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Original Article

Cause of Death in Children With Mitochondrial Diseases

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ABSTRACT

BACKGROUND: We investigated the clinical characteristics that represent risk factors for death in pediatric patients with mitochondrial diseases. **METHODS:** The medical records of mitochondrial disease pediatric patients attended between 2006 and 2015 (n = 221) were reviewed for clinical characteristics, diagnosis, hospitalization, follow-up, survival, and cause of death. **RESULTS:** The global mortality rate in the cohort was 14% (average age at death, six years). By syndromic diagnosis, the mortality rates were as follows: Leigh syndrome, 17% (15 of 88); mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, 50% (two of four); and nonspecific mitochondrial disease, 11% (14 of 129). Data regarding 31 patients (17 males) were included in the analysis of cause of death. The age at symptom onset, lead time to diagnosis, duration of illness, and duration of life were 1.8 ± 2.0, 1.7 ± 1.5, 4.3 ± 2.7, and 6.1 ± 2.9 years, respectively. The most common causes of death were sepsis, pneumonia, disseminated intravascular coagulation, and sudden unexpected death (55%, 42%, 29%, and 29%, respectively). Early death (age six years or younger) was associated with lesions in the thalamus, number of organs involved, and Leigh syndrome. **CONCLUSIONS:** Careful monitoring of the medical condition and early intervention are key to improving survival in pediatric patients with mitochondrial disease.

Keywords: mitochondrial disease, pediatric, children, cause of death, risk factor, mortality

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Introduction

The term "mitochondrial disease" refers to a group of disorders resulting from mitochondrial dysfunction and, in particular, from defects of the mitochondrial respiratory chain (MRC) and associated abnormal oxidative phosphorylation.[1] Mitochondrial dysfunction can happen in any organ, but it has a higher incidence in organs with high-energy requirements such as the brain, heart, liver, and skeletal muscle system.[2] At the genetic level, mitochondrial disease has dual origin, as it may develop because of abnormalities of the mitochondria or nuclear DNA.[3] These aspects contribute to the extreme genotypic and phenotypic diversity of mitochondrial diseases, leading to the involvement of multiple organs, each to a variable extent and with different severity of the manifestations, as well as different clinical outcomes.[4,5]

The survival and clinical findings generally associated with mitochondrial diseases have been reviewed in several reports. Debray et al.[5] evaluated 73 children with mitochondrial diseases, 80% of whom were younger than 3 years, and 46% of whom were deceased at a median age of 13 months; the age at onset of first symptoms (especially if less than six months) was highly associated with the risk of mortality, although such an association was not found for cardiac involvement, visceral involvement, or

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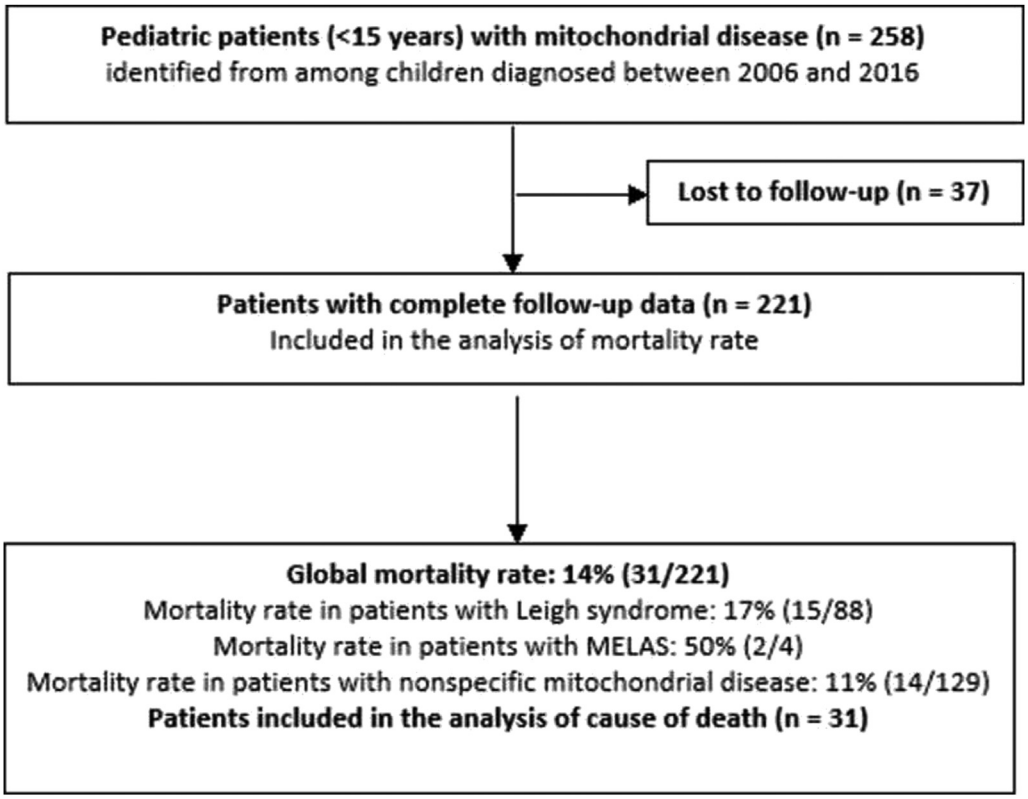

FIGURE.
Flowchart of patient inclusion to study mortality and cause of death in a cohort of pediatric patients with mitochondrial disease. MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

seizures. A Swedish group[2] reported a median survival of 12 years for patients with infantile onset of mitochondrial encephalomyopathies; on the other hand, an American group[1] reported no significant difference in terms of survival between patients with and without cardiomyopathy by the age of 16 years. Finally, for patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), status epilepticus is frequently associated with mortality.[6]

Although these previous investigations have provided insight into the survival time and outcome of patients with mitochondrial diseases, relevant data from in-depth systematic reviews are still scarce and mostly related to the survival curve, do not provide details regarding the death events, and were derived based on pooled populations of pediatric and adult patients. Therefore we systematically reviewed the clinical characteristics and cause of death in pediatric patients with mitochondrial diseases and establish potential risk factors associated with mortality.

Materials and Methods

Patients and study design

We reviewed the medical records of pediatric patients (aged less than 15 years) who were diagnosed with mitochondrial disease and followed regularly at the Department of Pediatrics of Gangnam Severance Hospital between January 2006 and January 2015. All patients satisfied the modified criteria for mitochondrial disease proposed by Bernier et al.,[7] which include clinical, histopathologic, enzymatic, and metabolic parameters. Patients who were lost to follow-up were excluded from the analysis of mortality. The patients who died during the study period were included in the analysis of cause of death and were divided into two groups based on the age at death: early death (less than six years of age) and later death (six or more years of age), in which early death represents preschool age and school age represents later death. The two groups were compared in terms of clinical variables. The study was approved by the institutional review board for human research of our hospital.

Data collection regarding clinical characteristics and diagnostic evaluation

Disease-related clinical variables were collected, including age at onset of symptoms, nature of first symptom, age at diagnosis, lead time from first symptoms to diagnosis of mitochondrial disease (further referred to as time to diagnosis), time from first symptoms to death, duration of life, history of admission to the intensive care unit (ICU), organ involvement, and cause of death. We analyzed diagnostic data from muscle histopathology examinations, enzymatic assays for the MRC, laboratory findings, and neuroimaging findings. Syndromic diagnosis was performed. The diagnoses of MELAS and Leigh disease were confirmed based on the diagnostic criteria reported by Yatsuga et al.[3] and Rahman et al.,[8] respectively. The patients with nonspecific mitochondrial disease did not show classical clinical symptoms, abnormal biochemical results, or genetic mutations that conform to known and established mitochondrial syndromes. Surgical biopsy was performed on the quadriceps muscle, and the samples were assessed via routine histology, immunohistochemistry, and electron microscopy examinations. Biochemical assays to evaluate MRC enzyme activity were also performed, and defects were defined when residual enzyme activity was less than 10% of the reference value. The degree of serum lactic acidosis was defined as mild, moderate, or severe if the increase over the normal reference values was at least two-, three-, or four-fold, respectively.