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Barth Syndrome Is Associated with a Cognitive Phenotype

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Abstract

Objective—Barth syndrome is a rare, X-linked recessive disorder that affects only boys. The cardinal characteristics include growth retardation, cardioskeletal myopathy, chronic or cyclic neutropenia, and 3-methylglutaconic aciduria. A preliminary study of five young boys with Barth syndrome suggested a distinct cognitive phenotype.

Methods—The present study was designed to explore whether additional evidence for a cognitive phenotype emerged from a larger sample. A psychoeducational assessment battery was administered to 15 boys with Barth syndrome. Data from these boys were compared to data from 15 typically developing boys individually matched on age and grade in school to each of the 15 boys with Barth syndrome.

Results—Although boys with Barth syndrome had age-appropriate performance on all measures of reading-related skills, their performance on mathematics and visual spatial tasks was significantly lower than that of boys in the comparison group. Moreover, specific aspects of visual short-term memory also differed from available norms.

Conclusion—Our findings support the validity of the preliminary findings and reflect a higher incidence of cognitive difficulties in boys with Barth syndrome relative to boys in the comparison group. Coupled with the fatigue regularly experienced by boys with Barth syndrome, our findings indicate that educational support should be implemented during the early school-age years for children with Barth syndrome.

Index terms

Barth syndrome; cardiomyopathy; cognitive phenotype

Barth syndrome is a rare X-linked recessive metabolic disorder that is typically manifested in infancy or early childhood. The estimated birth incidence of Barth syndrome is 1/500,000, based on 10 to 15 new diagnoses out of approximately 3.5 to 4 million births per year (R.I. Kelly, unpublished data), but missed diagnoses probably are common and the incidence could be as high as one in 250,000 births. As an X-linked disorder with extreme skewing of X-

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inactivation in heterozygote females, Barth syndrome has been diagnosed only in males.¹ The Barth syndrome phenotype is well established and includes growth retardation, cardioskeletal myopathy, chronic or cyclic neutropenia, increased excretion of 3-methylglutaconic acid in the urine, and moderate hypocholesterolemia.^{2,3} In view of the life-threatening features of the syndrome, most research has been devoted to medical intervention and genotyping. Nevertheless, in 2001, Mazzocco and Kelley⁴ published the first report suggesting that boys with Barth syndrome may also have a syndrome-specific cognitive phenotype, characterized by stronger verbal skills relative to weaker visual spatial and mathematics performance. However, because of the rarity of the disorder, their report was based on only five boys. The present study was designed to examine evidence of a cognitive phenotype in a larger group of boys with Barth syndrome.

Barth Syndrome Genotype

In the past 15 years, significant advances have been made in understanding the Barth syndrome phenotype and genotype. With these advances, clinical intervention has significantly improved survival rates.² For instance, in 1991, Kelley and colleagues⁵ reported that 3-methylglutaconic aciduria was a characteristic biochemical abnormality associated with Barth syndrome. Thereafter, DNA studies led to identification of familial and de novo mutations of the *G4.5* gene^{1,6–8} located at Xq2.^{9–12} The *G4.5* gene, now designated *TAZ*, encodes one or more tafazzin proteins that appear to function as fatty acyltransferases and play an essential role in the synthesis of cardiolipin and possibly other phospholipids.¹³ Barth syndrome is the first known defect in the biosynthesis of cardiolipin, which, as an essential phospholipid in the mitochondrial inner membrane, confers stability and function to many inner membrane proteins, including most components of the mitochondrial electron transport chain and many different solute and protein transporters. Diagnostically, tissue and cellular levels of tetralinoleoyl cardiolipin are almost undetectable in children with Barth syndrome.^{14,15} However, because recent studies have shown abnormalities in other phospholipids such as phosphatidylcholine in other cell compartments, the prenatal and postnatal developmental abnormalities of Barth syndrome may reflect multiple biochemical abnormalities caused by the *TAZ* acyltransferase deficiency.¹⁶

Barth Syndrome Physical Phenotype

Most males with Barth syndrome become symptomatic in early infancy, usually with signs of dilated cardiomyopathy and congestive heart failure, but also with neutropenia-related infections and, somewhat later in infancy, poor growth and gross motor delay. By age 3 years, most boys with Barth syndrome have heights and weights that have fallen to 2 to 6 SDs below normal, but growth velocity thereafter remains normal and the boys continue to grow and gain weight parallel to the 3rd centile.^{5,9,11,17} During adolescence, puberty typically is delayed by 1 to 3 years, but growth rates increase such that normal adult height is attained in late adolescence or early adulthood for all boys with Barth syndrome.¹⁸ Among boys with Barth syndrome who survive early childhood, most clinical features persist, but improve with age; although unexplained periods of clinical worsening can occur at any time and especially during periods of rapid growth. Thus, despite its relative infrequency in the general population, these potentially life-threatening consequences of Barth syndrome warrant screening for this disorder among males with idiopathic growth retardation, motor delays, dilated cardiomyopathy, or recurring infection.

Compared to the intensive study of the physical problems of the disorder, far less is known about a possible cognitive phenotype of Barth syndrome, although parental and clinician concerns about poor academic performance have been noted in several case studies. Despite these anecdotal concerns, there is frequent reference to “normal cognitive development” in

these case reports.^{5,9,11,19} Yet there have been no large-scale studies of cognitive function in boys with the disorder. The single published report of “mental deficiency” in boys with Barth syndrome was attributed to effects of cardiac transplantation that occasionally is required in Barth syndrome.³ However, our preliminary data from five untransplanted boys with Barth syndrome indicate that there exists a mild but consistent cognitive phenotype.⁴

The lack of research on cognitive abilities in Barth syndrome results, in part, from the rarity of the disorder. Also, cognitive studies have been less of a priority than the research efforts devoted to the serious medical complications associated with Barth syndrome. Yet, the survival rate has increased substantially over the past two decades, and now most boys with Barth syndrome survive early childhood.² As more boys with Barth syndrome approach school age, it is essential that we determine whether the intellectual and academic challenges they may face warrant special services or support. Moreover, if educational problems are likely, early intervention for improving academic skills should be implemented.

On the basis of our clinical experience and the existing literature reviewed above, we know that Barth syndrome does not lead to mental retardation. However, this information is insufficient to address the question of a possible cognitive phenotype, as it does not preclude cognitive consequences, nor does it address whether the cognitive phenotype of Barth syndrome, if one exists, is mild or moderate and global or specific. The present study was carried out to address the existence and potential nature of the cognitive phenotype of Barth syndrome.

METHOD

Participants

Barth Syndrome Group—The participants included 15 boys with Barth syndrome recruited either through the First International Barth Syndrome conference (n = 5), through the Barth Syndrome Foundation (n = 6), or through developmental pediatrician referrals (n = 4). Diagnosis was confirmed through molecular testing. Only children who had completed kindergarten, first, second, third, or fourth grade were recruited because comparison data for this age range were available from a larger, ongoing normative study of academic achievement, described elsewhere in more detail.^{2,20} The participants ranged in age from 5 years, 7 months to 10 years, 6 months (mean age, 8 years, 5 months). Data on each boy’s age and grade level appear in Table 1.

Selection of the Comparison Group—The children in the comparison group were selected from 120 boys who were volunteer participants in the larger study, described earlier. This larger group of participants represents 65% of children enrolled in one of seven public elementary schools in a suburban school district. All kindergartners from these schools were invited to participate in this normative study, so the overall longitudinal sample is fairly representative of typically developing children. Each kindergartner was then evaluated annually through the fourth grade. Ideally, we could have included all 120 boys in the comparison group to maximize statistical power. However, we could not do so because most of the 120 boys could not be matched simultaneously for grade and age to the boys with Barth syndrome because so many of the boys with Barth syndrome were old for their respective grade. This made it challenging to find suitable matches using both school grade level at testing and age (within 1 year) at testing. That is, the boys with Barth syndrome were relatively old for their grade level, having either repeated a school grade during primary school (n = 8; 60%) and/or having participated in the study during the summer following completion of a school grade (n = 7). In contrast, only 12 of the 120 (10%) of the boys from the initial comparison group had repeated a school grade, and all the boys in this group had been tested during the school year. As a consequence of these differences, it was necessary to select a matched

comparison group of 15 boys each of whom could be individually matched, on age and grade at testing (as best as possible), to one boy with Barth syndrome. Thus, the final comparison group was less representative of a random sample than was the initial group of 120 boys: it included five boys (33%) who had repeated a school grade and boys relatively old for their grade placement in school. When mismatches in age were necessary in selecting the optimal comparison participant, we erred on the side of the boy with Barth syndrome being older than the participant with whom he was paired. Note that the group of boys with Barth syndrome had an age advantage in terms of performance on a given cognitive task, both in terms of age (being older) and having completed a school grade (versus still being in that grade) at the time of testing.

Informed consent was obtained from the parents or legal guardians of all participants, according to the study protocol approved by an institutional review board. Families were not paid for their participation; however, depending on the family's location of residence, some families received partial reimbursement for travel expenses.

Procedures

Eleven of the boys with Barth syndrome were seen during their visit to either the First, Second, or Third International Barth Syndrome Conference, each of which was held in the United States. Three others were evaluated in their hometowns, and one child was evaluated in our research office. The boys in the comparison group were tested either at the public school they attended or at the investigators' offices. Each of these 30 participants was assessed individually over one to two sessions lasting no more than 2 to 4 hours each by an examiner from the ongoing longitudinal study. Each boy was administered a battery of tests measuring overall intellectual functioning, reading ability, math ability, and visual spatial skills, as described below. Although we tried to maintain the same order of test presentation for all participants, at times the order varied due to child fatigue, and for a few participants, selected tests were not completed. The sample size for each group is included in Table 2 and Table 3.

Intellectual Functioning

Each child was administered a test of overall intellectual functioning. The standardized I.Q. tests used provided descriptive information about our participant groups and permitted assessment of potential group differences in global verbal and nonverbal skills. Either the Wechsler Abbreviated Scale of Intelligence (WASI)²¹ or the Stanford-Binet, Fourth Edition (SB-IV)²² was administered to each child, depending on the child's age at the time of testing. For the Barth syndrome group, two boys who were less than 6 years old received the SB-IV, one boy failed to complete an IQ test, and 12 boys 6 years or older received the WASI. For the comparison group, WASI scores were available from the third-grade assessment of all 15 boys. We also administered the WASI to the biological mothers of nine boys with Barth syndrome to assess the correlation between parent and child scores. Both the WASI and SB-IV tests are widely used standardized assessments that include both verbal tasks (such as expressive vocabulary) and nonverbal tasks (such as copying abstract block patterns). The variables included in the present study were the age-referenced standard scores for Full Scale I.Q. and for the four individual subtests of the WASI.

Reading Ability

Tests of basic reading skills were administered to assess either academic achievement or phonological processing skills important for successful reading. Single letter and word reading were assessed with the Woodcock Johnson-Revised (WJ-R)²³ Letter-Word Identification (LWID) subtest, which tests for recognition of individual letters and words. The WJ-R Word Attack (WA) subtest is a nonword reading task, and it was administered to assess phonological decoding skills. For both WJ-R subtests, standard scores were based on age-referenced norms.

The internal reliability for LWID for ages 4 through 13 years is $>.880$; and for Word Attack it is $>.876$ for ages 6 through 13 years. The final reading-related task was a measure of phonological retrieval during rapid naming. Three separate Rapid Automatized Naming (RAN) 24 task subtests were administered: colors, numbers, and letters. Total reaction time was recorded for each subtest.

Mathematical Ability

Several standardized measures of math performance were used to evaluate math achievement and math ability. The Test of Early Math Ability, Second Edition (TEMA-2)²⁵ was used to assess a variety of formal and informal math concepts through verbal and written questions. The TEMA-2 is normed for children ages 3 through 8 years. Because some of the participants were 9 or 10 years old, primary analyses for this task were based on raw scores for the age-matched pairs. For analyses of standard scores, projected scores were generated for the participants older than 8 years. Test-retest reliability for the standard scores of the TEMA-2 is .94.

For math achievement testing, two standardized math subtests were administered. The WJ-R Calculations subtest is a paper and pencil test of increasingly difficult math problems; it was used to assess arithmetic problem solving. The internal consistency of the Calculations subtest, for ages 6 through 13 years, is $>.89$. The Key-Math-Revised²⁶ Numeration subtest is used to assess basic counting and number sequencing skills. The reliability was reported for grade and ranged from .80 to .85 for grades kindergarten through 4. For both subtests, standard scores are based on age-referenced norms.

Supplemental measures of math ability were developed by the investigators. First, a modified magnitude judgment task was used to assess participants' reliance on numeric versus spatial information when asked which of two numbers is "closer" to a target number (i.e., "which is closer to 7, 3 or 5?"). All number sets were visually presented on a single page; response choices varied with respect to their physical and numeric distance from the target number. Each set was scored as correct (identifying the number that is numerically closer to the target number) versus incorrect (selecting the number that is physically "closer" to the target number). A total of five number sets was presented, so the maximum possible score was 5. Because this task was only routinely administered to first graders, analyses of the total number correct were limited to participants in or above first grade.

A counting trials task was administered to evaluate children's recognition of violations of counting principles, such as one-to-one correspondence. During this task, the examiner counted sets of seven to 14 individual 19-mm dots arranged in a straight line. Following each trial, the dots were covered, and the child was asked to determine whether the examiner had counted the correct number of dots. A total of 24 trials was presented. The total number of correctly identified accurate counting trials was added to the number of correctly identified erroneous counting trials, for a maximum of 24 correctly identified trials. This task was routinely administered only to first graders, so analyses of the total number correct were limited to participants in or above first grade.

Visual Spatial Skills

Two standardized tests of visual spatial skills were administered, including one that was motor involved and another that was motor reduced. The Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI)²⁷ was used to measure ability to integrate visual-spatial perception with fine motor skills by having children manually copy a series of drawings in a booklet. Two supplements to the VMI were also administered to seven of the boys with Barth syndrome to separately assess the visual and the motor contributions to visual spatial skills.

Test-retest reliability for the VMI and two supplements is .87, .84, and .83, respectively. The four motor-reduced subtests of the Developmental Test of Visual Perception, Second Edition (DTVP-2)28 were used to assess visual perception skills. Specifically, these subtests are used to measure the ability to identify and match the direction of stimuli (Position in Space), the ability to identify embedded shapes (Figure Ground), the ability to recognize an incomplete shape (Visual Closure), and the ability to match shapes that vary in size, orientation, and color (Form Constancy). Test-retest reliability for all four subtests of the DTVP-2 is $\geq .80$. Standard scores for the VMI and for the DTVP are based on age-referenced norms.

To assess object recall and location memory, two experimental memory tasks corresponding to the DTVP-2 were also given. These tests were presented immediately after completing the Figure Ground subtest and involved the 10 shapes that appeared in the same order, in a 2×5 gridlike array on each page of this subtest. During the object recall task, participants were asked to determine whether each of 20 shapes presented in a stimulus book had been presented during the previously administered DTVP-2 Figure Ground subtest. The total number of correct “yes” responses was added to the total number of “no” responses, with a maximum score of 20. For the location memory task, participants were presented with cut-out versions of the 10 individual shapes that had repeatedly appeared during the DTVP-2 Figure Ground subtest and were asked to arrange the shapes in the correct order. Scoring was based on the number of locations correctly recalled, with a maximum total score of 10, as well as whether the 10 shapes were accurately positioned in a gridlike versus nongridlike array, with a dichotomous score (pass/fail).

RESULTS

Analyses

For most analyses, the two groups included up to 15 individually matched pairs of boys from the Barth syndrome and comparison groups. Exceptions to this are noted in Table 2. The data obtained from most of the variables either were not normally distributed or could not be assessed for normality due to the small sample size. Therefore, we used nonparametric procedures for the majority of analyses. Wilcoxon signed rank tests were used as a paired analysis when possible as a means by which to maximize statistical robustness. However, because some participants did not complete all the testing, if the number of pairs available for analysis was fewer than seven, we used the unpaired Mann-Whitney *U* test to increase the number of participants included in a given analysis. For both the Wilcoxon and Mann-Whitney tests, in all cases of tied ranks, tied *p* levels and tied test statistics are reported. In addition, a Cohen’s *d* was calculated to measure effect sizes. In cases of frequency data, chi-square statistics were carried out; if any expected cell values fell below 5, a Fisher exact test was substituted for that analysis. Finally, for one set of visual memory scores for which insufficient data were available from the comparison group, alternative comparison groups were included, based on published reports, as specified below.

I.Q. Test Scores

Although mean Full Scale I.Q. scores (FSIQ) from the Wechsler Abbreviated Scale of Intelligence (WASI) were in the average range for both groups, boys with Barth syndrome had significantly lower scores than boys in the comparison group, $Z = -2.12$, $p = .03$. However, this discrepancy in scores was not apparent for all four WASI subtests. On only one subtest, Block Design, did boys with Barth syndrome score significantly more poorly than boys in the comparison group, $Z = -2.44$, $p = .01$. There was no significant group difference for the WASI verbal scores or for the vocabulary subtest of the Stanford-Binet, Fourth Edition. These results suggest that if a cognitive impairment occurs in Barth syndrome, it is less likely to involve

verbal skills and may involve spatial difficulties. The following results are consistent with this notion.

Reading Related Skills

On measures of reading related skills, boys with Barth syndrome showed no indicators of difficulty. In fact, the two groups of boys had comparable scores on Woodcock-Johnson Letter Word Identification, $p = .10$; and on the Word Attack nonword reading task, $p = .36$. There were no group differences on Rapid Automatized Naming of Colors or Numbers, $p > .12$. Boys with Barth syndrome had significantly faster response times on the RAN Letters subtest, $Z = -2.28$, $p = .02$, although the effect size was very small, $d = 0.14$. Overall, boys in both the Barth syndrome and comparison groups performed within normal limits for children their age on reading-related tasks (Table 2).

Mathematical Skills

In contrast, boys with Barth syndrome showed significantly poorer performance on all measures of math ability and math achievement relative to boys in the comparison group. Group means for the latter were well within the average range; for boys with Barth syndrome, group mean scores were well below average for both the Test of Early Math Ability, Second Edition (TEMA-2) (a measure of formal and informal mathematics ability), $Z = -2.87$, $p = .004$, and the Woodcock Johnson Math Calculations subtest, $Z = -2.08$, $p = .04$. Although boys with Barth syndrome had scores in the low average range on the KeyMath-Revised Numeration subtest, the comparison of eight pairs of boys was not significantly different, $p = .11$. However, the unpaired comparison showed that performance by boys with Barth syndrome was significantly lower than that of boys in the comparison group, $U = 20.50$, $p = .03$. Effect sizes for all three of these math scores were large, $d > 1.0$. Boys with Barth syndrome also showed significantly poorer performance on our experimental measures of math skills relative to boys in the comparison group, including slightly lower performance on a numeric magnitude judgment task, $Z = -2.33$, $p = .02$. The analysis for the magnitude judgment task was limited to nine of our 15 pairs of boys, so we carried out an unpaired comparison of 20 boys (11 with Barth syndrome), and the group difference remained significant, $U = 18.00$, $p = .004$; this group difference resulted from the fact that all boys in the comparison group were at ceiling on this task (responding correctly to all items) versus 36% of the boys with Barth syndrome. Boys with Barth syndrome also made more errors on a measure of basic counting skills; this difference emerged from the comparison of the seven pairs of boys who completed the counting task, $Z = -2.05$, $p = .04$, and from the unpaired comparison with 18 boys (eight with Barth syndrome), $U = 7.00$, $p = .003$. Poorer counting performance was driven primarily by fewer instances of identifying correct counting trials, $U = 17.50$, $p = .02$, rather than from recognizing fewer violations of counting errors, $p = .09$, although both types of correct responses were less frequent in the Barth syndrome group than in the comparison group.

In addition to poorer performance on mathematics, boys with Barth syndrome had below average performance on visual spatial tasks, including tasks with or without a motor component. Boys with Barth syndrome had deficient performance on the visual motor integration task relative to average performance by boys in the comparison group, $Z = -2.52$, $p = .01$. It appears that low performance on the Beery-Buktenica Developmental Test of Visual-Motor Integration (VMI) was not driven exclusively by motor deficiencies, because for the seven boys with Barth syndrome who completed the motor and visual supplemental VMI tasks, four had higher motor than visual scores (discrepancies ranging from 3 to 24 standard scores), and three had higher visual than motor scores (discrepancies ranging from 2 to 21 standard scores). When visual and motor scores were compared to each other for these seven boys, there was not a significant difference, $p = .55$. On one of the four motor reduced tasks of visual perception, boys with Barth syndrome had below average performance on the visual closure

task, whereas the boys in the comparison group performed well within the average range on this task, $Z = -2.80$, $p = .005$. Although the boys with Barth syndrome also had lower scores on the Position in Space and Form Constancy tasks, these differences were not statistically significant when examined among matched pairs of participants, $p = .07$ and 0.06 , respectively. There was no difference on performance on the Figure Ground task, $p = .69$.

The supplemental visual memory analyses was based on two tasks given to the boys in the Barth syndrome group, but not to the comparison group, which had been developed for use in a study of the fragile X and Turner syndrome phenotypes.³⁰ Using a One-Sample Sign test, we compared performance by the Barth syndrome group to the published group means for the fragile X and Turner syndrome groups and to the comparison group included in that earlier study. On the object recall task, boys with Barth syndrome had near perfect performance, correctly identifying whether each of 20 shapes had been presented during an immediately preceding shape matching task (mean = 18.64, SD = 1.21). This was also the case for all three groups reported in the earlier study, for which group means were 18.00, 18.04, and 19.19, respectively.³⁰ Therefore, no group differences emerged from the three One-Sample Sign tests corresponding to the object recall task, $p > .22$. For the location memory task, none of the three One-Sample Sign tests was significant, although the group mean for the Barth syndrome group (4.82, SD = 2.40) was closest to that of the fragile X group (4.20), $p > .99$, comparable to that of the comparison group (5.94), $p = .23$, and most discrepant from the below average score from the Turner syndrome group (3.28), $p = .065$. The array created during this location task was accurate, thus gridlike, for 100% of boys with Barth syndrome, a finding that is inconsistent with the below average Visual Closure task performance. This 100% frequency was significantly higher than that reported for girls with fragile X (46.7% of whom accurately reproduced the gridlike array), Fisher exact test $p = .007$; but not different from the >90% accuracy observed in the Turner syndrome and comparison groups, $p > .59$.

Considered together, the results from the visual spatial tasks suggest that visual motor skills may be affected by the motor difficulties that comprise part of the Barth syndrome physical phenotype because performance on the VMI was well within the deficient range for seven of the 10 boys who completed this task, but that some aspects of visual perception are also deficient. Still, it is clear that visual perception skills are not globally deficient and that boys with Barth syndrome show intact visual memory as measured by two specific memory tasks designed to assess location and object identification skills. Our final set of analyses further addresses whether spatial difficulties are part of the Barth syndrome cognitive phenotype.

Mother-Child Discrepancy Scores—Only nine of our participants had a mother who also completed cognitive testing with the WASI. This allowed us to compare the discrepancy between mothers and their own sons, using paired Wilcoxon tests, for Full Scale, Verbal, and Performance I.Q. scores. Boys with Barth syndrome had significantly lower WASI Full Scale I.Q. scores than did their mothers, $p = .011$. The discrepancy was large (18 points) and highly variable (SD = 12.31). Both Verbal and Performance I.Q. scores were also significantly lower in boys with Barth syndrome relative to their own mothers, $p = .04$ and 0.01 , respectively, although the discrepancy was most pronounced for the Performance I.Q. score (Table 3). By examining all four WASI subtest scores, we observed that the discrepancy for both Performance I.Q. tasks were >13 points, $p < .022$, whereas there was no significant difference on the Vocabulary task. The findings from this subtest analysis support the notion of spared language skills and more deficient spatial skills in the Barth syndrome phenotype.

DISCUSSION

Barth Syndrome Has a Cognitive Phenotype

To our knowledge, this is the first group-based empirical study of cognitive skills in children with Barth syndrome. This study supports our earlier, preliminary report that was based on only five boys. Whereas the preliminary report was limited to this small sample and by the brief 1-hour test battery used in our earlier study, the present study was based on 15 boys who completed a thorough psychoeducational assessment. Our findings support the notion of a cognitive phenotype in Barth syndrome. This phenotype is characterized by spared language ability including age-appropriate vocabulary and basic reading skills, below average performance in mathematics observed as early as the primary school years, and selective difficulties in visual spatial skills that cannot be attributed to the impaired motor functioning due to the significant myopathy of Barth syndrome. Coupled with the fatigue regularly experienced by boys with Barth syndrome, our findings recommend that educational support be implemented during the early school-age years for children with Barth syndrome.

Generalization of these findings is influenced by the extent to which the study sample represents all boys with Barth syndrome. One possible source of ascertainment bias is disease severity: if study participants are among the most severely affected by Barth syndrome, our findings could be skewed toward *poorer* cognitive performance. However, this outcome is improbable because, as was the case for the preliminary study, participants in this study were likely to be among the healthiest boys with Barth syndrome. Indeed, most of the study participants had traveled to a conference location at the time of testing; and only three of the 15 participants with Barth syndrome were tested in their hometown. The organizers of the conferences have noted that a boy's poor general state of health is a commonly stated reason for a family's not attending one of the three international conferences that have been held. A second potential source of ascertainment bias is parental concern about a child's academic performance, with parents of boys experiencing school difficulties demonstrating more interest in study participation. Although it was not possible to assess this possibility directly, our recruitment efforts were focused on including as many known cases of Barth syndrome as possible, evident by our willingness to travel more than 2000 miles for data collection. We believe that a significant majority of known cases of Barth syndrome in the US meeting inclusion criteria were included in the present study. We base this contention on the extraordinary efforts of the Barth Syndrome Foundation to identify all affected boys in the United States and on the fact that boys within the targeted age group for the study, 5 to 10 years, were recruited over a 5-year period (2000–2005). Moreover, Barth and colleagues² reported 15 living boys between the ages of 5 and 9 based on the Barth Syndrome Foundation registry in 2002. Although patient confidentiality requirements prevent the direct comparison of overlap between our participants and those recorded by Barth and colleagues, the size and age range of the groups are very similar. Therefore, we believe that the study sample is a good representation of the children with Barth syndrome and that any ascertainment bias that may have occurred was more likely to skew our findings toward the least affected rather than the most affected boys. Moreover, we believe that we were conservative in our approach to statistical analyses by using nonparametric tests and paired analyses whenever possible; nevertheless, significant findings emerged. We thus conclude that our findings provide empirically sound evidence of a cognitive phenotype of Barth syndrome.

Although we do not believe that the phenotypic profile to emerge in this study is highly specific to boys with Barth syndrome, there is reason to believe that the profile is fairly sensitive to boys with Barth syndrome. Indeed, the 16th participant in the Barth syndrome group, whose performance differed remarkably from that of the other boys in the study sample (Fig. 1), was excluded from the study after his participation because it was discovered that he did not have the Barth syndrome *TAZ* mutation. This boy's learning difficulties were consistent with a

dyslexic profile: he had slow rapid naming and was unable to complete two of the three rapid naming subtests and his scores were below average for letter identification, single word reading, and decoding skills tasks. As evident in Figure 1, this child's reading related scores were >1 SD below the group mean for both the Barth syndrome and comparison groups. This child did not have the same degree of deficits on mathematics or visual motor integration. It is worth noting that the investigator (M.M.) who had completed the cognitive assessment for many of the study participants, including participant 16, had remarked on the discrepancy between this boy's cognitive profile and that from the other boys in the Barth syndrome group; moreover, this observation was reported prior to her learning that the boy's diagnosis was genetically unproven. Clearly, it is possible to inherit genes for dyslexia regardless of the presence of a *TAZ* mutation, in which case, a boy with Barth syndrome could manifest a dyslexic profile. However, it is also clear that a dyslexic profile is not a component of the Barth syndrome phenotype observed in the present study and that the only participant to enroll in the Barth syndrome group to manifest a dyslexic profile ultimately was found to have a normal *TAZ* sequence despite manifesting three of the cardinal clinical characteristics of Barth syndrome.

Prior to concluding that the Barth syndrome phenotype is a direct consequence of the *TAZ* mutation, possible confounding variables must be considered in future research. One such confound concerns school absence, which children with Barth syndrome may experience more frequently than their peers due to illness. Although the present study did not include a systematic assessment of the days of school missed during the year of testing, this issue was explored by asking parents to estimate the number of school days missed and by comparing the number of boys per group that had repeated a school grade. Parent recall data were available for 11 boys in the comparison group, who were reported to have missed 0 to 18 days of school during the year of study participation. For the 14 boys with Barth syndrome for whom such data were available, parents' estimates ranged from 0 days to several months. Excessive school absence (and many other factors) may increase the likelihood of failing to advance a grade in school at the conclusion of the school year. Although most boys with Barth syndrome (eight boys) had repeated kindergarten or first or second grade, this rate (60%) was not statistically different from the 33% rate reported for boys in the age- and grade-matched comparison group. It is unclear to what extent exposure to school curriculum influences manifestation of the phenotype presented in this report. However, despite the school absences and repeated school grades, there were no group differences in reading-related scores or in all areas of spatial perception. This suggests that school absence alone is an unlikely explanation for the group differences to emerge in the present study. Also, the boys with Barth syndrome who repeated an early grade may have needed to not because of academic failure but because of their small size or many weeks or months of illness-related missed classes.

Future research efforts are needed to understand the biological mechanisms that underlie phenotypic within-group variation, such as possible correlations between genetic or biochemical indices of disease severity and severity of mathematics difficulties. In addition to persistent biochemical abnormalities, such as cardiolipin deficiency, 3-methylglutaconic aciduria, and hypocholesterolemia in Barth syndrome, there also are signs of abnormal early embryological development, most notably, left ventricular compaction.³⁰ Moreover, recent evidence suggests effects of *TAZ* mutations that may extend to nonmitochondrial lipid metabolism.³⁰ Therefore, a challenge to future research on the Barth syndrome cognitive phenotype will be determining the relative roles of prenatal development and postnatal biochemistry in determining the cognitive phenotype and if there are any correlations between biochemical markers of Barth syndrome and specific aspects of cognitive performance. If found, such correlations may have implications for cognitive disabilities in other biochemical disorders as well.

Future studies are also needed to address the trajectory of the phenotype throughout the school-age years. For instance, it is unknown whether delayed acquisition of normal achievement scores will parallel the delayed acquisition of normal height observed in boys with Barth syndrome. Regardless of whether the cognitive consequences of Barth syndrome are primary or secondary, our research demonstrates that boys with Barth syndrome are at increased risk of academic difficulties. These findings support the contention that educational support be provided for boys with Barth syndrome during the early or preschool years.

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Figure 1.

Individual test scores for participant 16, and group means (with SD bars) for the Barth syndrome and comparison groups. All scores except Reaction Times (RTs) are converted to a common standard scale (mean = 100, SD = 15). Note that RTs for RAN numbers and letters are imputed because participant #16 could not complete either of these two subtests. The imputed scores used as best estimates of performance were based on the total study sample group mean + 2 SDs. SB-IV, Stanford-Binet, Fourth Edition; WJ-R, Woodcock Johnson-Revised; RAN, Rapid Automated Naming; TEMA-2, Test of Early Math Ability, Second Edition; VMI, Beery-Buktenica Developmental Test of Visual-Motor Integration; DVTP, Developmental Test of Visual Perception.

Table 1

Participant Characteristics

Group	K	Grade				Age in Years		
		1	2	3	4	Mean	SD	Range
Barth								
syndrome								
(n = 15)	4	1	4	5	1	8.45	1.58	5.61–10.47
Comparison								
(n = 15)	4	1	4	5	1	8.16	1.43	5.60–10.14

Table 2

Performance Scores on Cognitive Measures

	Barth Syndrome			Comparison			Mann-Whitney <i>p</i> Value	Effect Size	Total Pairs	Wilcoxon <i>p</i> Value
	Mean	SD	n	Mean	SD	n				
WASI FSIQ	88.58	8.30	12	102.67	15.43	15	0.02	-0.98	12	0.03
WASI Vocabulary (<i>T</i> score)	44.92	5.05	12	50.93	6.57	15	0.01	-0.91	12	0.07
WASI Block Design (<i>T</i> score)	40.08	4.34	12	52.00	9.60	15	0.00	-1.23	12	0.01
WASI Similarities (<i>T</i> score)	48.58	4.52	12	54.47	11.19	15	0.21	-0.64	12	0.11
WASI Matrix (<i>T</i> score)	40.00	10.97	12	47.93	11.17	15	0.06	-0.68	12	0.09
SB-IV Vocabulary (SS)	49.33	4.03	9	47.60	7.12	15	0.79	0.28	9	0.11
SB-IV Quantitative (SS)	47.57	5.47	7	50.20	7.00	15	0.12	-0.40	7	0.99
WJ-R Letter-Word Identification (SS)	95.43	15.54	14	104.60	13.22	15	0.06	-0.62	14	0.99
WJ-R Word Attack (SS)	97.36	10.64	14	102.33	17.01	15	0.46	-0.35	14	0.36
RAN Colors (reaction time)	57.00	12.04	15	53.00	14.64	15	0.19	0.30	15	0.24
RAN Numbers (reaction time)	43.00	16.74	15	39.87	21.49	15	0.32	0.16	15	0.12
RAN Letters (reaction time)	44.20	18.51	15	50.47	61.14	15	0.26	-0.14	15	0.02
TEMA-2 raw score out of 65	38.21	12.22	14	48.60	16.07	15	0.08	-0.69	14	0.02
TEMA-2 quotient	80.50	11.11	14	103.57	13.03	14	0.00	-1.38	14	0.00
WJ-R Calculations (SS)	78.07	19.21	14	97.91	14.03	11	0.01	-1.01	10	0.04
KM-R Numeration (SS)	8.73	1.49	11	11.44	2.70	9	0.03	-1.10	8	0.11
Magnitude judgment task ^a	4.27	0.65	11	5.00	0.00	9	0.00	-1.22	9	0.02
Counting (correct trials out of 24) ^a	19.75	2.05	8	22.90	1.37	10	0.00	-1.37	7	0.04
Counting (recognize correct trials/12) ^a	8.63	1.51	8	9.90	0.32	10	0.02	-1.07	7	0.13
Counting (recognize errors/12) ^a	11.13	2.75	8	13.00	1.41	10	0.09	-0.83	7	0.18
VMI (SS)	78.80	5.33	10	97.36	11.66	14	0.00	-1.40	9	0.01
DTVP-2 (scaled scores)										
Visual closure	4.67	1.72	15	9.64	4.31	14	0.00	-1.23	14	0.01
Form constancy	8.87	1.96	15	10.79	2.36	14	0.03	-0.82	14	0.06
Position in space	6.80	2.54	15	9.00	3.19	14	0.08	-0.73	14	0.07
Figure ground	8.00	2.54	15	8.64	3.67	14	0.69	-0.21	14	0.69

^a Analyses limited to participants in first grade and above.

WASI, Wechsler Abbreviated Scale of Intelligence; FSIQ, Full Scale I.Q.; SB-IV, Stanford-Binet, Fourth Edition; SS, standard score; WJ-R, Woodcock Johnson-Revised; RAN, Rapid Automatized Naming; TEMA-2, Test of Early Mathematics Ability, Second Edition; VMI, Beery-Buktenica Developmental Test of Visual-Motor Integration; DTVP-2, Developmental Task of Visual Perception, Second Edition.

Table 3
WASI IQ Scores for Child Participants with Barth Syndrome and Their Mothers

	Mother			Child			Discrepancy		
	Mean	SD	n	Mean	SD	n	Mean	SD	Sig. (2 tailed)
Test FSIQ ^a	107.33	8.15	9	89.33	9.54	9	18.00	12.31	.011
VIQ ^a	104.25	7.11	8	95.38	6.70	8	8.88	8.87	.046
PIQ ^a	108.88	10.06	8	84.63	11.87	8	21.56	16.68	.017
Vocabulary ^b	51.44	7.23	9	44.89	4.28	9	6.56	7.84	.050
Block Design ^b	53.88	8.76	8	40.00	5.18	8	13.88	9.33	.021
Similarities ^b	53.88	4.22	8	49.13	5.08	8	4.75	4.23	.018
Matrix Reasoning ^b	57.67	4.36	9	40.67	11.84	9	17.00	11.70	.011

^aStandard score.

^bT score.

FSIQ, Full Scale I.Q.; VIQ, Verbal I.Q., PIQ, Performance I.Q.