

The Barth Syndrome Registry: Distinguishing Disease Characteristics and Growth Data From a Longitudinal Study

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Barth syndrome (BTHS; MIM accession # 302060) is a rare X-linked recessive cardioskeletal mitochondrial myopathy with features of cardiomyopathy, neutropenia, and growth abnormalities. The objectives of this study were to further elucidate the natural history, clinical disease presentation, and course, and describe growth characteristics for males with BTHS. Patients with a confirmed genetic diagnosis of BTHS are referred to the BTHS Registry through the Barth Syndrome Foundation, self-referral, or physician referral. This study is based on data obtained from 73 subjects alive at the time of enrollment that provided self-reported and/or medical record abstracted data. The mean age at diagnosis of BTHS was 4.04 ± 5.45 years. While the vast majority of subjects reported a history of cardiac dysfunction, nearly 6% denied any history of cardiomyopathy. Although most subjects had only mildly abnormal cardiac function by echocardiography reports, 70% were recognized as having cardiomyopathy in the first year of life and 12% have required cardiac transplantation. Of the 73 enrolled subjects, there have been five deaths. Growth curves were generated demonstrating a shift down for weight, length, and height versus the normative population with late catch up in height for a significant percentage of cases. This data also confirms a significant number of patients with low birth weight, complications in the newborn period, failure to thrive, neutropenia, developmental delay of motor milestones, and mild learning difficulties. However, it is apparent that the disease manifestations are variable, both over time for an individual patient and across the BTHS population. © 2012 Wiley Periodicals, Inc.

Key words: Barth syndrome; cardiomyopathy; neutropenia; growth delay; Registry

INTRODUCTION

Barth syndrome (BTHS; MIM accession # 302060) is an X-linked cardioskeletal mitochondrial myopathy with additional features of

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neutropenia and growth abnormalities. Since the first description of the syndrome in 1983 [Barth et al., 1983], understanding of the phenotype, genetic basis, and pathophysiology of this disease has evolved tremendously. Bione et al. [1996] demonstrated that mutations in the tafazzin (TAZ) gene on Xq28 were associated with BTHS. Since that time it has been shown that alternative splicing of TAZ results in a family of proteins termed tafazzins, phospholipid acyltransferases crucial in the remodeling of cardiolipin (CL) [Vreken et al., 2000; Schlame et al., 2002; Schlame and Ren, 2006]. Abnormalities in CL remodeling result in markedly reduced concentration and altered composition of CL, a mitochondrial-specific phospholipid comprising the major component of the inner mitochondrial membrane. Specifically, the

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tetralinoleoyl-cardiolipin species, the dominant species of CL in the heart and skeletal muscle, is radically reduced in most Barth patients [Schlame et al., 2002]. This results in membrane destabilization and generalized electron transport chain dysfunction although the specific role CL plays in mitochondrial function and biogenesis is not fully understood [Schlame et al., 2000; Vreken et al., 2000; McKenzie et al., 2006; Schlame and Ren, 2006; Claypool et al., 2008]. BTHS is the only known metabolic disease affecting CL [Barth et al., 2004; Claypool et al., 2011].

Phenotypic descriptions suggest that cardiomyopathy (CM) is the most common presenting feature, including dilated, left ventricular non-compaction and less often hypertrophic forms [Barth et al., 2004; Spencer et al., 2006]. Additional cardiac issues include serious arrhythmia [Barth et al., 2004; Spencer et al., 2005] and fetal CM with or without intrauterine fetal demise [Steward et al., 2010]. Marked reduction in exercise functional capacity and oxygen consumption, likely due to both impaired oxygen extraction as well as limited cardiac contractile reserve, have been demonstrated [Spencer et al., 2011]. Neutropenia is variable, for an individual over time and within the population, although it may be absent in some patients. Moreover, neutropenia in BTHS can lead to serious bacterial infection and death [Barth et al., 2004]. Skeletal muscle weakness is an early feature of the disease, often described as proximal and leading to motor delays [Barth et al., 1983, 2004; Christodoulou et al., 1994]. Growth deficiency is described as proportional [Barth et al., 2004] although there is some suggestion of catch up growth in height after puberty [Spencer et al., 2006]. Characteristic facial features have been described, including full cheeks, prominent ears, and deep-set eyes [Hastings et al., 2009]. A mild cognitive phenotype has been described in a small cohort of patients with specific delays in mathematics, visual spatial tasks and specific aspects of visual short-term memory versus controls [Mazzocco et al., 2007]. Reported metabolic derangements include hypocholesterolemia, increased urine 3-methylglutaconic acid [Kelley et al., 1991] and a suggestion of increased lactic acidosis with exercise [Spencer et al., 2011]. Overall there appears to be wide variability in phenotypic expression and symptoms in the patient population as well as variations in the clinical picture in individual patients over time [Barth et al., 2004; Spencer et al., 2006]. To date, specific genotype–phenotype correlations have not been clearly demonstrated [Johnston et al., 1997; Spencer et al., 2006]. Female carriers have not been proven to be affected.

The incidence of BTHS is not known though it is thought to be under-diagnosed [Cantlay et al., 1999]. Initial reports suggested high mortality in infancy and childhood [Barth et al., 1983, 2004; Christodoulou et al., 1994]. A decrease in early mortality has been observed with current management strategies that include rigorous medical management of CM, use of internal cardiac defibrillators (ICD) [Spencer et al., 2005], cardiac transplantation [Adwani et al., 1997], and better recognition and prophylaxis of neutropenia/infection [Barth et al., 2004].

The natural history of BTHS is only partially described [Barth et al., 1999, 2004; Spencer et al., 2006]. Cases have been reported from throughout the world without a known racial or ethnic predilection. Additionally, there is no known curative treatment for BTHS other than supportive care for CM, neutropenia, and nutrition. Given the rare nature of the disease as well as wide

variability in the phenotype and clinical characteristics, the Barth Syndrome Foundation (BSF) and investigators interested in BTHS initiated the BTHS Registry in 2006. The Registry is comprised of a database of both self-reported and medically abstracted data as well as a biorepository consisting primarily of extracted DNA and lymphoblast cell lines that are linked by subject ID to archived data. The objectives of this study were to further elucidate the natural history, clinical disease presentation, and course, and to describe growth characteristics for males affected with BTHS.

METHODS

Patients with a confirmed genetic diagnosis of BTHS are referred to the BTHS Registry through the BSF, the BSF website (www.barthsyndrome.org), the Barth Syndrome Trust (UK) or the biennial Barth Syndrome International Scientific, Medical & Family Conference. The BTHS Registry was approved by the IRBs of the two participating institutions; the University of Florida and Boston Children's Hospital. Inclusion criteria for the Registry are a diagnosis of BTHS, *TAZ* gene mutation and the provision of informed consent.

Beginning in 2006, consented patients/families completed an intake questionnaire consisting of queries regarding demographics, diagnosis details, family history, development, review of systems, and medical history. The initial subject intake questionnaire includes questions dating back to the birth of the subject in an effort to obtain retrospective self-reported data. Participating families fill out an update form every 1–2 years. At the time of enrollment and/or update, participants may choose to fill out a release of medical information form to the Registry as well as donate blood for DNA extraction and/or development of lymphoblast cell lines. Self-reported data is entered into a secure, password protected, web-based database using a subject ID. Specific medical record data that the Registry obtains is also entered (including growth data, laboratory results, echocardiography reports, results from procedures, and clinic notes). This data is linked by subject ID to any blood, tissue, or cell lines that are obtained. When possible, medical record data retrospective to subject enrollment was included.

This study is based on data obtained from the 73 enrolled subjects with self-reported and/or medical record abstracted data as of September 1, 2011. For three subjects, only limited self reported data was available. Data collection started in July 2006 with 32 subjects. The majority of the medical updates and new enrollment occurred in 2010.

All growth points and cardiac function data were taken from medical records and from subjects who enrolled and were evaluated during the biennial Barth Syndrome International Scientific, Medical & Family Conference. For shortening fraction (SF) and ejection fraction (EF), abstracted results from echocardiogram reports and clinic letters were converted to age appropriate z-scores (number of standard deviations from the sample mean) using regression equations developed at Boston Children's Hospital [Sluysmans and Colan, 2005].

Birth, developmental, and medical histories were taken primarily from self-reported data and verified by medical records when

possible. Birth weight percentiles were derived from <http://www.infantchart.com>; Reference: Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008; <http://www.cdc.gov/growthcharts/>.

Statistics

Growth curves for height versus age and weight versus age were generated separately for boys from birth to 36 months and 2 to 20 years. Since these relationships were not assumed to be linear, restricted cubic splines were first used to explore the nature of the nonlinearity. Smoothed centile curves were then generated using quantile regression. Polynomial and piecewise regression models were used to reproduce the forms of the relationships for predicting the 50th centiles of height and weight. The same models were then used to predict additional centiles. For curves displaying ages from birth to 36 months, the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th centiles were generated. For ages 2–20 years there was insufficient data to estimate the 3rd and 97th centiles accurately, so they are not shown. Growth curves representing the United States population for calendar year 2000 were obtained from the Centers for Disease and Prevention and superimposed on the growth curves for patients with BTHS for comparison. Data tables for normative data were obtained from the Centers for Disease Control (<http://www.cdc.gov/growthcharts/>). Insufficient growth points were available over the age of 20 years to make further statistical analysis or growth curves. Evaluation of SF and EF as it relates to age was performed using linear regression models which accounted for the correlation among repeated measurements on the same subject.

RESULTS

The age range was from 0.3 years (at time of enrollment) to 28.7 years (at time of last update). Enrollees were 90% Caucasian, 7% black, and 3% Hispanic or multi-ethnic with Hispanic background. The geographic distribution included patients from USA (57.1%), United Kingdom (21.4%), Australia (7.1%), Canada (5.7%), South Africa and Belgium (2.9% each), and France and Germany (1.4% each). Data included a total of 156.6 patient years between an individual subject's enrollment and that subject's last update (mean: 2.14 ± 1.81 years) and 860.9 years between birth and last update (mean: 11.79 ± 7.41 years).

Diagnosis

The mean age at diagnosis of BTHS was 4.04 ± 5.45 years although the age of onset of symptoms was 0.76 ± 1.6 years. The primary reason for further DNA diagnostic testing confirming BTHS was CM (70%) with other reported reasons including neutropenia, growth delay/failure to thrive and family history. Specific TAZ gene mutation results were provided for 50 cases. The majority (64%) had missense substitutions, 16% had partial gene deletions, 12% had partial gene duplications, and fewer than 5% had a complete gene deletion, nonsense mutation, or splice site mutation.

Survival

Of the 73 enrolled subjects, there have been five deaths between initial enrollment and most recent follow-up. Ages at time of death were 5.8, 7.4, 16.2, 23.0, and 25.4 years. Causes of death included: congestive heart failure (CHF) awaiting transplant ($n = 2$), CHF not awaiting transplant ($n = 1$), sepsis ($n = 1$), and multi-factorial with CHF, sepsis and probable gastric erosion due to gastrostomy tube ($n = 1$). Two subjects (both older than 20 years with severe left ventricular dysfunction and proven ventricular arrhythmia) had an ICD at the time of death.

Growth

Growth curves were generated for weight, boys 0–36 months (Fig. 1a); length, boys 0–36 months (Fig. 1b); weight, boys 2–20 years (Fig. 1c); and height, boys 2–20 years (Fig. 1d) and superimposed on the CDC growth curves for the appropriate male curves for that age range. There were 764 growth points available on 60 patients, with 205 growth points between birth and 36 months of age and 605 growth points between 2 and 20 years of age. Between age 27 and 36 months, the 50th centile for weight for boys with BTHS roughly overlaps the 3rd centile on the normative curve. Between ages 6 and 36 months, the 50th centile for length for boys with BTHS roughly overlaps the 3rd centile on the normative curve. After age 12–14 years there is an increase in growth velocity for height for boys with BTHS compared both to their previous velocity and to the normative population. After age 16 years there is an increase in growth velocity for weight for boys with BTHS compared both to their previous velocity and to the normative population. Fewer weight and height measurements were available in the 16–20 year range which may explain the lack of apparent leveling off of growth at the end of the age range though late catch up growth has been documented [Spencer et al., 2006].

Cardiomyopathy, Transplantation, and Use of Defibrillators

Of 73 subjects enrolled, 69 provided self-reported information regarding a history of CM. Of these 69 subjects, 4 stated there was no history of cardiac dysfunction (three of these four provided echo reports to the Registry confirming normal function; one did not provide medical records). There was no difference in age at last update between those who confirmed versus those who denied a history of CM (11.7 ± 7.7 years vs. 11.1 ± 3.9 years, respectively). All of those who reported a negative history for CM were diagnosed with BTHS due to a positive family history. Age at diagnosis of CM is shown in Table I, demonstrating that at least 70% of subjects who develop CM are recognized as having it in the first year of life. These data also show that although patients may receive a molecular diagnosis at an older age, there are no reports of late onset (>5 years of age) CM in the Registry. Families are not asked to distinguish between types of CM (dilated, hypertrophic, and non-compaction). Echocardiogram reports provided to the Registry from primary cardiologists are variable in the nature and type of numeric data included, making it difficult to determine the exact type of CM and/or left ventricular morphology.

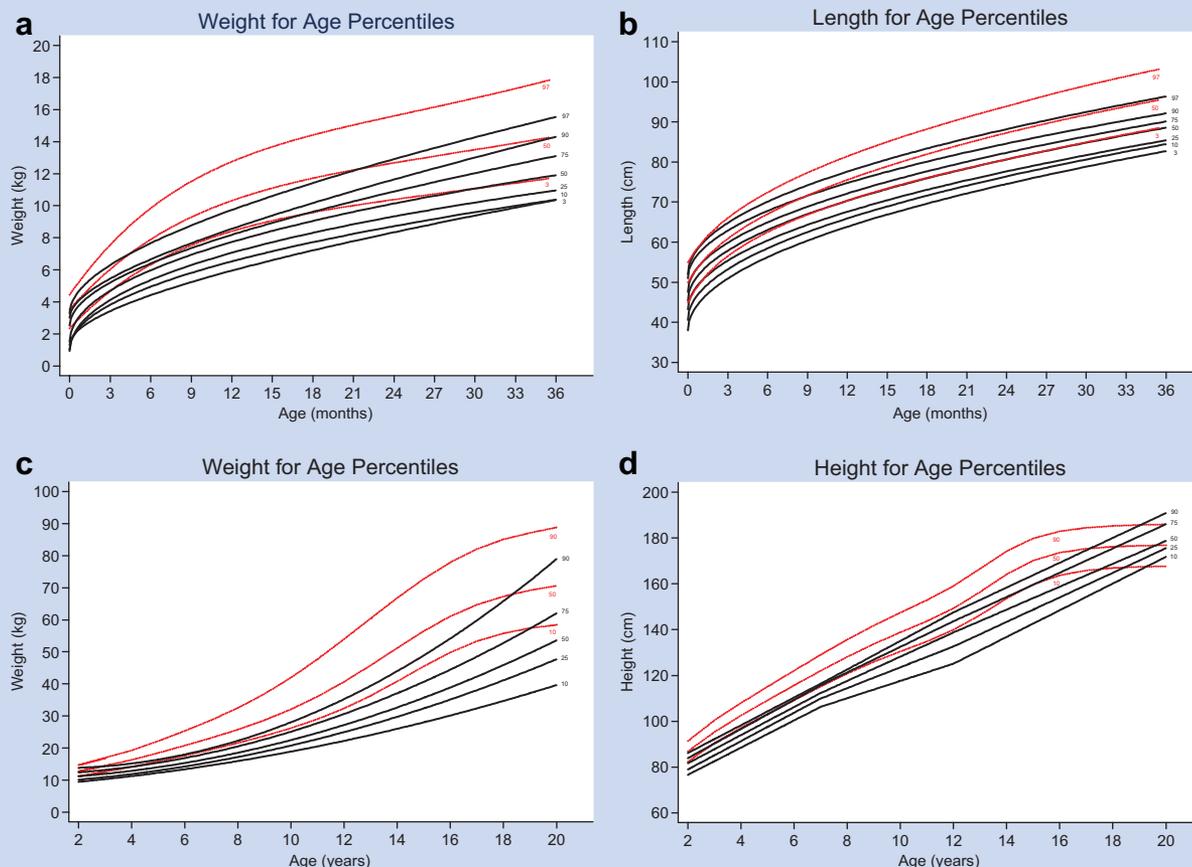


FIG. 1. a: Weight for age centiles, boys 0–36 months of age Barth syndrome (black solid) versus general United States population (red dashed). b: Length for age centiles, boys 0–36 months Barth syndrome (black solid) versus general United States population (red dashed). c: Weight for age centiles, boys 2–20 years Barth syndrome (black solid) versus general United States population (red dashed). d: Height for age centiles, boys 2–20 years Barth syndrome (black solid) versus general United States population (red dashed).

Nine registry participants (of 73 total) have undergone cardiac transplantation and all recipients were alive at the last update. The mean age at transplantation was 3.8 ± 5.3 (range: 3 months to 16 years). All subjects who were transplanted reported having cardiomyopathy and none of these subjects had ICDs at the time of transplant. The exact indication for transplantation was not reported for all subjects. Of 70 subjects with completed information

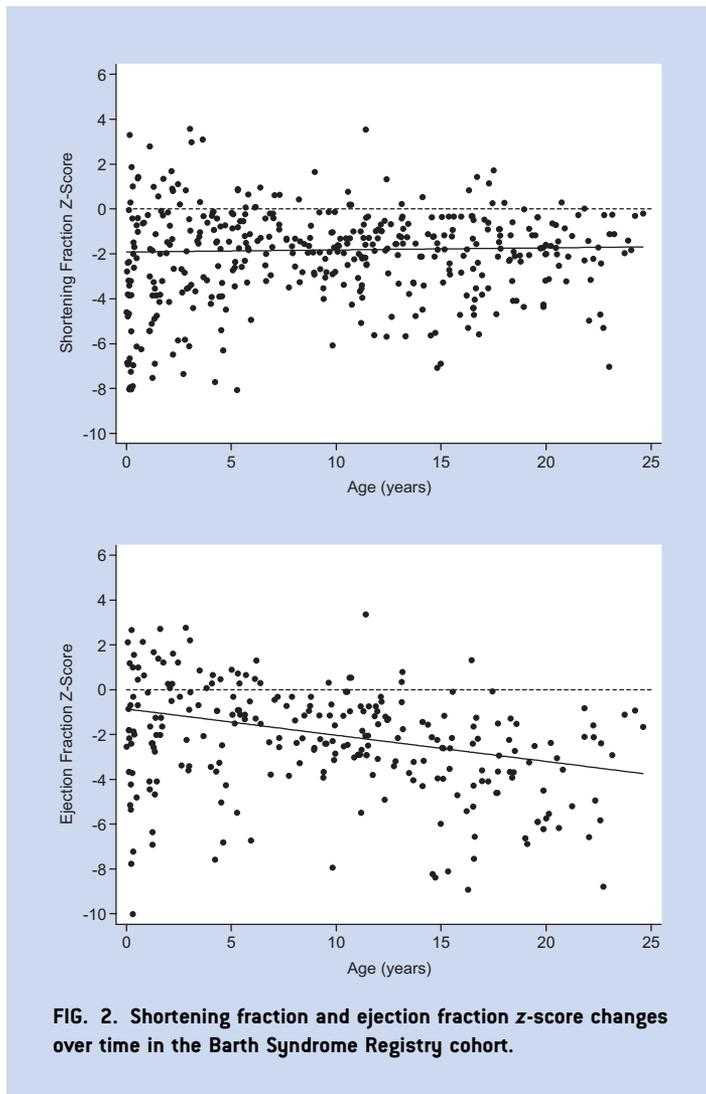
on ICD placement, there are 9 subjects who underwent ICD placement and two subsequent deaths. All subjects with ICDs have a diagnosis of CM.

Cardiac Functional Changes With Age

Cardiac function data by SF and/or EF was abstracted from echocardiogram reports and clinic letters. There were 261 reports available stating EF and 415 reports available with SF, excluding data from those after heart transplantation. Using heights and weights provided in the reports, the SF and EF z-scores for age were determined. Overall there is significant variability of cardiac function in the BTHS population, although the majority of echocardiograms demonstrate SF and EF that are only mildly abnormal (SF and EF z-score better than -3 reported in 71% and 67% of echocardiograms, respectively). There was no relationship between SF z-score and age ($P = -0.49$) although there appears to be an inverse correlation with EF z-score and age ($P = 0.001$). For each 5 year increase in age, EF z-score decreases by 0.6 on average (estimated median EF z-score is -0.86 at age 0 years, and -3.75

TABLE I. Age at Diagnosis of Cardiomyopathy

Age at diagnosis of cardiomyopathy (n = 65)	n (%)
Prenatal	2 (3.1)
Birth–1 month	27 (41.5)
1–6 months	17 (26.1)
6–12 months	2 (3.1)
1–2 years	8 (12.3)
2–5 years	9 (13.8)
>5 years	0



at age 25 years), suggesting that in the group as a whole there may be a decline in function over time (Fig. 2). As age is closely related to growth and body surface area, this data does not suggest that poor cardiac function is responsible for global growth failure in the group.

Neutropenia and Infections

Neutropenia has been observed in 69.1% of subjects by self-report with 25% reporting no prior diagnosis of neutropenia and 5.9% being unsure. Of all subjects, self-reported data indicates that 49.2% have been on granulocyte colony stimulating factor (G-CSF) at some point and 27.5% were on G-CSF at the last update.

Overall 60.2% of subjects report episodes of mouth ulcers. Of subjects who report a positive history of neutropenia, 65% also report recurrent mouth ulcers. Of those who report a negative history of neutropenia, only 35% report a history of mouth ulcers. Overall, 28% report mouth ulcers with a frequency of at least 4 episodes per year. Other infections reported include 28% with a history of pneumonia and 10% reporting a history of blood infections. Sixty-two subjects report a total of 250 hospitalizations. The primary self-reported reason for hospitalization included heart failure/cardiomyopathy/arrhythmia (29%), fever/infection (26%), emesis/diarrhea/dehydration (4.4%), hypoglycemia (4%), and failure to thrive/feeding issues (4%) with the remainder including reasons such as elective surgeries.

Development and Assistive Therapies

Table II describes reported incidence of developmental delays, learning difficulties and use of speech, occupational, and physical therapy in boys with BTHS. These data indicate that many BTHS patients have some developmental motor delay, have used assistive therapies and/or may have some degree of learning difficulties. Additionally, 34% report the use of foot and/or leg braces, walkers, or wheelchairs at some point.

Pregnancy and Birth History

Sixty-five families provided at least partial pregnancy and birth history details. The mean maternal age at birth was 29.3 ± 5.5 years. Of these 65 patients, 9 were born pre-term at 36 weeks or less (range: 29–36 weeks) with 4 of 9 being products of some type of assisted reproduction and 2 of 9 being from a multiple pregnancy. Of all 65 families, 6 reported conception from some form of assisted reproduction.

There were 48 infants with gestational age reported as full term (≥ 38 weeks) with a mean birth weight (BW) centile for the group of 19.2 ± 16.5 (range: 0.6–61.6%). Birth complications in term infants

TABLE II. Developmental Delay Measures

Developmental measure (n = 67 unless specified)	n (%)
Delay in sitting up	44 (65.7)
Delay in walking	48 (71.6)
Reported "concern about developmental delay"	41 (61.2)
Participated in physical therapy	41 (61.2)
Participated in occupational therapy	3 (4.5)
Participated in speech therapy	31 (46.2)
Older than 3 years at last update, reporting either delay in first words or putting words together, n = 60	30 (50)
Older than 7 years at last update, reporting some form of "learning disabilities," n = 46	22 (47.8)
Older than 7 years at last update, reporting some form of "special education," n = 46	15 (32.6)

TABLE III. Birth Complications in Term Infants

Complications at birth in term infants (n = 48)	n (%)
Caesarian section	17 (26.5)
"Complication" in the newborn period per parental report	23 (47.9)
Low birth weight (<2.5 kg)	9 (18.8%)
Hospitalization >1 week at birth ^a	18 (37.5)

^aReasons for prolonged hospitalization at birth in 18 infants (not exclusive): poor heart function (n = 11), feeding issues (n = 10), need for oxygen (n = 7), infection (n = 3), and hypoglycemia (n = 2).

are reported in Table III with the data demonstrating a significant proportion having a prolonged hospitalization at birth, including 23% who report poor heart function in the neonatal period.

Other Medical Issues

In 70 patients, 38 (54.3%) report a history of failure to thrive with 23 (32.9%) reporting need for assisted enteral feeds via gastrostomy or nasogastric tube feedings. Scoliosis is also reported in (20%) and delayed bone age documented in 58%.

DISCUSSION

Disease registries, especially for rare diseases, are becoming valuable resources for obtaining and reporting information [Basso et al., 2004; Moss and Schwartz, 2005; Wilkinson et al., 2010; Byrne et al., 2011; Clarke et al., 2011]. Centralized longitudinal and natural history data as well as the potential to link specific clinical data with DNA or tissue specimens are becoming useful tools for evaluating pathophysiology, genotype–phenotype correlation, genetic modifiers, and potential therapies [Basso et al., 2004; Moss and Schwartz, 2005; Wilkinson et al., 2010]. Registries are also recognized for the potential to evaluate outcomes and efficacies of certain therapies [Basso et al., 2004; Clarke et al., 2011] and are increasingly being used by industry for this purpose in rare diseases [Byrne et al., 2011; Clarke et al., 2011].

This is the first report of data from the BTHS Registry although investigators have accessed cell lines and data with current projects underway [Spencer et al., 2011]. This report also confirms the international effort required to collect data in patients with rare diseases, as more than 40% of subjects in the BTHS Registry are not from the USA. The Registry collects both self-reported as well as medically abstracted data, using both types of information to increase the understanding of the disease.

CM and heart failure are the primary reasons for diagnosis and death in BTHS [Barth et al., 2004]. However, a small subset of patients with BTHS may not have clinically apparent CM. Due to the well known inconsistency in measurement techniques of SF and EF between many different practitioners and centers [Lipshultz et al., 2001], the SF and EF data abstracted from medical records and presented here is variable but demonstrates low normal to mildly abnormal function in most subjects. Using EF z-score as a measure of cardiac function, there is a suggestion of declining cardiac

performance over time. However, confirmation of this finding would require a much more stringent method of measuring and reporting this type of data. This data also confirms that cardiac transplantation can be a successful therapy for those with severe CM and appears to increase survival in some patients with BTHS. Of note, there is a previous report of post-cardiac transplant non-Epstein–Barr virus-associated T-cell lymphoma in BTHS [Ronghe et al., 2001]. At this time, 12% of subjects in the Registry have had heart transplants, with 2.3–20.2 years of survival to date since initial transplant. Similarly, 12% of subjects have had an ICD. However, some patients have had an ICD implanted prophylactically and this may over-estimate the number of subjects with documented serious arrhythmia. There may also be patients with serious arrhythmia that do not have an ICD.

These are the first published growth curves for boys with BTHS and provide excellent guidelines for expected growth patterns in this diagnosis as well as confirming the presence of significant growth delay and late catch up in height compared to the normative population.

Review of this data also confirms the significant number of patients with low birth weight, complications in the newborn period, neutropenia, developmental delay, and learning difficulties. However, it is apparent that the disease manifestations are variable, both in an individual patient and across the BTHS population.

There are several limitations in collection and analysis of Registry data. The limits of self-reported data are well-documented [Klungel et al., 1999; Newell et al., 1999; Lois et al., 2011]. The BTHS Registry attempts to collect both self-reported and medically abstracted data. Medical record data that is provided is variable in both quantity and quality. In addition, only subjects alive at the time of enrollment were included in this data and there may be a survival bias in this small cohort. With respect to growth, there are insufficient data points in older boys to determine the extent of catch up growth after age 20. Specifically regarding CM, there is intra- and inter-institutional variability in definitions and descriptions of CM subtypes [Saleeb et al., 2011] as well as how cardiac function is measured and reported, thus limiting the accuracy of CM description in BTHS. Other difficulties may include language barriers with international patients and reports. Laboratory data will be reported separately. Nonetheless, this is the most complete report on growth and reported medical complications in BTHS.

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