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Cognitive characteristics of mitochondrial diseases in children

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ABSTRACT

Introduction: This retrospective descriptive study was undertaken to further define the intelligence profiles of children with mitochondrial disorders, in the context of seizures and age of symptom onset.
Methods: We retrospectively identified forty-nine pediatric patients with definitive mitochondrial disease diagnoses and complete intelligence or adaptive functioning testing data. Patients were 0–216 months at onset of symptoms and 61–250 months of age at testing. Twenty-four of 49 patients had seizures. Twenty-one of the 24 patients with seizures had medically intractable seizures. All patients had Wechsler Intellectual Quotient (IQ) testing, except nine patients with seizures who were unable to engage in IQ testing and were assessed with a structured parent interview measure, the Vineland Adaptive Behavior Scales. We used descriptive and exploratory data analysis methods to characterize test results.
Results: Distribution of ages for patients with the Vineland assessment was younger than those given the Wechsler. The median overall score (combining Wechsler and Vineland summary scores) for all patients was 85 (interquartile range [IQR]: 50, 102), with the group without seizures obtaining a higher median Full Scale IQ (FSIQ) of 100 (IQR: 86, 109), compared to the group with seizures with a median FSIQ of 67 (IQR: 49.5, 89), a difference that is both statistically and clinically different ($\Delta = 33$; 95% CI: 9, 52). The adaptive function measure was composed of patients only with intractable epilepsy and yielded the lowest overall median summary score of 43 (IQR: 37, 50). This general trend in differences between the FSIQ scores of the groups with and without seizures was also seen across all subscale measures analyzed—IQ index scores and two subtest scores, Digit Span and Coding—though differences were not always statistically different. Vargha–Delaney's *A* effect sizes ranged between 0.68 and 0.90, trends that mirrored those of distributional and median differences. Groups without versus with seizures differed most distinctly in Performance IQ (PIQ), with the group without seizures' median PIQ being 100 (IQR 94, 112) versus the group with seizures' median PIQ being 63 (IQR 54, 84), a difference of 37 points (95% CI).
Discussion: Results suggest that patients with mitochondrial diseases with seizures and early onset disease represent a worse cognitive phenotype, as compared with those with no seizures, who can have average intelligence. Results are discussed in the context of current literature.

1. Introduction

Mitochondria are essential energy producing organelles that through a process of oxidative phosphorylation produce the chemical energy source, adenine triphosphate (ATP). Each nucleated cell typically contains hundreds of mitochondria, with cells requiring more energy having corresponding increased numbers to adequately support energy requirements [1]. Mitochondria are also responsible for other cellular functions including calcium homeostasis, biosynthesis of steroids and heme, and cell cycle regulation via retrograde signaling [2]. Mitochondria constantly fuse and undergo fission and, together with organelle division, produce a dynamic intracellular network. These processes are constantly occurring whether the cell is actively undergoing cell division or are post-mitotic, like neurons and muscle. Although much of the genetic maintenance of mitochondrial structure and function are known, many of the >1500 gene products still remain unknown [3,4]. Alterations in mitochondrial-encoded and any of the nuclear-encoded genes can impact any organ system. The interactions of gene products

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and multiple numbers of mitochondria per cell can produce a diverse cadre of diseases.

The brain is particularly susceptible to disease effects due to the high energy demand for efficient and complex functioning. The complex balance of communication of excitation and inhibition between neurons and glia is required for higher brain functions such as cognition, movement, vision, and hearing as well as lower functions of heart rate and breathing. Brain and muscle functioning are so intimately involved in mitochondrial diseases that early on the concept of multisystemic abnormalities was described as "mitochondrial encephalomyopathy" [5].

Seizures are one feature of brain dysfunction. Patients with mitochondrial disease have increased risk for seizures, with most beginning at an early age, and most are intractable to medication management [6]. In the Seattle cohort of patients with primary mitochondrial disease, 86/180 children developed seizures, with 68% occurring in patients younger than 3 years of age, and 90% were intractable to seizure medications [6]. In three other large studies, 40%–65% of children with primary mitochondrial disease developed seizures [7–9]. Yet, in adults with mitochondrial disease, only 23.1% had epilepsy, with the seizure onset mean being 29.4 years [10]. Children with epilepsy have more involved disease, as they often die younger and have more episodes of status epilepticus [6]. The predominant interictal electroencephalography (EEG) pattern of multifocal independent discharges with background slowing has been associated with mental retardation [11]. However, in the mitochondrial population mental retardation has not yet been fully characterized.

Cognitive impairment is frequent in mitochondrial diseases, but only loosely described by clinical impression [12]. Many studies simply report the presence of "developmental delay" [13] or "encephalopathy" [14], without a more specific measurement. Other studies have reported on percentages of individuals with developmental delay (92.6%) as indicated by presumably clinical report or observation [15] or percentage of individuals with learning disability (approximately 40%) or intellectual disability (approximately 35%) as indicated by survey report [16].

The difficulty of defining specific cognitive deficits in patients with mitochondrial disease is the vast heterogeneity of disease. Most studies have only looked at small numbers of patients, ranging from single case reports to small populations of only up to 15 subjects [17–26]. In addition, many studies have focused on adults [18,20,27–31] or have included only older adolescents with adults [21,22,32]. These studies are limited in scope and unadaptable to the wide range of childhood mitochondrial diseases. The larger pediatric studies on patients with disease plus measurement of functioning to date have reported primarily on Developmental Quotients using specific testing for developmentally impaired toddlers less than 5 years of age [33] or Developmental Quotients with some Intelligence Quotient measurements primarily in very young patients [34]. One small study (n = 22 patients) reported on functional skills of self-care, mobility, and social function [35].

The above studies have been important initial steps toward a better understanding of cognition or functioning in mitochondrial diseases, despite limited generalizability between diseases and from children to adults. Samples often reveal variability between patients [20,32], even within specific disease categories [34]. The question of intellectual deterioration has been raised, with one sample of adults not showing intellectual decline [27] versus another sample of adults showing deterioration in more than half of the sample [20]. In pediatric patients, intellectual or developmental impairment and deterioration is often indicated [32,33,35,36]. Nissenkorn and associates [35] identified 42 patients "with highly suspect mitochondrial disorders," eighteen (43%) of whom had normal intelligence and 60% of whom showed regression, although scores were not shown. Kartsounis and associates evaluated 36 patients with mitochondrial disease and found intellectual deterioration in 58% of their sample, with varying focal cognitive deficits [32]. A recent study of 53 patients demonstrated that children with very early onset disease (mean age of symptom onset = 0.95 years) show clear decline in developmental quotients, suggesting worse disease in younger patients [33]. All aspects of the developmental quotient, gross motor, fine motor, social–personal, language, and cognitive-adapted skills were found to be altered.

Some neurocognitive and developmental studies in adults with specific mitochondrial syndromes have focused on specific neurocognitive findings and/or specific diseases. Lower nonverbal or visuospatial versus verbal abilities has emerged in a number of studies of brain disease [18,21,27,30], a finding that is consistent with the general understanding of verbal intelligence measurements being more insensitive to insults due to difference in acquisition. Cognitive slowing has been reported [21,31,37], as have deficits in areas of executive function [21,27]. Specific cognitive or focal deficits, with variability, have also been reported [20,27,32]. Waisbren and associates found that very young children with fatty acid oxidation disorders show developmental concerns, such as speech or motor delays, though not impaired Developmental Quotients/Intelligence Quotients [34]. Kaufman and associates documented that in adults with the syndrome of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) due to the mitochondrial deoxyribonucleic acid (DNA) (mtDNA) mutation, m.3243A>G, is associated with worse disease than the syndrome of myoclonus, epilepsy, with ragged-red fibers (MERRF) arising from the mutation, m.8344A>G. Disease-related decline was found to the level of lactic acid and associated with neuropsychological scores [38]. Disease induced by nuclear pathological mutations in tryptophanyl mt-tRNA synthetase, *WARS2*, has been shown to induce intellectual deficiency and adolescents [22].

Given the genetic and phenotypic heterogeneity of mitochondrial diseases, precise definition of typical cognitive profiles is challenging, yet at the same time, additional information regarding presentation may be helpful to aid in further understanding these disorders. To help refine our understanding, we chose to focus initially on intelligence and, where intelligence measures could not be obtained via direct testing because of the patient's low level of functioning, on adaptive functioning, and to evaluate this information in the context of seizures and age of disease onset.

2. Material and methods

This retrospective chart review cohort study was carried out in strict accordance with the institutional review board (IRB) of Seattle Children's Hospital (IRB #13150).

2.1. Participants and procedures

We identified patients who were seen in the Mitochondrial Disease Clinic at Seattle Children's Hospital between September 2001 and March 2016 and who had both confirmed mitochondrial disease diagnoses and neuropsychological or psychoeducation evaluations. Diagnoses were confirmed by biochemical testing, muscle biopsy with electron transport chain enzyme assay, and/or gene sequencing of mtDNA or nuclear genes involved in mitochondrial disease (Table 1). When available, molecular genetic testing that confirmed pathological variants in either nuclear or mtDNA-encoded genes were obtained from Clinical Laboratory Improvement Amendments (CLIA) approved laboratories. All patients met clinical criteria of modified Walker criteria for diagnosing mitochondrial disease [39]. Subject 15 was included because he was the identical twin of subject 11 who had a confirmed diagnosis. This led to 49 patients.

Our cohort represents mitochondrial disease diagnoses over a prolonged period of time. Until recently, gene testing was only available in a research setting. As testing became more clinically relevant, insurance began to allow more widespread testing. Furthermore, over time the knowledge of mitochondrial physiology and identification of candidate genes has evolved. Mitochondrial function has expanded to other cellular components such as calcium regulation, and this evolution has resulted in a wider definition of mitochondrial disease. Our study has