatest attention, emergent care is often required for infections. All fevers or localized infections must be evaluated immediately. In most cases, no special dietary management is required. However, because Barth children require fewer calories to maintain a normal growth velocity, their diets should be evaluated carefully to assure they do not become deficient in calcium and other minor nutrients. Rarely, gastrostomy feedings may be required for children who develop true food aversion, which occurred in one child who was put on a high-calorie, high-protein diet because of his growth retardation. Despite published claims to the contrary [Ino et al, 1988], no significant benefit has been afforded by supplementation with pharmacological amounts of carnitine, and acute deterioration of cardiac function with increasing mitochondrial dysfunction has occurred several times when a Barth child was given large doses of carnitine [Ostman-Smith et al, 1994][Kelley, unpublished]. Thus, unless the carnitine level be truly low, supplementation with carnitine is now considered contraindicated in Barth syndrome. The related speculation that treatment with pantothenic acid may be beneficial [Ostman-Smith et al, 1994] has not been supported by a treatment trial with pantothenic acid in more than 20 patients with Barth syndrome.

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