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REVIEW

Successful management of Barth syndrome: a systematic review highlighting the importance of a flexible and multidisciplinary approach

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Abstract: This review describes and summarizes the available evidence related to the treatment and management of Barth syndrome. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards were used to identify articles published between December 2004 and January 2015. The Cochrane Population, Intervention, Control, Outcome, Study Design (PICOS) approach was used to guide the article selection and evaluation process. Of the 128 articles screened, 28 articles matched the systematic review inclusion criteria. The results of this review indicate the need for a flexible and multidisciplinary approach to manage the symptoms most commonly associated with Barth syndrome. It is recommended that a comprehensive care team should include individuals with Barth syndrome, their family members and caregivers, as well as medical, rehabilitative, nutritional, psychological, and educational professionals. The evidence for specific treatments, therapies, and techniques for individuals with Barth syndrome is currently lacking in both quality and quantity.

Keywords: Barth syndrome, rare disorders, rehabilitation, cardiac, systematic review

Introduction

Barth syndrome is a rare X-linked genetic disorder first described by Dr Peter G Barth in 1983.[1] It is caused by mutations in the *TAZ* gene, which is known to encode for the protein tafazzin. Tafazzin plays an important role in the remodeling of cardiolipin, a component of the mitochondrial membrane necessary for maintaining mitochondrial structure as well as for mitochondrial apoptosis and functioning of the electron transport chain.[2,3] Heart failure is the most common clinical feature identified at birth and is the leading cause of death in infants with Barth syndrome. The most common cardiac features of Barth syndrome include dilated cardiomyopathy, left ventricular non-compaction, endocardial fibroelastosis, and serious disturbances of heart rhythm such as ventricular fibrillation or tachycardia.[4] Sepsis due to neutropenia may also be present at birth and is the second leading cause of infant mortality in Barth syndrome.[5] Though survival past infancy is now common in Barth syndrome, cardiovascular and hematological features (ie, neutropenia) in addition to 3-methylglutaconic aciduria often continue throughout the individual's lifespan.[6]

Clinical presentation of Barth syndrome also includes neuromuscular features such as skeletal myopathy, hypotonia, delayed motor milestones, exercise intolerance, and abnormal fatigability.[7] Growth delay is common in childhood; however, catch-up growth often occurs during late adolescence with achievement of normal adult height in most boys. Often in Barth syndrome, there is the presence of sensory or oral–motor feeding problems, nutritional deficiencies, and episodic or chronic diarrhea.[8,9]

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Specific feeding-related behaviors include difficulty transitioning to solid foods, frequent gagging or difficulty swallowing, and a strong preference for salty or spicy foods while rejecting many other foods eaten by the family.[10] There is no definitive cognitive or neurological profile associated with Barth syndrome, though mild learning disabilities, attention deficits, visual spatial deficits, and auditory processing difficulties have been reported.[7,9,11]

Considering that Barth syndrome is a multisystem disorder, it may be first identified by many different specialists or generalists.[7] While there is currently no cure for Barth syndrome, management of clinical features is possible in many cases. Subsequently, individuals with Barth syndrome are likely to interact with a wide range of health care professionals throughout the course of their lifespan in order to address the myriad of symptoms associated with the disorder. The purpose of this review was to identify interventions that are being used to manage symptoms of the disorder and to evaluate the evidence for these interventions related to health and function-related outcomes.

Methods

Prior to initiating a literature search, a protocol using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was established. Five databases were strategically searched: PubMed, CINAHL, Physiotherapy Evidence Database, Dentistry and Oral Sciences Source, and ProQuest index of Dissertation and Theses. This initial search was followed by secondary selection of articles based on a review of references in relevant articles and articles published online by the Barth Syndrome Foundation. Following PRISMA guidelines, titles of all articles were reviewed for appropriateness, followed by a review of relevant abstracts and appraisal of full-text articles.[12] Selection was based on preestablished inclusion and exclusion criteria (the information is described in the paragraph below). The search strategy was initiated using the following question: What treatments, therapies, or techniques are recommended for the management of symptoms seen in males with Barth syndrome? Search terms included Barth AND Syndrome. Only articles published in the last 10 years (December 2004–January 2015) were considered; nonelectronic sources of literature were not considered and only those articles written in English were appraised.

The population was specifically defined as males with a diagnosis of Barth syndrome. Studies using in vitro methods or models (eg, rodent or yeast models) were not considered. To meet the inclusion criteria for intervention, each publication needed to report on the use of a treatment, therapy, or technique to improve the health, well-being, or level of functioning for an individual with Barth syndrome. Interventions focused on end-of-life care were not considered. No comparative intervention or population was required. The studies included were required to assess outcomes relevant to the management of symptoms commonly seen in Barth syndrome including, but not limited to, cardiac function, feeding/eating, nutrition, motor skill development, education, growth, and fatigue. The following standards were used for assessing the levels of evidence and to evaluate the study design and quality of the reviewed articles:

- Level I: systematic reviews, meta-analyses, randomized controlled trials
- Level II: two groups, nonrandomized studies (eg, case–control)
- Level III: one group, nonrandomized (eg, before and after, pretest and posttest)
- Level IV: descriptive studies that include analysis of outcomes (single-subject design, case series)
- Level V: case reports and expert opinion that include narrative literature reviews and consensus statements.[13,14]

Results

Initial search strategies of the five databases yield 309 articles, with an additional 16 records identified through reference review and supplemental searches (Figure 1). After duplicates were removed (n=19) and titles were screened for relevance, a total of 129 articles remained.[2–11,15–133] Within the screened publications, descriptive studies, case reports, narrative reviews, consensus statements, and expert opinion articles were represented. Of the 129 abstracts screened, 86 were excluded with reasons, while 17 appeared to match the Cochrane Population, Intervention, Control, Outcome, Study Design (PICOS) inclusion criteria. An additional 27 articles did not have enough information in the abstract to justify exclusion, received the designation of "maybe", and were included in the next phase of the review. A comprehensive list of the reviewed abstracts with rationale for exclusion is presented in Table 1. Based on established exclusion criteria, 24 studies did not meet population criteria (28.6%) and 71 studies did not fulfill the intervention criteria (84.5%). Among the abstracts reviewed, there were none that met both population and intervention criteria but were excluded due to irrelevant outcome measures.

A total of 44 articles were assessed for eligibility through a full-text review. Each of the 44 articles was read and evaluated based upon the preestablished inclusion/exclusion

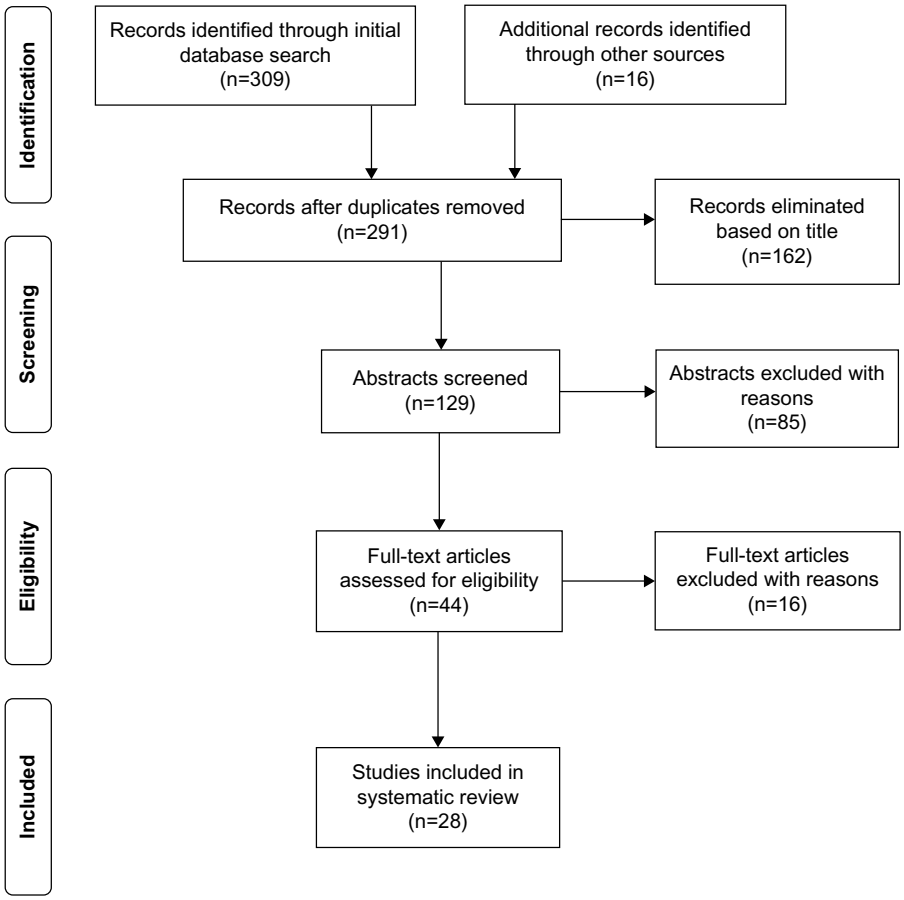

Figure 1 PRISMA flow diagram.
Note: Articles identified, screened, eligible, and included in this systematic review.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

criteria and level of evidence rating. Sixteen articles did not meet inclusion criteria and were therefore excluded (Table 2). Twenty-eight studies met all inclusion criteria; two articles were ranked at Level IV and 26 were ranked at Level V. Table 3 identifies the characteristics of all the 28 articles meeting inclusion criteria, including all PICOS components.

Study design

Of the 28 articles selected for this systematic review, 15 were case reports,[17,21,39,54,60,69,70,84,85,91,101,105,113,114,131] six were literature reviews,[2,3,7,19,47,82] and five were fact sheets.[8,20,23,24,26] The selected articles also included one descriptive cohort study[6] and one descriptive comparison design.[112] Of the 28 articles included in this review, only two used statistical analysis procedures for the analysis of outcomes. Rigaud et al used descriptive and multivariate statistics in a natural history cohort study of 22 individuals with Barth syndrome.[6] In this paper, the Kaplan–Meier method was used to estimate survival rates and survival was compared between groups of individuals based on birth year using a log-rank test. Storch et al compared a sample of 34 boys with Barth syndrome with 22 healthy male controls.[112] Independent sample *t*-tests were used to compare the two groups on a variety of psychosocial outcomes. In this study, the alpha level for significance was set at $P<0.05$; no corrections were made for the possibility of type I error with multiple *t*-tests.

Population

Across all the 28 reviewed articles, 74 males with the diagnosis of Barth syndrome were enrolled. The sample varied in ethnic origin with representation from American, European, and Asian countries. Case reports described the clinical courses of individuals with Barth syndrome ranging in age from birth to 30 years.

Interventions

Medical interventions

Medical interventions were the most common interventions reported, with 23/28 articles reporting on the use of prescription

Table 1 Master citation table of reviewed abstracts

Citation	Level of evidence	Include yes/no	Maybe (explain)	If no, reason to exclude
Acehan et al[15]	IV	No		P, IT
Acehan et al[16]	IV	No		P
Aljishi and Ali[17]	V		IT	
Ances et al[18]	V	Yes		
Aprikyan and Khuchua[19]	V		IT	
Avery[20]	V	Yes		
Bachou et al[21]	V		IT	
BSF[22]	V	No		IT
BSF[23]	V	Yes		
BSF[24]	V	Yes		
BSF[25]	V	No		IT
Bowen et al[26]	V	Yes		
Bowron et al[27]	IV	No		IT
Bowron et al[28]	IV	No		IT
Brady et al[29]	V	No		IT
Brandner et al[30]	IV	No		P, IT
Cade et al[31]	IV	No		IT
Chang et al[32]	V	No		IT
Chicco and Sparagna[33]	V	No		IT
Clarke et al[7]	V	Yes		
Claypool et al[34]	IV	No		P, IT
Claypool et al[35]	IV	No		IT
Claypool et al[36]	IV	No		P
Day et al[37]	IV	No		IT
Debnath and Addya[38]	IV	No		IT
Dedieu et al[39]	V	Yes		
DiMauro[40]	V	No		IT
DiMauro and Gurgel-Giannetti[41]	V	No		IT
Donati et al[42]	V	No		IT
Fan et al[43]	V	No		IT
Feillet-Coudray et al[44]	V		P, IT	
Ferri et al[5]	V		IT	
Finsterer[45]	V		P, IT	
Finsterer[46]	V	No		IT
Finsterer and Frank[47]	V	Yes		
Finsterer and Stöllberger[48]	V	Yes		
Finsterer and Stöllberger[49]	V		IT	
Finsterer and Stöllberger[50]	V	No		P, IT
Finsterer et al[51]	V		IT	
Finsterer et al[52]	IV	No		IT
Finsterer et al[53]	V	No		IT
Folsi et al[54]	V		IT	
Garratt et al[4]	V		IT	
Gerbert et al[55]	V	No		IT
Gilbert-Barness and Barness[56]	V	No		IT
Gonzalez[57]	IV	No		IT
Gonzalvez et al[58]	IV	No		IT
Gonzalvez et al[59]	IV	No		P
Hanke et al[60]	V	Yes		
Hastings et al[61]	V	No		IT
Hauff[62]	IV	No		IT
Hauff and Hatch[63]	V	No		IT
Hauff and Hatch[64]	IV	No		P
Honzik et al[65]	IV		IT	
Houtkooper et al[66]	IV	No		IT
Houtkooper et al[67]	IV	No		IT
Houtkooper and Vaz[68]	V	No		IT
Huang et al[69]	V		IT	
Huhta et al[70]	V		IT	
Jefferies[3]	V	Yes		
Joshi[71]	IV	No		P
Karkucinska-Wieckowska et al[72]	IV	No		IT
Kelley[8]	V	Yes		
Kim et al[73]	V	No		IT
Kirwin et al[74]	V	No		IT
Kirwin et al[75]	V	No		IT
Kleefstra et al[76]	V	No		P
Kulik et al[77]	IV		IT	
Lamari et al[78]	V	No		P
Li et al[79]	IV	No		P, IT
Makaryan et al[80]	IV	No		P
Malhotra et al[81]	IV	No		P
Malhotra et al[82]	V		IT	
Man et al[83]	V	No		IT
Mangat et al[84]	V	Yes		
Marziliano et al[85]	V		IT	
Mayr[86]	V	No		IT
Mazurová et al[87]	V	No		IT
Mazzocco et al[11]	IV	No		IT
McCanta et al[88]	V		IT	
McKenzie et al[89]	IV	No		IT
Mejia et al[90]	V	No		P, IT
Momoi et al[91]	V	Yes		
Monteiro et al[92]	V		P	
Moric-Janiszewska and Markiewicz-Łoskot[93]	V	No		IT
Osman et al[94]	IV	No		P
Poloncová and Griač[95]	V	No		P
Raches and Mazzocco[96]	IV	No		IT
Raja and Greenberg[97]	V	No		IT
Raval and Kamp[98]	V	No		P, IT
Reynolds et al[9]	IV	No		IT
Reynolds et al[10] (in press)	IV	No		IT
Rigaud et al[6]	IV		IT	
Roberts et al[99]	IV	No		IT
Ronvelia et al[100]	V	No		IT
Sabater-Molina et al[101]	V		IT	
Saini-Chohan et al[102]	V	No		IT
Schlame and Ren[103]	V	No		IT
Schug et al[104]	V	No		IT, P
Singh et al[105]	V		IT	
Soustek et al[106]	IV	No		P
Sparagna and Lesnefsky[107]	V	Yes		
Spencer et al[108]	IV	No		IT
Spencer et al[109]	IV	No		IT
Spencer et al[110]	V	No		IT
Steward et al[111]	V	No		IT

Table 1 (*Continued*)

Citation	Level of evidence	Include yes/no	Maybe (explain)	If no, reason to exclude
Storch et al[112]	IV		IT	
Sweeney et al[113]	V		IT	
Tajima et al[114]	V	Yes		
Takeda et al[2]	V	Yes		
Takeda et al[115]	V	No		IT
Tikhomirov et al[116]	V	No		IT
Towbin[117]	V	No		P, IT
Valianpour et al[118]	IV	No		IT
van Raam and Kuijpers[119]	V	No		IT
van Werkhoven et al[120]	IV	No		P, IT
Vernon et al[121]	IV	No		IT
Wan et al[122]	IV		IT	
Wang et al[123]	IV		IT	
Whited et al[124]	IV	No		P, IT
Wilson et al[125]	IV	No		IT
Wortmann et al[126]	V	No		IT
Xing et al[127]	IV	No		IT
Xu et al[128]	IV	No		P
Xu et al[129]	IV	No		IT
Ye et al[130]	V	No		IT
Yen et al[131]	V		IT	
Zaragoza et al[132]	V	No		IT
Zweigerdt et al[133]	V		P, IT	

Notes: P indicates population that does not include human males with Barth syndrome; IT indicates that intervention used cannot be classified as a medical or rehabilitative treatment, therapy, or technique used to improve health, well-being, or level of functioning.
Abbreviation: BSF, Barth Syndrome Foundation.

medications and/or surgical techniques. Medical management of heart failure often used a polypharmacological approach. Cardiac hypertension and congestive heart failure (CHF) were frequently reported to be treated with cardiac glycosides such as digoxin, diuretics such as furosemide, and angiotensin-converting enzyme inhibitors such as captopril; beta-adrenoceptor blockers (β-blockers) such as carvedilol were also reported to be frequently used for the treatment of hypertension, CHF, and/or arrhythmia.[2,3,6,7,17,21,23,54,69,70,82,85,91,101,113]

In addition to pharmacological therapy to address heart failure, surgical techniques were also identified. Case reports indicated cardiac transplants in six individuals with Barth syndrome,[60,84,105] while two additional case reports indicated mitral valve replacement or valvuloplasty.[69,131] Three case reports[39,60,105] and one cohort study[6] identified the use of a ventricular assistance device (eg, the Berlin Heart EXCOR) as a successful bridge to cardiac transplant. An implantable cardioverter defibrillator was utilized in one case to prevent sudden death due to life-threatening ventricular arrhythmias.[70]

Medical management of neutropenia was most frequently accomplished with the use of granulocyte colony-stimulating factor (G-CSF), as reported in four case reports.[21,54,60,70] In their cohort study of 22 individuals with Barth syndrome, Rigaud et al indicated that G-CSF was used in six patients, with two individuals receiving long-term G-CSF therapy and the other four using G-CSF "on demand" when an infection occurred.[6] In the same study, four individuals also received antibiotic prophylaxis for the treatment of infections secondary to neutropenia.

Table 2 Articles excluded after full-text review

Citation	Level of evidence	Reason to exclude
Ances et al[18]	V	IT
Feillet-Coudray et al[44]	IV	P
Ferri et al[5]	V	IT
Finsterer[45]	V	P
Finsterer and Stöllberger[48]	V	P, IT
Finsterer and Stöllberger[49]	V	P
Finsterer et al[51]	V	P
Garratt et al[4]	V	IT
Honzik et al[65]	IV	IT
Kulik et al[77]	IV	IT
McCanta et al[88]	V	IT
Monteiro et al[92]	V	P
Sparagna and Lesnefsky[107]	V	P
Wan et al[122]	IV	P
Wang et al[123]	IV	P
Zweigerdt et al[133]	V	P

Notes: P indicates population that does not include human males with Barth syndrome; IT indicates that intervention used cannot be classified as a medical or rehabilitative treatment, therapy, or technique used to improve health, well-being, or level of functioning.

Dietary interventions

Dietary interventions were identified in 11/28 of the reviewed articles. The use of oral carnitine supplementation (eg, L-carnitine) was identified in one case report,[17] one fact sheet,[23] and two literature reviews.[7,47] Dietary supplementation with argentine was recommended in two literature reviews[7,3] and one cohort study.[6] Other nutritional supplements recommended as dietary interventions in the Barth population included cornstarch given before bedtime,[7,20] parenteral amino acid nutrition or intravenous supplemental amino acids,[8,24] magnesium supplementation,[114] potassium supplementation,[8,23,24] and daily multivitamins.[23,24] Storch et al noted that boys with Barth syndrome may also need a special diet at school, suggesting the need for dietary interventions across multiple settings.[112]

Feeding aids and strategies

Feeding aids were identified in 5/28 of the reviewed articles. Nasogastric and gastronomy tubes were recommended in cases where boys with Barth syndrome could not take adequate amounts of food or drink by mouth and therefore needed nutrients to be placed directly into the stomach.[6,7,24,70,91] Other feeding aids recommended by the Barth Syndrome Foundation[24] included preemie nipples, Hab-

Table 3 Articles included in systematic review

Study/Design	Population	Interventions/services recommended	Related outcomes
Aljishi and Ali[17] Case report	6-year-old male with Barth syndrome	Medical: digoxin, furosemide, and captopril Dietary: oral carnitine supplementation	Acquisition of developmental milestones, normalization of liver size, improvement of ejection fraction on echocardiogram Poor tolerance of carnitine
Aprikyan and Khuchua[19] Literature review	Barth syndrome	Medical: Granulocyte Colony-Stimulating Factor (G-CSF)	Increased levels of circulating neutrophils resulting in reduced frequency of infection
Avery[20] Fact sheet	Barth syndrome	Dietary: cornstarch given before bedtime	Prevention of hypoglycemia and minimization of muscle protein loses overnight
Bachou et al[21] Case report	5.5-month-old with Barth syndrome	Medical: G-CSF Medical: digoxin, diuretics, and angiotensin converting enzyme (ACE inhibitors)	Neutrophil count sustained near normal levels, fewer infections Cardiac function deteriorated leading to heart failure and death at 28 months
Barth Syndrome Foundation[23] Fact sheet	Barth syndrome	Medical: ACE inhibitors, diuretics, vasodilators, β-blockers, cardiac glycosides (eg, digoxin), inotropes, anticoagulants, angiotensin II receptor blockers, calcium channel blockers Medical: antiarrhythmic medications, pacemaker, or implantable cardioverter defibrillator (ICD) Medical: G-CSF, antibiotics Dietary: daily vitamin–mineral supplement, mitochondrial cocktail (eg, mitochondrial cofactors), vitamin C (eg, ascorbic acid), and potassium, L-carnitine	Medicines are often given in combination to prevent symptoms of heart failure. Side effects are common Medicines for arrhythmias alter electrical conduction in the heart or block impulses that can lead to abnormal heart rhythms. If drug therapy does not work, implanted devices are an alternative option G-CSF stimulates formation and maturation of neutrophils in bone marrow, decreasing infection. Side effects include headache and bone pain. Antibiotics can be used to stop spread of infection No significant benefit has been found with the use of the supplement carnitine. Prescription of potassium should be based on blood levels and closely monitored
Barth Syndrome Foundation[24] Fact sheet	Barth syndrome	Dietary: intravenous (IV) fluids containing potassium Dietary: daily multivitamin with minerals Feeding aids: Nasogastric (NG) tube, gastrostomy button, IV fluid bag, bolus feedings Feeding aids: preemie nipple, supplemental nutrition system, syringe, Habermann feeder, consultation with lactation specialist Feeding strategies: giving choices to a child, do not force feed, small portions, slowly introduce new foods	Potassium in IV fluids can cause hyperkalemia, must be done with caution Multivitamins can be used to prevent vitamin and other minor nutrient deficiencies Feeding tubes can provide appropriate nutrition and caloric intake to help maintain/gain weight Adaptive feeding strategies may increase feeding capabilities for children with low muscle tone, oral fatigue, or poor coordination of suck
Bowen et al[26] Fact sheet	Barth syndrome	Medical: topical or oral corticosteroids, mouth rinses	Used for treatment and pain relief of mouth ulcers secondary to neutropenia
Clarke et al[7] Literature review	Barth syndrome	Medical: cardiac medications (ACE inhibitors, β-blockers, digoxin, and diuretics), cardiac transplant, ICD, G-CSF, prophylactic antibiotics Rehabilitative: mobility aids Educational: special education Dietary: L-carnitine, pantothenic acid supplements, dietary supplementation with arginine, cornstarch supplements may be used at bedtime Feeding aid: NG or gastrostomy tube	Most Barth patients need to be maintained on standard cardiac medications throughout childhood; no published studies had analyzed the efficacy of these ICD may minimize sudden death due to ventricular arrhythmia G-CSF is widely used for the treatment of neutropenia Mobility aids used to conserve energy No evidence for use of carnitine or pantothenic acid supplements No drug or food supplement has so far been shown to be conclusively beneficial
Dedieu et al[39] Case report	3-year-old with Barth syndrome	Medical-prolonged ventricular assistance with the Berlin Heart EXCOR	Successful bridge to heart transplant

Finsterer and Frank[47] Literature review	Barth syndrome	Rehabilitative: physiotherapy Dietary: carnitine supplementation Medical: application of lactate-lowering agents, biweekly injection of G-CSF Medical: ventricular assist device as bridge to heart transplant, placement of an in-line oxygenator to maintain end-organ function	May improve muscle weakness Normalized levels of carnitine Reduction of lactic acidosis and increase in neutrophil count Successful cardiac transplantation
Folsi et al[54] Case report	Male with Barth syndrome (birth to 2 years)	Medical: G-CSF, furosemide intravenously, captopril, spironolactone, carvedilol, enalapril, aldactazide medications	Discharge from hospital in stable cardiac condition with maintenance of function post-discharge
Hanke et al[60] Case report	Male with Barth syndrome (3 days old)	Medical: mechanical circulatory support, in-line oxygenator (Quadrox iD), Berlin EXCOR biventricular device (Bi-VAD), cardiac transplant, G-CSF	Successful cardiac transplantation 24 days after Bi-VAD placement
Huang et al[69] Case report	11-month-old male with Barth syndrome	Medical: mitral valvuloplasty, furosemide, captopril, and aspirin	Mitral annuloplasty could be used as an alternative to heart transplant for infant with severe heart failure and mitral regurgitation
Huhta et al[70] Case report	18-year-old male with Barth syndrome	Medical: G-CSF, carvedilol, methadone, atrial intracardiac defibrilalator (AICD) implantation Feeding aid: gastrostomy and PEG tube	Carvedilol improved heart function, while G-CSF was used to address neutropenia
Jefferies[3] Literature review	Barth syndrome	Medical: G-CSF possibly combined with appropriate prophylactic antibiotics Medical: Growth hormone (GH) supplementation Dietary: arginine supplementation Medical: ACE inhibitors, angiotensin receptor blockers, β-blockers, potassium-sparing diuretics, IV agents such as vasodilators and inotropes Medical: mechanical circulatory support (Berlin EXCOR device), cardiac transplantation Medical: ICDs	Treatment of neutropenia GH supplementation is not routinely used to address growth delays since levels seem to normalize in the late teens and early 20s. Arginine supplementation may be used as possible treatment to improve growth rate Cardiac medications can be used to alleviate symptoms of heart failure and prolong life Successful transplants and bridges to transplant have been reported Limited data regarding the effectiveness of ICDs for management of arrhythmias in Barth syndrome
Kelley[8] Fact sheet	Barth syndrome	Dietary: IV fluids containing potassium, parenteral amino acid nutrition, or IV supplemental amino acids	Management of diarrheal illness
Malhotra et al[82] Literature review	Barth syndrome	Medical: β-blockers (eg, carvedilol, metoprolol, bisoprolol), cardiac glycosides (eg, digoxin), diuretics (eg, furosemide, ethacrynic acid), cytokines (eg, G-CSF)	Use of multiple drugs simultaneously (polypharmacy) may lead to inadvertent life-threatening consequences in some children with Barth syndrome
Mangat et al[84] Case reports	Four males with Barth syndrome: ages 2 years, 3.5 years, 1.5 years, and 10 months	Medical: cardiac transplant	To date, all children have normal coronary angiography No clear benefit to using either carnitine or pantothenic acid
Marziliano et al[85] Case report	12-year-old male with Barth syndrome	Medical: inotropic agents, ACE inhibitors, and diuretics	Progressive improvement of left ventricle function

(*Continued*)

Table 3 (*Continued*)

Study/Design	Population	Interventions/services recommended	Related outcomes
Rigaud et al[6] Cohort study	22 males with Barth syndrome	Medical: inotropic support, invasive ventilation, ventricular assist device, cardiac transplant, echocardiograms Medical: ACE inhibitors, β-blockers, digoxin, diuretics, anticoagulants, aspirin Medical: G-CSF, antibiotic prophylaxis Feeding aid: long-term enteral nutritional support Dietary: arginine supplementation	Systematic use of β-blockers and modern inotropic drugs such as milrinone has decreased the incidence of heart failure Neutropenia seemed to respond well to G-CSF, though two episodes of severe infection occurred while patients were on G-CSF therapy Arginine may improve growth rate of patients with Barth syndrome
Sabater-Molina et al[101] Case report	30-year-old male with Barth syndrome	Medical: β-blockers, losartan	Good tolerance of medications: symptom benefit related to fatigue and muscular claudication
Singh et al[105] Case report	7-month-old male with Barth syndrome	Medical: mechanical support via a Berlin left ventricular assistive device implantation followed by extra corporeal membrane oxygenation (ECMO), orthotropic cardiac transplantation at the age of 2 years Rehabilitative: physical therapy	Muscle tone improved with physical therapy
Storch et al[112] Descriptive comparison	Boys with Barth syndrome (n=34) and healthy controls (n=22); ages 2–25 years	Educational: accommodations including classroom seating changes, rest periods, schedule adjustments, note takers, extra books for home use, alternative assignments, medication administration at school, extra tutorials, use of tape recorders, peer mentors Psychological: monitored by school psychologist or guidance counselor Dietary: special diet at school	Supports were in place to improve school functioning in boys with Barth syndrome
Sweeney et al[113] Case report	Male with Barth syndrome (birth to 20 months)	Medical: treatment with digoxin, captopril, lasix; sent home from hospital on monitor and supplemental oxygen	Patient died at 20 months of age Digoxin therapy appeared to have been effective in improving heart function as evidenced by the patient's decompensation upon its withdrawal
Tajima et al[114] Case report	18-year-old male with Barth syndrome	Dietary: magnesium supplementation	Slight improvement in muscle strength, normalization of serum magnesium levels
Takeda, et al[2] Literature review	Barth syndrome	Medical: ACE inhibitors, β-blockers, diuretics, cardiac transplantation Medical: G-CSF, parenteral antibiotics Medical: ICD placement	Heart failure is mostly responsive to standard medication therapy; successful heart transplantation has also been reported in patients with severe heart failure Neutropenia can usually be managed with parenteral antibiotics and GCS-F therapy Prevention of sudden death has been documented with placement of ICD No treatment needed for hypotonia because it usually improves spontaneously
Yen et al[131] Case report	11-month-old male with Barth syndrome	Medical-emergent mitral valve replacement	Improved symptoms related to mitral insufficiency; patient waitlisted for cardiac transplantation

Abbreviations: Bi-VAD, biventricular assist device; PEG, percutaneous endoscopic gastrostomy.

ermann Feeders®, and Supplemental Nutrition Systems™. Feeding strategies for boys with Barth syndrome were also described in cases where the child had strong food and eating preferences (eg, picky eaters or sensory sensitivities). These strategies included giving the child control over food choices or having the option to spit something out, consuming small portions of food throughout the day instead of eating three large meals, and slowly introducing new foods into the child's diet.[24]

Rehabilitative

Limited rehabilitative interventions were identified in this review. One case study[105] and one literature review[47] identified physical therapy (ie, physiotherapy) as a possible intervention to improve muscle weakness and tone in boys with Barth syndrome. Another literature review acknowledged that mobility aids such as wheelchairs may be used to conserve energy.[7]

Educational

Storch et al reported a significant need for academic accommodations for boys with Barth syndrome as compared to healthy male controls.[112] Specific accommodations identified in this study were classroom seating changes, rest periods, schedule adjustments, note takers, extra books for home use, alternative assignments, extra tutorials, use of tape recorders, and peer mentors. In addition, some boys with Barth syndrome may need medication administration at school. As noted by Clarke et al, approximately 33% of boys with Barth syndrome require some form of special education.[7]

Psychological

In addition to academic and educational supports, Storch et al found that out of the 34 boys – with Barth syndrome – surveyed, 26% were monitored by a school psychologist, while 22% had close contact with a guidance counselor.[112] No other psychological interventions were identified in the 28 articles included in this review.

Outcomes

The most frequent outcomes reported in the 28 reviewed articles were related to the core features of Barth syndrome, which are cardiac complications (eg, CHF, hypertension, and arrhythmia) and neutropenia. Specific outcomes related to heart function included improvement of ejection fraction on echocardiogram,[17] progressive improvement of left ventricular function,[85] improvement in cardiomegaly with reduced pulmonary edema,[91] and decreased incidence of heart failure[6] with the use of cardiac medications. However, since most articles reported on the use of multiple medications simultaneously, the individual contributions of each medication or medication type are indistinguishable from the overall effects of the medication regime. In contrast, neutropenia was primarily treated using G-CSF, and therefore outcomes such as increased neutrophil count and reduced infection can be more specifically linked with this medical treatment.[6,21] Interestingly, the simultaneous use of multiple drugs (polypharmacy) was questioned in one review, indicating that coadministration of contraindicated medications may prove to be life threatening in some children with Barth syndrome.[82]

Objective outcomes related to dietary interventions or use of feeding aids were limited in this systematic review. While one literature review suggested that carnitine deficiency in Barth syndrome may be ameliorated by means of substitution,[47] other articles suggested no significant benefit with the use of carnitine supplements.[7,17,23] Similarly, one published review[7] and one case report[84] suggested that there is no evidence for the use of pantothenic acid supplements in this population. Magnesium supplementation was utilized in one case report of an 18-year-old male with Barth syndrome.[114] In this report, magnesium supplementation led to a slight improvement in muscle strength and normalization of serum magnesium levels. Specific outcomes data related to caloric intake, weight gain, and/or growth were not reported in the other reviewed articles which utilized dietary interventions, feeding aids, or feeding strategies.

Rehabilitative outcomes were also limited in this review. Singh et al reported on a 7-month-old African-American male with Barth syndrome whose muscle tone improved with physical therapy; however, the frequency and duration of physical therapy were not reported, nor were any specific measures of muscle strength or tone.[105] In line with this outcome, Finsterer and Frank indicated in their 2013 review that physiotherapy may help to improve muscle weakness in boys with Barth syndrome.[47] Interestingly, Takeda et al argued in their review of the literature that no treatment is needed for hypotonia because it usually resolves spontaneously.[2]

No outcomes related to educational or psychological interventions were reported.

Discussion

Medical management of Barth syndrome

The interventions and outcomes identified in this review reinforce that treatment of medical complications associated with Barth syndrome is of primary importance in this

population. However, the types of articles available for this systematic review represent reports that are not based on scientific analysis of clinical outcomes. Of the 28 reviewed articles, 15 were case reports. While case reports have a role in medical literature, particularly for detecting novelties and describing unique cases, findings from case reports often lack generalizability and are reliant upon the author's memory of events or availability of information in medical records.[134]

Though lacking direct evidence, the accumulation of descriptive data from case reports and expert clinical opinion suggest that cardiac medications (eg, β-blockers, angiotensin-converting enzyme inhibitors) can be used to alleviate symptoms of heart failure and prolong life in boys with Barth syndrome. In addition, several sources reported increased levels of circulating neutrophils following G-CSF treatment, suggesting that G-CSF, possibly combined with appropriate prophylactic antibiotics, is the best available treatment for neutropenia in this population.[19,21,70] While neutropenia appears to respond well to G-CSF, Rigaud et al noted that 2 of the 22 Barth patients in their cohort study had episodes of severe infection while on G-CSF therapy.[6] It is also important to note that some medications, either in isolation or coadministered with other medications, may cause symptoms to worsen, and therefore starting or stopping of any new medications or increasing the dosage of the existing ones should be closely monitored in boys with Barth syndrome.[23]

While several successful surgeries, including cardiac transplants, were reported in the 28 reviewed articles,[60,84,105] none of the articles provided data on how many boys with Barth syndrome failed to survive the surgery or what was the long-term survival rates post discharge. Since journals often prefer publication of cases with positive outcomes, there is a risk in overstating or generalizing the surgical outcomes gleaned in this review.[134]

Despite the lack of specific outcomes in this review, it is clear that medical management of Barth syndrome is essential for growth and survival. Medical team members involved in the care of boys with Barth syndrome may include specialists in cardiology, hematology, metabolism, endocrinology, neurology, and genetics, as well as developmental pediatricians and primary care physicians.

Feeding and dietary interventions for Barth syndrome

The literature supporting nonmedical interventions for Barth syndrome is much scarcer. While it has been identified that feeding issues are stressful for families of boys with Barth syndrome, very little research has been directed toward interventions that support feeding behaviors or nutritional concerns.[9,10] Further, there does not appear to be consensus about which nutritional supplements are effective in this population or what process should go into the selection of a supplemental regime.

Given the complexity of feeding and nutritional issues in boys with Barth syndrome, multiple disciplines may be involved in the management of these clinical features. Dietitians and nutritional specialists will likely work closely with medical doctors, including metabolic specialists, to determine what and how much food/liquid the child should be consuming. Decisions about the placement of nasogastric tubes or other long-term enteral nutritional support will likely be made by a team of individuals familiar with the specific child and familiar with the complexities of Barth syndrome. Throughout the lifespan of a boy with Barth syndrome, the needs of the child and the family will likely require consultation or intervention by a variety of other health care professionals. During infancy, lactation consultants, pediatric nurses, and occupational therapists may work with families in order to facilitate good positioning for breastfeeding and recommend appropriate feeding aids and strategies to assist the child with oral sucking and self-regulation during the feeding process. When the child begins transitioning to solid foods, rehabilitative professionals (ie, physical therapists, occupational therapists, and speech and language pathologists) may be consulted for issues related to proper positioning, coordination of chewing and swallowing, or sensory sensitivities leading to picky eating patterns. As the child grows, nutritional concerns related to growth will likely become important and ongoing case management with the medical team may be necessary. During the school years, special dietary or feeding needs may need to be documented on the child's individualized education plan and consultation between the school team and medical team may be required. Since eating is a big part of normal socialization patterns, practitioners should be mindful of the need for children, adolescents, and adults with Barth syndrome to participate in these types of activities as part of their overall psychosocial health.

Interventions to support participation and well-being

This systematic review identified a relative gap in the literature in regard to the interventions that support the participation and well-being of boys with Barth syndrome and their families. Physical therapy was identified as one rehabilitative service that could potentially help enhance muscle strength and tone; however, it was unclear from the review whether these improvements in strength and tone led to increased play with peers, greater participation due to lack of fatigue, or an

improvement in self-concept or self-esteem. Research using mouse models of Barth syndrome are beginning to provide insights into the physiological benefits of exercise and endurance training;[135] however, translation of these findings into practice are nonexistent. As basic science research begins to work its way from bench to bedside, it will be important for researchers and clinicians alike to focus on the functional and participation benefits of exercise in addition to changes in muscle physiology.

Finally, this review did not identify any currently researched interventions to address the psychosocial needs of boys with Barth syndrome and their families. As noted by Storch et al, youth with Barth syndrome tend to have more internalizing and externalizing symptoms, social problems, and loneliness compared to healthy children; in addition, they rate their overall quality of life much lower than that of healthy controls and other children with cardiac problems.[112] Parents of boys with Barth syndrome also report higher stress levels compared to parents of health controls. Psychologists, licensed clinical social workers, occupational therapists, and other mental health professionals may be able to help children and families with these issues through a variety of therapeutic interventions. There is a current need to examine the usefulness and applicability of these types of services in the Barth population.

Conclusion

This systematic review highlights the paucity of objective, high-level evidence supporting interventions for males with Barth syndrome. While case reports and literature reviews on this rare disorder are important contributions to the literature, future studies should aim to include systematic and objective analyses of outcomes using research designs with methodological rigor. This level of research is needed across multiple disciplines in order to develop best practices for the management of the symptoms most commonly associated with the Barth syndrome. Clinically, it is recommended that a comprehensive care team be established, which includes individuals with Barth syndrome, their family members and caregivers, as well as medical, rehabilitative, nutritional, psychological, and educational professionals. While medical management of symptoms that preserves life is of primary importance, services that enhance the child's and family's quality of life and participation should also be included as part of the individual's care plan.

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