Kenneson *et al. J Transl Genet Genom* 2024;8:285-97
DOI: 10.20517/jtgg.2024.22

Journal of Translational Genetics and Genomics

Original Article

Open Access

Check for updates

The diagnostic odyssey, clinical burden, and natural history of Barth syndrome: an analysis of patient registry data

Aileen Kenneson[1], Yonglin Huang[2], Erik Lontok[3], Lindsay Marjoram[2]

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA.
[2]Barth Syndrome Foundation, Larchmont, NY 10538, USA.
[3]Coalition for Aligning Science, Chevy Chase, MD 20815, USA.

Correspondence to: Dr. Yonglin Huang, Barth Syndrome Foundation, 2005 Palmer Avenue #1033, Larchmont, NY 10538, USA. E-mail: melissa.huang@barthsyndrome.org

How to cite this article: Kenneson A, Huang Y, Lontok E, Marjoram L. The diagnostic odyssey, clinical burden, and natural history of Barth syndrome: an analysis of patient registry data. *J Transl Genet Genom* 2024;8:285-97. https://dx.doi.org/10.20517/jtgg.2024.22

Received: 6 May 2024 **First Decision:** 18 Jul 2024 **Revised:** 26 Aug 2024 **Accepted:** 9 Sep 2024 **Published:** 24 Sep 2024

Academic Editor: Sanjay Gupta **Copy Editor:** Yu-Fei Wang **Production Editor:** Yu-Fei Wang

Abstract

Aim: Barth syndrome (BTHS; OMIM 302060) is an ultra-rare, complex, multi-system X-linked disorder that arises from pathogenic mutations in the gene *TAFAZZIN*. BTHS is characterized by cardiomyopathy, skeletal myopathy, muscle weakness, and neutropenia. To better understand the natural history and lived experience of affected individuals, the Barth Syndrome Foundation maintains the patient-inputted Barth Syndrome Registry and Repository (BRR).

Methods: Available cross-sectional and longitudinal participant data (n = 115) were analyzed to illustrate the diagnostic odyssey, manifestations, and healthcare utilization across a broad range of affected individual age groups.

Results: Individuals who experienced cardiomyopathy or heart failure as the first manifestation had the shortest times to diagnosis compared to less appreciated manifestations (e.g., frequent infections, poor muscle tone, growth delay). The most frequently reported manifestations across all ages were due to cardiac disorders (80.7%), gastrointestinal (GI) disorders (68.7%), neutropenia or frequent infections (67.2%), and fatigue (60.9%), with 47.1% of participants scoring in the moderate-to-severe range of the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Short Form 8A survey. Participants saw, on average, 3.6 specialists in the

previous year, with cardiologists (97.9%) and hematologists (58.2%) being the most commonly seen specialists.

Conclusion: The data suggest that cardiac disorders are the most common manifestations of BTHS, but also reveal a high frequency of feeding and GI-related issues that previous reports have not captured. Physician-targeted education on the lesser-known symptoms and population-based screening for BTHS may aid in timely diagnosis and improved clinical management.

Keywords: Barth syndrome, natural history, diagnostic odyssey, cardiomyopathy, neutropenia, gastrointestinal, fatigue

INTRODUCTION

Barth syndrome (BTHS; OMIM 302060) is a complex, multi-system disorder that arises from pathogenic variants in the gene *TAFAZZIN* (formerly TAZ; OMIM 300394)[1,2]. Discovered in 1996 by Bione *et al.*, *TAFAZZIN* is located on the distal portion of Xq28, a locus originally termed the *G4.5* gene[3]. As an X-linked disorder, BTHS primarily affects males, but female cases have also been reported[4,5].

TAFAZZIN is a mitochondrial transacylase that remodels monolysocardiolipin (MLCL) into mature cardiolipin (CL)[6]. Pathogenic mutations in *TAFAZZIN* result in aberrant accumulation of MLCL in the mitochondrial inner membrane and a reduction in the total abundance and composition of CL molecular species[7]. Accumulation of MLCL in the inner mitochondrial membrane promotes interactions with cytochrome c that cause subsequent peroxidation of phospholipids[8]. Because cardiolipin accounts for up to 20% of phospholipids in the mitochondrial membrane, the cellular and organismal implications of this imbalance impact mitochondrial function at a structural and functional level, resulting in aberrant mitochondrial morphology and impaired metabolism[9-11]. The resulting imbalance of CL (decreased levels) and MLCL (increased levels) has been leveraged into a highly specific and sensitive mass spectrometry blood spot assay (MLCL:CL ratio) to diagnose individuals affected by BTHS[12].

The cardinal manifestations of BTHS of cardiomyopathy, skeletal myopathy, and neutropenia were comprehensively described in a pedigree published in 1983 by the eponymous Dr. Peter Barth[13]. In subsequent case reports of seven patients, Dr. Richard Kelley *et al.* similarly noted dilated cardiomyopathy, growth delay, neutropenia, and 3-methylglutaconic aciduria[14]. Longitudinal clinical and patient registry research has further broadened the spectrum of BTHS natural history. The cardiomyopathy observed in BTHS now includes a description of an undulating cardiomyopathy, which may be dilated, hypertrophic, involve left-ventricular non-compaction (LVNC), or a mixed phenotype[15]. Beyond the burden of cardiac manifestations, heart monitoring, and transplantations, patients frequently demonstrate growth and developmental delays, and report failure to thrive alongside the need for gastrostomy or nasogastric tube feedings[16]. In BTHS patients, the pattern of neutropenia was either intermittent and unpredictable, chronic and severe, or cyclical with regular oscillations[17]. These reported clinical and survey findings were reflected in the BTHS Patient-focused Drug Development (PFDD) meeting, wherein these challenges were contextualized into daily challenges and impact on the quality of life for affected individuals[18] and served as guidance for priorities in therapeutic development.

Tracking and treating the multi-system and heterogeneous manifestations of BTHS involves a multidisciplinary clinical approach[19]. This may include medical, pharmacological, and surgical management of cardiac disorders and neutropenia, dietary interventions and feeding aids, and rehabilitative, educational, and psychological services[20]. Thus, individuals with BTHS may require visits with cardiologists, hematologists, metabolic specialists, endocrinologists, neurologists, geneticists,

nutritionists, physical therapists, occupational therapists, and psychologists[20].

Previously published natural history reports have thoroughly described the most commonly reported aspects of BTHS; however, other disease manifestations have been underappreciated and underexplored [e.g., gastrointestinal (GI) issues, nutritional challenges, fatigue]. In 2006, the Barth Syndrome Foundation (BSF; https://barthsyndrome.org), a patient advocacy group serving those affected with BTHS and their families[21], partnered with researchers and clinicians to develop the BTHS Registry and Repository (BRR)[22]. The BRR is a patient-reported and medically abstracted registry and was established to further the understanding of the natural progression of BTHS. Enrollment is open to all living or deceased individuals affected by BTHS worldwide. The objective of this study was to provide a comprehensive overview of the disease across the lifespan and illustrate its diagnostic odyssey and clinical burden. Moreover, advancements in diagnosis and disease management have led to an increased number of BTHS-affected individuals surviving later into adulthood[23]. We sought to incorporate data from a wider age range (i.e., infants to adults >50 years of age) of affected individuals to help better understand disease progression over time. To better elucidate the natural history and lived experience of BTHS, we used patient- and/or caregiver-reported cross-sectional and longitudinal data from the BRR to gather detailed information on the prevalence of BTHS signs and manifestations by age group, the diagnostic timeline based on presentation, and healthcare utilization.

METHODS

Barth syndrome registry and repository

The Barth Syndrome Registry and Repository (BRR)[22], which is maintained by the BSF, stores detailed information about individuals diagnosed with BTHS, and was developed in conjunction with clinicians with expertise in the disease. The BRR acts as a platform to amass data about the natural history of BTHS. Individuals diagnosed with BTHS or their caregivers (if the affected individual is under 18 years of age or unable to provide consent) can participate by enrolling at the BRR website (http://barthsyndromeregistry.org). After providing consent or assent to participate,
participants are asked to complete several surveys that focus on basic demographic information,
medical history, heart transplant status, quality of life (fatigue),and other clinical information.
Participants are requested to complete the clinical, heart transplant, and quality of life surveys annually.
The self- and/or caregiver-reported data are entered into a secure password-protected, web-
based database via the Invitae Patient Insights Network. Institutional Review Board approval of the BRR was obtained from North Star Review Board (IRB #: NB300158).

Participants

Only registry participants with a confirmed genetic test or clinical diagnosis of BTHS were included in this analysis (n = 115). The study population was categorized as probands (n = 90) or other family members. Non-probands (n = 10) were defined as participants who had a relative in the BRR diagnosed at an earlier time, as well as those who reported being diagnosed before manifestations appeared due to an affected relative. For the analysis of manifestations by age, all participants, both living and deceased, were included. However, for the analysis of medication usage by age and the analysis of specialist medical care, only living participants were included. Each individual was included once per age group, and was classified as having the clinical phenotype if they reported having it at any time period within that age group.

Medical history and clinical information

Medical history and clinical information were obtained via self- or caregiver report via a clinical survey. The questions covered the age at which the diagnosis was made, whether there was any family history of BTHS, what specialists the participant visited throughout a 12-month period and the frequency, their clinical manifestations and medications, transplantation status, and significant medical events. Individuals were

defined as having a cardiac disorder if they reported cardiomyopathy, cardiac arrest, cardiac failure, or an implantable device.

Fatigue

Fatigue was evaluated via the clinical survey ("Has the participant experienced excessive fatigue in the past 12 months?" or report of a diagnosis of chronic fatigue in the clinical history questions). Additionally, the Patient-Reported Outcomes Measurement Information System Fatigue Short Form 8A (PROMIS-F SF-8A)[24] was used to assess fatigue more comprehensively. The questionnaire contains 8 items with a 5-point Likert-rating scale (e.g., "Not at all," "A little bit," "Somewhat," "Quite a bit," "Very much"). Examples of items include: "During the past 7 days, I have trouble starting things because I am tired," "In the past 7 days, to what degree did your fatigue interfere with your physical functioning?" A summative raw score was computed for each participant and then converted into the corresponding T-score based on the PROMIS scoring tables[24].

RESULTS

Clinical survey data were available for 115 BRR participants with BTHS, including 114 males and 1 female. Characteristics of the study population are provided in Table 1. Ten males were deceased at the time of data analysis: four from arrhythmia and/or heart failure, three from stroke, two from sepsis, and one from electromechanical dissociation following transplant. Twenty of the participants indicated they were related to another participant in the BRR. Twenty-five males in the BRR had had at least one heart transplant, with two participants having received two heart transplants.

We analyzed the data regarding initial presenting manifestations. Four BRR participants reported that they had no manifestations at diagnosis but were instead diagnosed due to the presence of another affected individual in the family. Table 2 provides the presenting manifestations and age at first manifestation as reported by 102 participants. The most commonly reported presenting manifestations were cardiomyopathy/heart failure and feeding difficulty/weight loss/failure to thrive, reported by 57% and 25% of BRR participants, respectively. Of those who reported cardiomyopathy/heart failure as a presenting manifestation, 96% reported the onset of this clinical phenotype before one year of age. Overall, the initial clinical manifestation occurred by one year of age in 89% of cases. Only 4 cases reported a first manifestation onset at greater than 5 years of age: two with feeding difficulty/weight loss/failure to thrive and two with low muscle tone.

Age at diagnosis was available for 100 participants [Table 3]. Ninety of these participants were the first person in the family to be diagnosed (probands), while 10 were diagnosed after a positive family history. Those with a family history were more likely to be diagnosed earlier. We also looked at the time to diagnosis from first manifestation for 89 probands for whom we had complete data on age at first manifestation, age at diagnosis and presenting manifestation. Time from first manifestation to diagnosis is presented according to first manifestation [Table 4] and year of birth [Table 5].

Overall, the frequency of a reported history of the following conditions included cardiac disorder (80.7%), GI disorders (68.7%), and neutropenia or frequent infections (67.2%). The most commonly reported GI disorders were chronic constipation (n = 16), chronic diarrhea (n = 20), dysphagia (n = 7), feeding difficulties (n = 51), and gastroesophageal reflux (GERD) (n = 25).

Of the 22 individuals with BTHS who reported no cardiac disorders, there was a mean age of 21.4 years (SD = 15.8) at the most recent survey data entry. Two individuals were under the age of 6 months, with the rest

Table 1. Description of study population

Living participants (*n* = 105) (104 male, 1 female)	
Age at most recent survey (years)	Mean (SD): 14.4 (13.0) Minimum: 0.05 Maximum: 58.3
Deceased participants (*n* = 10) (all male)	
Age at death (years)	Mean (SD): 4.1 (7.0) Minimum: 0.04 Maximum: 23
All participants (*n* = 115) (114 male and 1 female)	
Known family history? n (%)	
·Yes	54 (47.0%)
·No	25 (21.7%)
·Unsure	3 (2.6%)
·Missing or incomplete	33 (28.7%)
All participants (*n* = 115)	
Geographical location:	
·United States	63 (54.8%)
·Other	52 (45.2%)
All participants (*n* = 115)	
Results of genetic testing:	
·Yes - findings = confirmed to have pathological mutations of BTHS	94 (81.7%)
·Yes - findings = variant of unknown significance	2 (1.7%)
·No - the healthcare provider indicated the participant does not need genetic testing	2 (1.7%)
·No - the healthcare provider indicated the participant does not need genetic testing	5 (4.3%)
·Unsure	4 (3.5%)
·Missing[1]	8 (7.0%)
Living participants (*n* = 105)	
Have health insurance? *n* (%)	
·Yes	83 (79.0%)
·No	11 (10.5%)
·Don't know	3 (2.8%)
·Missing	8 (7.6%)

[1]Genetic testing was done (*n* = 6) or clinical diagnosis was made (*n* = 2), but participants did not provide a response to the question. SD: Standard deviation.

Table 2. Age at presentation by first manifestation of BTHS

	Age at first manifestation					
First manifestation	**Prenatal**	**At birth**	**< 1 year**	**1-2 years**	**3-5 years**	**> 5 years**
Cardiomyopathy/heart failure (*n* = 57)	3	30	22	1	1	0
Neutropenia/frequent infections (*n* = 4)	0	2	2	0	0	0
Growth delay (*n* = 1)	0	1	0	0	0	0
Motor development delay (*n* = 3)	0	0	2	1	0	0
Feeding difficulty/weight loss/failure to thrive (*n* = 27)	0	11	11	3	0	2
Poor muscle tone (*n* = 7)	1	2	1	0	1	2
Other[1] (*n* = 3)	0	2	1	0	0	0
ANY (*n* = 102)	4	48	39	5	2	4

[1]Stroke, hypoglycemia, and carnitine deficiency. BTHS: Barth syndrome.

Table 3. Age at diagnosis of BTHS for probands and non-probands

	Age at diagnosis					
Group	**Prenatal, *n* (%)**	**At birth, *n* (%)**	**< 1 year, *n* (%)**	**1-2 years, *n* (%)**	**3-5 years, *n* (%)**	**> 5 years, *n* (%)**
All (*n* = 100)	1 (1%)	6 (6%)	36 (36%)	16 (16%)	18 (18%)	23 (23%)
Proband only (*n* = 90)	0 (0%)	4 (4.4%)	33 (36.7%)	16 (17.8%)	16 (17.8%)	21 (23.3%)
Non-probands (*n* = 10)	1 (10%)	2 (20%)	3 (30%)	0 (%)	2 (20%)	2 (20%)

BTHS: Barth syndrome.

Table 4. Time from first manifestation to diagnosis of BTHS by presenting manifestation among probands

First manifestation	Time to diagnosis			
	< 1 year, *n* (%)	1-2 years, *n* (%)	3-5 years, *n* (%)	> 5 years, *n* (%)
Cardiomyopathy/heart failure (*n* = 48)	27 (56.2%)	9 (18.8%)	3 (6.2%)	9 (18.8%)
Feeding difficulty/weight loss/failure to thrive (*n* = 26)	12 (46.2%)	5 (19.2%)	3 (11.5%)	6 (23.1%)
Other[1] (*n* = 15)	5 (33.3%)	3 (20.0%)	2 (13.3%)	5 (33.3%)
ANY (*n* = 89)	44 (49.4%)	17 (19.1%)	8 (9.0%)	20 (22.5%)

[1]Growth delay, motor development delay, neutropenia/frequent infections, poor muscle tone, stroke, hypoglycemia, hypoglycemia with carnitine deficiency and low oxygen saturation. BTHS: Barth syndrome.

Table 5. Time from first manifestation to diagnosis of BTHS by birth year among probands

Year of birth	Time to diagnosis (probands only)				Number (%) of patients presenting with a cardiac manifestation as a first manifestation
	< 1 year	1-2 years	3-5 years	> 5 years	
1960-1989 (*n* = 13)	0	1	2	10	5 (38.5%)
1990-1999 (*n* = 17)	8	2	3	4	10 (58.8%)
2000-2009 (*n* = 25)	11	7	3	4	17 (68.0%)
2010-2019 (*n* = 31)	23	7	0	1	19 (61.2%)

BTHS: Barth syndrome.

ranging in age from 6.0 to 58.2 years. Three individuals without cardiac disorders indicated they had been diagnosed by genetic testing after another family member was diagnosed with BTHS.

Common clinical manifestations and medication usage are presented by age in Figure 1.

Additionally, 60.9% of individuals with BTHS reported experiencing excessive or chronic fatigue. Figure 2 provides the frequency of excessive or chronic fatigue by age. Among those with additional data on fatigue via the PROMIS Fatigue 8A SF (*n* = 51), 47.1% scored in the moderate-to-severe fatigue range. The average T-score was higher in BTHS-affected individuals at 57.06 (*SD* = 10.45, *range* = 33-77.8) than in the general population with a mean score of 50 [Figure 3].

Finally, we documented the use of specialist medical providers in the past year [Table 6]. Participants saw, on average, 3.6 specialists in the previous year (range 0-10). Cardiologists and hematologists were the most commonly visited specialists, seen by 97.9% and 58.2% of participants for a median number of 3 or 2 visits per year, respectively. Visits with a variety of other specialists were also reported within the past year.

DISCUSSION

This analysis includes patient- and caregiver-reported data from the BRR. Our current study population of 115 individuals, 105 of whom were still living at the time of the study, represents nearly one-third of the BTHS population known to the Barth Syndrome Foundation. This updated natural history analysis builds

Table 6. Visits to specialists in the previous year

Specialist	Percentage who saw specialists in the past year (95%CI)	Age of individuals who saw specialists in the past year, median	Number of visits in the past year among those who saw specialists, median (range)
Cardiologist	97.9% (92.6%-99.4%)	13.4 years	3 (1-12+)
Hematologist	58.2% (48.0%-67.8%)	19.6 years	2 (1-12+)
Nutritionist/dietitian	57.2% (46.7%-66.8%)	19.8 years	1 (1-12+)
Metabolic specialist	44.4% (34.6%-54.7%)	21.2 years	1 (1-12+)
Gastroenterologist	27.5% (19.4%-37.4%)	17.4 years	1 (1-4)
Neurologist	24.5% (16.0%-34.0%)	9.2 years	1 (1-6)
Orthopedic specialist	23.0% (16.4%-33.6%)	10.4 years	1 (1-4)
Endocrinologist	20.9% (13.8%-30.3%)	10.6 years	1 (1-4)
Immunologist/allergy specialist	16.8% (10.5%-26.0%)	12.7 years	1 (1-2)
Hepatologist	3.3% (1.1%-9.2%)	8.5 years	1 (1-2)

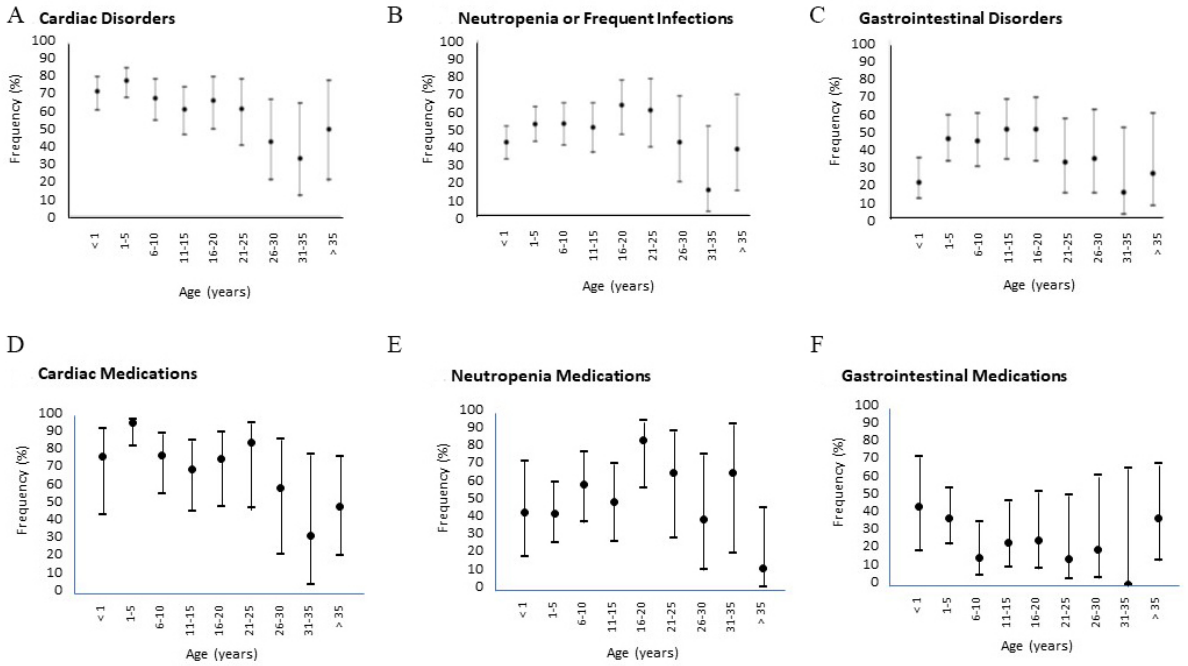

Figure 1. Proportion (and 95% confidence intervals) of individuals with BTHS who experience 1A) cardiac, 1B) neutropenia, and 1C) GI manifestations and use medications for those respective categories (1D-1F) by age group. Cardiac disorder was defined as cardiomyopathy, cardiac arrest, cardiac failure, or the presence of an implantable device. GI disorder was defined as constipation, chronic diarrhea, dysphagia, feeding difficulties, or gastroesophageal reflux. BTHS: Barth syndrome; GI: gastrointestinal.

upon previous reports by including evaluations of manifestations by age, descriptions of manifestations that led to diagnosis, and assessment of levels of healthcare utilization.

Diagnostic odyssey

Our analysis showed similar results to previous studies of individuals with BTHS, wherein cardiomyopathy began in childhood, with the majority experiencing cardiomyopathy before the age of one year[16,25]. Analysis of the registry data indicated that diagnostic odysseys were often long, with slightly less than half of participants receiving a diagnosis within one year of onset of manifestation(s). Although a range of

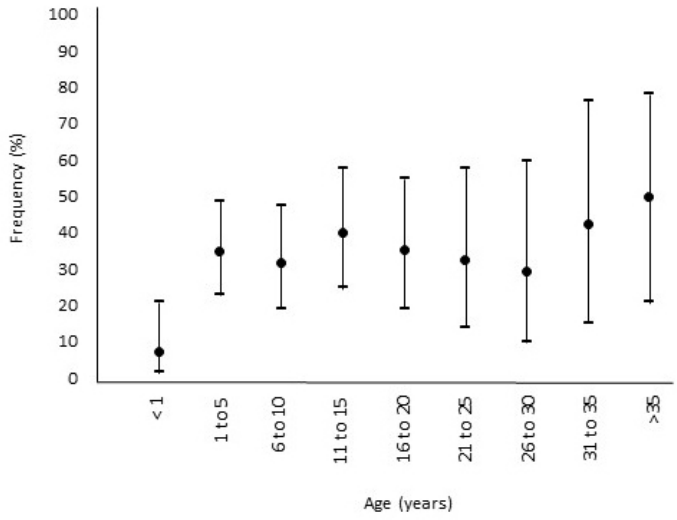

Figure 2. Proportion [and 90% confidence intervals (CI)] of individuals with BTHS who experience excessive or chronic fatigue by age group. BTHS: Barth syndrome.

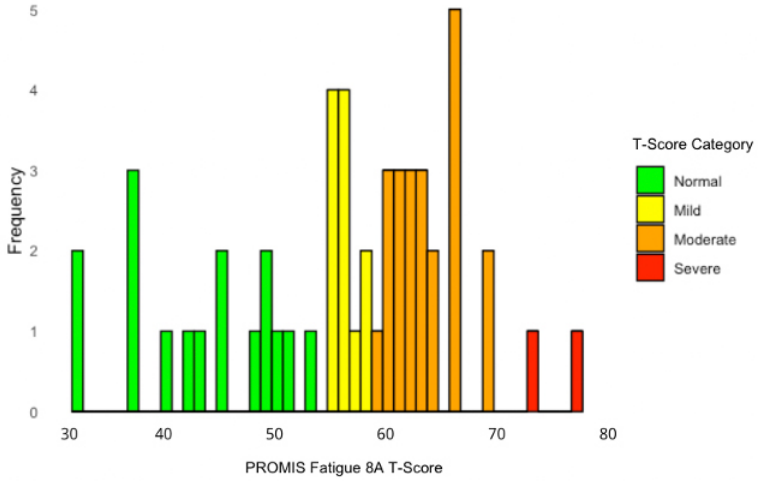

Figure 3. Histogram of the distribution of T-scores in affected individuals with PROMIS Fatigue SF 8A available (*n* = 51). PROMIS: Patient-reported outcomes measurement information system.

diagnostic timespans was seen for all presentations, those who presented with cardiomyopathy/heart failure were the most likely to be diagnosed within one year of onset while those with less common presentations were most likely to have a diagnostic odyssey greater than five years. This stark contrast illustrates the need for further clinical and community awareness of the less prevalent manifestations of BTHS. Physician-targeted educational programs (e.g., continuing medical education courses) regarding early recognition of BTHS and testing of infants with the less prevalent manifestations of feeding challenges and failure to thrive could be helpful in shortening the diagnostic odyssey.

It is currently still unclear whether the time from first manifestation to diagnosis has decreased over the years. Based on the raw data, there appears to be a shift toward faster diagnosis over time. However, patients diagnosed in the earlier decades may represent milder cases, as those surviving to adulthood were more

likely to be entered into the registry. This is supported by the observation that a smaller percentage of patients diagnosed in the earlier time period had cardiac manifestation as their first manifestation compared to those born and diagnosed in the later decades. Since it is possible that milder cases may be more difficult to recognize and therefore take longer to diagnose, this may skew the results for the earlier time periods toward longer diagnostic odysseys. In addition, births in 2010-2019 may include children who have not yet been diagnosed, which may skew results for this time period toward shorter diagnostic odysseys. Thus, more studies are needed to assess whether or not the diagnostic journey has shortened over the years.

BTHS is not currently included in newborn screening tests, despite data demonstrating that early BTHS diagnosis is critical for favorable prognosis as mortality is especially high during infancy[26]. Newborn screening in the United States is guided by the principles defined by Wilson and Jungner in 1968, which includes an acceptable screening test and consensus on how to treat patients with the disorder[27]. For newborn screening to be conducted ethically without rigorous informed consent of the parents, it is necessary that the test and consequent follow-up offer clinical benefit to the child[28]. However, in the past few decades, there has been increasing interest in population-based screening for disorders that do not meet the classic criteria, with emphasis on benefits beyond those to the child, such as avoidance of the diagnostic odyssey, provision of reproductive information to the family, and opportunities to study the impact of early treatment[28,29]. It has been suggested that screening for disorders that do not meet the classic criteria be conducted after the newborn period and with explicit informed consent from the parents in a second tier of screening[28], and this approach is currently being piloted in a research setting[30]. As new technology and methods emerge with the potential for early detection of BTHS, adding BTHS to newborn screening panels should be considered.

Clinical manifestations

The prevalence of cardiomyopathy in individuals with BTHS has been reported to be about 90%-95%[16,31,32]. In the present study, however, the frequency of individuals with BTHS who had a documented cardiac disorder was 80.7%. Three of the individuals in our analysis who did not have a cardiac disorder reported that they were genetically diagnosed after another family member was diagnosed with BTHS and two of the individuals were less than six months old. When these five individuals were excluded, the frequency of cardiac disorders increased to 84.5%, which is still lower than previous reports. Likewise, the frequency of neutropenia/frequent infections in our study (67.2%) is less than previous reports of 84%-86%[17,31]. Steward *et al.* analyzed data from individuals who were diagnosed clinically, while Rigaud *et al.* included individuals who were diagnosed through family-based testing, as in our BRR data[17,31]. The studies by Rigaud *et al.* and Kang *et al.*, however, included clinical assessment of individuals, while our study is based on self-report[31,25]. Lack of clinical assessment, inclusion of individuals diagnosed through family screening, and biases in self-reported data may explain the lower frequency of these manifestations in our analysis.

Because cardiomyopathy is a predominant clinical feature of BTHS, with >70% of affected individuals reporting cardiomyopathy as a manifestation in various reports[16,25,31-33], cardiologists may be more aware of BTHS than other specialists. In our analysis, cardiac disorders were the most common presenting manifestation for individuals with BTHS but accounted for 57% of individuals with BTHS. The second most common presenting manifestation was feeding difficulty, weight loss, and/or failure to thrive. Furthermore, two-thirds of registry participants reported a GI disorder, the most common being chronic constipation, chronic diarrhea, dysphagia, feeding difficulties, and GERD. The number of patients with chronic constipation or diarrhea is higher than expected based on general population data[34]. Nutritional challenges and GI disorders in BTHS have not been thoroughly described in most previous natural history reports. In fact, our results support the elevation of nutritional and GI issues as cardinal characteristics of the disorder, as over half of BTHS-affected individuals report experiencing them at some point in life.

Moreover, we found that cardiac disorders, neutropenia or frequent infections, and GI manifestations all decreased in frequency after ~25 years of age. This decrease could be due to increased mortality in childhood and early adulthood for those with more severe manifestations. Under 20 years of age, cardiac disorders were the most reported manifestation of BTHS, with neutropenia/frequent infections and GI disorders being reported with equal frequencies in the older age groups. Thus, GI disorders occur with similar frequencies and in a similar age profile to cardiac and hematological manifestations. Medication use for cardiac and neutropenia manifestations largely mirrored the frequency of manifestations across ages. In contrast, GI manifestations and medication use did not follow this pattern of results, which may be driven by different clinical care approaches to GI issues, since there is a general lack of knowledge about GI involvement in relation to BTHS and may represent an area for improved care management. Cardiac- and neutropenia-related medication use correlated with the frequency of manifestations by age, as expected. Interestingly, usage of GI medications was less frequent from ages 6-20, although GI disorders were higher in those age groups. Available from the BSF website is educational material on the management of diarrhea[35]. As more knowledge is gained on the GI aspects of BTHS, the development of additional educational resources with expert input on other GI manifestations may be helpful for the patients and providers.

Fatigue

Fatigue was reported more frequently in our study (60.9%) than in a previous report (53%)[17]. We found that excessive fatigue did not decrease in frequency as individuals aged, suggesting that fatigue is chronic and persists throughout life. This observation is consistent with prior qualitative reports of the enduring and worsening nature of fatigue in BTHS[23]. Although early and chronic fatigue is common in disorders of mitochondrial energy metabolism[36], the subjective impact of fatigue in BTHS is underappreciated. Fatigue in BTHS is postulated to be intertwined with, but distinct from, skeletal myopathy and muscle weakness[37]. Unlike cardiac, neutropenia, and GI manifestations which have medications available for their management and/or supportive care, supportive measures currently do not exist for fatigue. Despite this lack of available care, BTHS-affected individuals and families have voiced that fatigue is the manifestation that causes the most profound impact in their daily lives[18] and is significantly correlated with impaired health-related quality of life[38]. Recent qualitative investigations to better understand fatigue have revealed that it can manifest in a variety of ways: physically (e.g., muscle soreness, overall weakness, muscle endurance), cognitively (e.g., slowed thinking, trouble focusing), and psychosocially (e.g., self-care, emotion regulation), which may have significant implications on quality of life[39]. Although our results largely echo prior reports on the high prevalence of fatigue in BTHS, this analysis is the largest cohort analyzed to date. Fatigue in BTHS is debilitating and remains an unmet need that urgently warrants further research and the development of appropriate therapies.

Healthcare utilization

In addition to manifestations, we also documented the healthcare utilization of individuals with BTHS. A variety of medical specialists were involved in managing the care of patients with BTHS. Participants saw, on average, 3.6 different specialists, with cardiologists and hematologists being the most commonly seen specialists. Only 28% of participants reported having seen a gastroenterologist in the previous year, despite the high frequency of individuals who reported GI disorders. However, 59% reported seeing a nutritionist/dietitian in the previous year, so it is possible that GI manifestations are being addressed by these providers. The heterogeneity of BTHS and varied specialists involved in the care of patients highlight the need for interdisciplinary clinics dedicated to BTHS diagnosis and care management. To date, two interdisciplinary centers of clinical expertise for BTHS exist: one in the United States at the Kennedy Krieger Institute and the second at the University Hospitals Bristol in the United Kingdom. Our data illustrate the need for additional centers across the globe that specialize in BTHS. Combining perspectives across different

disciplines could lead to a more holistic understanding of the affected individual's condition and multiple facets of the disease.

Strengths and limitations

One of the strengths of this study was including a relatively large sample size for an ultra-rare disease, accounting for approximately one-third of the known BTHS patients globally. In addition, many of the registry participants completed surveys multiple times, as often as yearly, resulting in longitudinal data. To our knowledge, this is the first study that reported on the diagnostic odyssey, medical provider utilization in BTHS, and manifestations across various age groups, including older adults. There are also several caveats to consider. Limitations include biases associated with retrospectively collected self- or caregiver-reported data, and the fact that follow-up intervals across participants may not have been equal. That is, not all participants completed the surveys each year, so some participants are represented to a greater extent in the data than others. Ascertainment bias should also be considered, as those with increased severity of manifestations are more likely to receive a diagnosis or seek medical care. This may lead to potential mismatches between the registry data and current clinical practice, as the registry cohort may not be fully representative of all those with BTHS.

Conclusion

Taken together, this study provides valuable insights into the natural history of BTHS. Our findings corroborate previous work that characterized cardiac manifestations and neutropenia as the most common clinical presentations in BTHS. Interestingly, we also found that GI and feeding challenges affected over half of the study population and that fatigue was even more frequent and severe than previously reported. Our analysis further illustrates the shared manifestations, medications, and healthcare needs reported by affected individuals and their caregivers. Additionally, we revealed that timely diagnosis remains a challenge, particularly for less common manifestations. Looking forward, a more detailed analysis of longitudinal data such as a survival analysis would be useful to study the potential impact of early diagnosis and management on outcomes, which could support the inclusion of BTHS in newborn screening programs in the future. Similarly, data from the BRR can be utilized to undertake a more rigorous genotype-phenotype analysis to determine if there is any correlation between the *TAFAZZIN* genotype and the corresponding phenotype, though previous studies did not identify any correlation[33]. Although there are currently no specific treatments approved for BTHS, natural history registries like the BRR will further inform unmet needs and may contribute to the development of emerging therapies including but not limited to small molecules, enzyme replacement therapy[40], and gene therapies[41,42]. As progress continues to be made in finding treatments for BTHS, the goal of the BRR is to be a meaningful resource for scientists, clinicians, and affected families alike. In addition to the research findings we have highlighted, we hope that the shared data will be useful for affected individuals and their families in navigating what to expect in terms of manifestations experienced, alongside medical and healthcare utilization across the lifespan of BTHS.

DECLARATIONS

Acknowledgments

We would like to thank the affected individuals and their families who participated in the Barth Syndrome Foundation's BTHS Registry and Repository. The data that they entered into the registry made this analysis possible. Special thanks to JW, KB, and RH for their perspectives as BTHS-affected individuals and their invaluable input in this manuscript. We also thank Chelsea Cole for assistance with data analysis.

Authors' contributions

The conceptualization of the project and development of the data analysis plan: Kenneson A, Huang Y, Lontok E

The interpretation of results and preparation of the manuscript: Kenneson A, Huang Y, Lontok E, Marjoram L
Conducted the analyses: Kenneson A, Huang Y

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Financial support and sponsorship

This project was supported by the Barth Syndrome Foundation (charity #22-3755704, barthsyndrome.org) and by the Southeast Regional Genetics Network (southeastgenetics.org). SERN is funded by the Health Resources and Services Administration of the U.S. Department of Health and Human Service as part of an award totaling $600,000 to Emory University (grant # 5UH7MC30772-06-00). The views expressed are those of the authors and do not necessarily represent the official views or endorsements of HRSA, HHS, or the U.S. Government. For more information, please visit HRSA.gov.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This study was carried out in accordance with the World Medical Association Declaration of Helsinki. Institutional Review Board approval of the Barth Syndrome Registry and Repository was obtained from North Star Review Board (IRB #: NB300158). Registry participants completed informed consent before entering data into the registry.

Consent for publication

Not applicable.

REFERENCES

1. Ferreira C, Pierre G, Thompson R, et al. Barth Syndrome. Available from: https://www.ncbi.nlm.nih.gov/books/NBK247162/ [Last accessed on 13 Sep 2024].
2. Gonzalez IL. Barth syndrome: TAZ gene mutations, mRNAs, and evolution. *Am J Med Genet A* 2005;134:409-14. DOI PubMed
3. Bione S, D'Adamo P, Maestrini E, Gedeon AK, Bolhuis PA, Toniolo D. A novel X-linked gene, G4.5 is responsible for Barth syndrome. *Nature Genetics* 1996;12:385-9. DOI PubMed
4. Cosson L, Toutain A, Simard G, et al. Barth syndrome in a female patient. *Mol Genet Metab* 2012;106:115-120. DOI
5. Avdjieva-Tzavella DM, Todorova AP, Kathom HM, et al. Barth syndrome in male and female siblings caused by a novel mutation in the TAZ gene. *Genetic Counseling* 2016;27:495-501. PubMed
6. Xu Y, Malhotra A, Ren M, Schlame M. The enzymatic function of tafazzin. *J Biol Chem* 2006;281:39217-24. DOI PubMed
7. Schlame M, Xu Y. The function of tafazzin, a mitochondrial phospholipid–lysophospholipid acyltransferase. *J Mol Biol* 2020;432:5043-51. DOI PubMed PMC
8. Kagan VE, Tyurina YY, Mikulska-Ruminksa K, et al. Anomalous peroxidase activity of cytochrome c is the primary pathogenic target in Barth syndrome. *Nature Metabolism* 2023;5:2184-205. DOI PubMed PMC
9. Ji J, Greenberg ML. Cardiolipin function in the yeast S: cerevisiae and the lessons learned for Barth syndrome. *J Inherit Metab Dis* 2022;45:60-71. DOI PubMed PMC
10. Paradies G, Paradies V, Ruggiero FM, Petrosillo G. Role of cardiolipin in mitochondrial function and dynamics in health and disease: molecular and pharmacological aspects. *Cells* 2019;8:728. DOI PubMed PMC
11. Ren M, Miller PC, Schlame M, Phoon CK. A critical appraisal of the tafazzin knockdown mouse model of Barth syndrome: what have we learned about pathogenesis and potential treatments? *Am J Physiol Heart Circ Physiol* 2019;317:H1183-H1193. DOI PubMed PMC

12. Vaz FM, van Lenthe H, Vervaart MAT, et al. An improved functional assay in blood spot to diagnose Barth syndrome using the monolysocardiolipin/cardiolipin ratio. *J Inherit Metab Dis* 2022;45:29-37. DOI PubMed PMC
13. Barth PG, Scholte HR, Berden JA, et al. An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes. *J Neurol SCI* 1983;62:327-355. DOI PubMed
14. Kelley RI, Cheatham JP, Clark BJ, et al. X-linked dilated cardiomyopathy with neutropenia, growth retardation, and 3-methylglutaconic aciduria. *J Pediatr-US* 1991;119:738-47. DOI
15. Hornby B, Thompson WR, Almuqbil M, et al. Natural history comparison study to assess the efficacy of elamipretide in patients with Barth syndrome. *Orphanet J Rare Dis* 2022;17:1-9. DOI PubMed PMC
16. Roberts AE, Nixon C, Steward CG, et al. The barth syndrome registry: distinguishing disease characteristics and growth data from a longitudinal study. *Am J Med Genet A* 2012;158:2726-32. DOI
17. Steward CG, Groves SJ, Taylor CT, et al. Neutropenia in Barth syndrome. characteristics, risks, and management. *Curr Opin Hematol* 2019;26:6-15. DOI PubMed PMC
18. A report on the externally-led patient-focused drug development meeting. Available from: https://barthsyndrome.org/newsevents/pfddmeeting/voiceofthepatient.html. [Last accessed on 13 Sep 2024].
19. Taylor C, Rao ES, Pierre G, et al. Clinical presentation and natural history of Barth Syndrome: an overview. *J Inherit Metab Dis* 2022;45:7-16. DOI
20. Reynolds S. Successful management of Barth syndrome. a systematic review highlighting the importance of a flexible and multidisciplinary approach. *J Multidiscip Health* 2015;8:345-58. DOI PubMed PMC
21. Lontok E, Milligan E, Bowen VM, McCurdy KR. Barth syndrome foundation. From humble beginnings to becoming an integral partner. *J Inherit Metab Dis* 2022;45:3-6. DOI PubMed
22. Barth syndrome registry and repository. Available from: https://barthsyndromeregistry.patientcrossroads.org. [Last accessed on 13 Sep 2024].
23. Mazar I, Stokes J, Ollis S, et al. Understanding the life experience of Barth syndrome from the perspective of adults. a qualitative one-on-one interview study. *Orphanet J Rare Dis* 2019;14:1-8. DOI PubMed PMC
24. PROMIS Fatigue Scoring Manual. Available from: https://www.fda.gov/media/137977/download [Last accessed on 13 Sep 2024].
25. Kang SL, Forsey J, Dudley D, Steward CG, Tsai-Goodman B. Clinical characteristics and outcomes of cardiomyopathy in Barth syndrome: the UK experience. *Pediatric Cardiology* 2016;37:167-17. DOI PubMed
26. Takeda A, Sudo A, Yamada M, et al. Eponym: Barth syndrome. *Eur J Pediatr* 2011;170:1365-7. DOI PubMed
27. Wilson JMG, Jungner F. Principles and practice of screening for disease. Available from: https://apps.who.int/iris/handle/10665/37650 [Last accessed on 13 Sep 2024].
28. Ross LF, Clarke AJ. A historical and current review of newborn screening for neuromuscular disorders from around the world: lessons for the United States. *Pediatric Neurology* 2017;77:12-22. DOI PubMed
29. Grosse SD, Boyle CA, Kenneson A, Khoury MJ, Wilfond BS. From public health emergency to public health service. the implications of evolving criteria for newborn screening panels. *Pediatrics* 2006;117:923-9. DOI PubMed
30. Gehtland LM, Bailey DB. Early Check. A north carolina research partnership. *NC Med J* 2019;80:59-61. DOI
31. Rigaud C, Lebre AS, Touraine R, et al. Natural history of Barth syndrome: a national cohort study of 22 patients. *Orphanet J Rare Dis* 2013;8:70. DOI PubMed PMC
32. Spencer CT, Bryant RM, Day J, et al. Cardiac and clinical phenotype in Barth syndrome. *Pediatrics* 2006;118:E337-46. DOI
33. Clarke SL, Bowron A, Gonzalez IL, et al. Barth syndrome. *Orphanet J Rare Dis* 2013;8:23. DOI PubMed PMC
34. Palsson OS, Whitehead W, Törnblom H, Sperber AD, Simren M. Prevalence of Rome IV functional bowel disorders among adults in the United States, Canada, and the United Kingdom. *Gastroenterology* 2020;158:1262-1273. DOI PubMed
35. Kelley R. Management of diarrheal illness in patients with Barth syndrome. Available from: https://www.barthsyndrome.org.uk/userfiles/Factsheets/ManagementofDiarrheainBTHSFactSheet.pdf [Last accessed on 13 Sep 2024].
36. Filler K, Lyon D, Bennett J, et al. Association of mitochondrial dysfunction and fatigue. a review of the literature. *BBA clinical* 2014;1:12-23. DOI PubMed PMC
37. Olivar-Villanueva M, Ren M, Phoon CK. Neurological & psychological aspects of Barth syndrome: clinical manifestations and potential pathogenic mechanisms. *Mitochondrion* 2021;61:188-95. DOI PubMed
38. Kim AY, Vernon H, Manuel R, Almuqbil M, Hornby B. Quality of life in Barth syndrome. *Ther Adv Rare Dis* 2022;3:26330040221093743. DOI PubMed PMC
39. Reynolds S, Babson I, Daw E. A qualitative investigation of fatigue & its daily impacts as perceived by individuals with Barth syndrome & their families. *Am J Occup Ther* 2023;77(Supplement 2):7711510338p1. DOI
40. Thompson R, Jefferies J, Wang S, et al. Current and future treatment approaches for Barth syndrome. *J Inherit Metab Dis* 2021;45:1. DOI
41. Suzuki-Hatano S, Saha M, Rizzo SA, et al. AAV-mediated TAZ gene replacement restores mitochondrial and cardioskeletal function in Barth syndrome. *Human Gene Therapy* 2019;30:139-54. DOI PubMed PMC
42. Wang S, Li Y, Xu Y, et al. AAV gene therapy prevents and reverse heart failure in a murine knockout model of Barth syndrome. *Circulation Research* 2020;126:1024-39. DOI PubMed PMC