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Original Article

Preliminary Study of Neurodevelopmental Outcomes and Parenting Stress in Pediatric Mitochondrial Disease

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ABSTRACT

BACKGROUND: Little is known regarding the neuropsychological profiles of pediatric patients with mitochondrial diseases or their parents, information that is crucial for improving the quality of life (QOL) for both patients and parents. We aimed to delineate neurodevelopment and psychological comorbidity in children with mitochondrial diseases in the preliminary investigation of adequate intervention methods, better prognoses, and improved QOL for both patients and parents. **METHODS:** Seventy children diagnosed with mitochondrial diseases were neuropsychologically evaluated. Neurocognitive (development, intelligence) and psychological (behavior, daily living function, maternal depression, parenting stress) functions were analyzed. Clinical variables, including the first symptom, epileptic classification, organ involvement, lactic acidosis, brain magnetic resonance imaging findings, muscle pathology, biochemical enzyme assay results, and syndromic diagnosis of mitochondrial diseases, were also reviewed. **RESULTS:** Prediagnostic assessments indicated that cognitive and psychomotor developments were significantly delayed. Group mean full scale intelligence quotient (IQ) scores indicated mild levels of intellectual disability, borderline levels of verbal IQ impairment, and mild levels of intellectual disability on performance IQ. Many children exhibited clinically significant levels of behavioral problems, whereas mothers of children with mitochondrial diseases exhibited significant increases in parenting stress relative to mothers of healthy children. Furthermore, 65% of mothers exhibited significant levels of depression. Early onset of the first symptoms, diffuse brain atrophy, and drug-resistant epilepsy negatively influenced neurodevelopmental and adaptive functions. **CONCLUSION:** Better understanding of the functional levels and profiles of neurodevelopment and psychological comorbidity in children with mitochondrial diseases in the prediagnostic period is essential for adequate support and QOL of children with mitochondrial diseases and their parents.

Keywords: mitochondrial disease, IQ, development, behavior, parenting stress, quality of life

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Introduction

Mitochondrial disease is a complex and heterogeneous multisystem disorder caused by abnormal intracellular adenosine triphosphate production in the mitochondrial respiratory chain,[1] affecting the structure and function of the brain and muscles.[1,2] Mitochondrial disease is the most common metabolic disorder and leads to severe disabilities in

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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most pediatric patients, significantly affecting patient quality of life (QOL).[3] In contrast to the extensive research done on the morphologic and metabolic aspects of the central nervous system affected by mitochondrial diseases, comparatively little is known regarding the neuropsychological effects of the disorder.[4,5] In particular, neurodevelopmental effects of mitochondrial diseases in pediatric patients have not been established. The incidence of cognitive dysfunction in patients with mitochondrial myopathies and encephalomyopathies has been higher than that predicted by routine clinical assessment.[6] Cognitive impairment appears to be particularly common in patients with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS),[7] especially in affected adults. Moreover, the burden of parenting a child with a metabolic disease is expressed in a remarkably lower health-related QOL compared with that for parents of healthy children.[8] Parents of children with metabolic diseases reported significant problems in the areas of cognitive functioning, sleep, pain, social functioning, daily activities, sexuality, vitality, and positive and negative emotions.

To plan adequate intervention and support for these patients and their parents, understanding of their neuropsychological profiles is necessary. We attempted to delineate the neurocognitive and psychological profiles of children with mitochondrial diseases, in terms of behavioral problems and parenting stress, as well as neurodevelopmental and intellectual decline, which are crucial for comprehensive care plans to improve QOL.

Methods

Procedures

Pediatric patients were identified from hospital records by both the presence of a mitochondrial diseases diagnosis and the results of a neuropsychological evaluation. All patients were diagnosed with mitochondrial respiratory chain complex defects through biochemical enzyme assay of muscle tissues and satisfied the modified mitochondrial diseases criteria proposed by Bernier et al.[9] Some individuals from our studies[10,11] were included in more than one analysis.

Standardized measures of neurocognitive function (development, intelligence, and daily living function) and psychological function (behavioral problems, parenting stress, and maternal depression) were administered (Supplementary Table 1). However, all measures could not be completed for all patients because of the limited functioning of some patients. Accordingly, the number of patients who completed each measure is indicated in each table.

Age-appropriate developmental evaluations or two types of intelligence tests were administered. Disease-related clinical variables were examined, including age at symptom onset, age at diagnosis, lead time to diagnosis, type of first symptom, severity of epilepsy, lactic acidosis severity, diffuse brain atrophy on magnetic resonance imaging (MRI), classification of myopathies by pathologic features, biochemical enzyme assay for mitochondrial respiratory chain, and syndromic diagnosis.

Lead time to diagnosis was defined as the time between the first symptom onset and the diagnosis of mitochondrial diseases. Patients were divided into three groups based on the severity and intractability of epilepsy. Drug-responsive epilepsy was defined as an epileptic condition responsive to antiepileptic treatment; drug-resistant epilepsy was defined as that requiring more than two antiepileptic drug treatments. The severity of serum lactic acidosis was defined as follows: mild, $\geq$ 2-fold increase from normal reference values; moderate, $\geq$ 3-fold increase; and severe, $\geq$ 4-fold increase. The severity of diffuse brain atrophy on MRI was defined as follows: mild, diffuse atrophic change only; or severe, diffuse atrophic change with other abnormal MRI findings. Myopathies were classified by the number of simultaneous pathologies observed by light or electron microscopy: none, one, or two. Confirmative diagnosis of MELAS or Leigh disease was based on reported diagnostic criteria.[7,12] Patients with nonspecific mitochondrial diseases showed no classical clinical symptoms, biochemical results, or mitochondrial DNA deletions/duplications/point mutations that conformed to known and established mitochondrial syndromes.

The results of neurodevelopmental and psychological function evaluations at prediagnosis in children with mitochondrial diseases were analyzed and compared according to subgroup. All procedures were approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine. Informed consent was obtained from all individual participants included in the study. As patients were minors, their parents gave informed consent on their behalf.

Neurodevelopmental measures

Prediagnostic assessments of neurodevelopmental and cognitive function were administered to children with mitochondrial diseases. The neurodevelopmental assessments included Bayley Scales of Infant Development, second edition (BSID-II)[13] Children of adequate age were administered two types of intelligence tests, the Korean Wechsler Preschool and Primary Scale of Intelligence (K-WPPSI)[14] and the Korean Wechsler Intelligence Scale for children, third edition (WISC-III)[15] according to their age. Children's adaptive function was measured using the Korean version of the Social Maturity Scale, which is based on the Vineland Social Maturity Scale, fifth version.

Psychological measures for child behavior and parenting stress

Behavioral problems were assessed by examining parent responses on the 99-item Korean Child Behavior Check List (K-CBCL) for children aged 1.5 to 5 years and the 118-item K-CBCL for children and adolescents aged 6 to 18 years.[16]

The Korean version of the Parenting Stress Index[17] was used to provide a total stress score and a score for 13 subscales across two broad domains: stress related to characteristics of the child (Child Domain) and stress related to characteristics of the parent (Parent Domain). The Beck Depression Inventory (BDI), a 21-item measure of depression, was used to evaluate the negative emotions experienced by the mothers.

Data analysis

An analysis of neurocognitive and psychological outcome variables was performed. Data processing and analysis were performed using SPSS Version 20.0. Descriptive statistics for sample characteristics were performed. In addition, bivariate analyses were conducted using the chi-square (χ^2) test, correlation analysis, or Mann-Whitney U test (for nonparametric ordinal data), as appropriate for the data. All P values are two-tailed, and the level of statistical significance was set at $P < 0.05$.

Results

Patient characteristics

Seventy children diagnosed with mitochondrial diseases who had completed prediagnostic neuropsychological assessments between March 2006 and February 2013 were included in the present study. Fifty-one (73%) had been diagnosed with nonspecific mitochondrial diseases, 16 (23%) with Leigh syndrome, and three (4%) with MELAS.

The mean age at the first symptom was 1.8 years (range: 0-9.9 years, SD: 2.5 years), and 40 children (57%) were male. The most common first symptom was seizure (n = 35, 50%), followed by delayed development (n = 25, 36%). A more detailed list of clinical characteristics is presented in Table 1.