Pediatric Neurology 64 (2016) 59–65

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Epilepsy Characteristics and Clinical Outcome in Patients With Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-Like Episodes (MELAS)

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ABSTRACT

BACKGROUND: Epileptic seizures in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) are heterogeneous with no pathognomonic features. We reviewed epilepsy characteristics and clinical outcome exclusively in a pediatric population. **METHODS:** Twenty-two children and adolescents (13 males) with confirmed mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes due to mitochondrial DNA A3243G mutation and epilepsy were recruited. Clinical data including seizure semiology, treatment response, neuroimaging findings, and electroencephalography were analyzed. We also examined the effect of the age at seizure onset and initial symptoms on the clinical variables. **RESULTS:** Seizure semiology and electroencephalography abnormalities showed no syndrome-specific findings. Focal seizures occurred in 21 of 22 subjects (95.5%), whereas generalized seizures developed in seven of 22 subjects (31.8%). Twenty of 22 subjects (90.9%) achieved partial to complete reduction of clinical seizures for more than one year with a combination of more than two antiepileptic drugs. The subgroup with earlier seizure onset presented significantly earlier and showed significantly higher rates of drug-resistant epilepsy compared with the late onset group, although there were no significant differences in the initial symptoms. The subjects with severe epileptic conditions tended to have more severe clinical dysfunction and more severe organ involvement. **CONCLUSIONS:** Both focal and generalized seizures occurred in patients with MELAS. Epilepsy in this population is drug resistant, but a certain degree of clinical seizure reduction was achievable with antiepileptic drugs, with more favorable outcomes than historically expected. Close observation and active epilepsy treatment of individuals with MELAS episodes and earlier seizure onset might improve the prognosis.

Keywords: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, mitochondria, pediatric, seizures, epilepsy, MELAS

Pediatr Neurol 2016; 64: 59-65

Introduction

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) is a well-defined syndrome with unique features of early-onset recurrent stroke-like episodes, associated epileptic conditions, and migraine-like headaches,[1,2] with the extreme clinical heterogeneity and variable age of onset resulting from a mitochondrial

Conflicts of Interest: The authors do not have any conflict of interest to disclose.

Article History:
Received June 12, 2016; Accepted in final form August 18, 2016

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http://dx.doi.org/10.1016/j.pediatrneurol.2016.08.016

respiratory chain defect and biochemical energy failure.[3,4] Almost 80% of MELAS patients harbor one specific mutation in the MT-TL1 gene encoding $tRNA^{Leu(UUR)}$, known as adenine to guanine transition at nucleotide 3243 (A3243G).[5,6] The disease encompasses multiple organ systems and manifests in various ways.[2]

Central nervous system presentation of MELAS can be diverse.[7] Epileptic seizures are common, occurring in 71% to 96% of patients with MELAS.[1,8] Previous reports suggest that epileptic conditions in MELAS may arise because of necrosis of the highly epileptogenic focus of the cerebral cortex and hippocampus[9] or from dysfunctional mitochondrial oxidative phosphorylation in those areas, and sometimes in association with stroke-like episodes.[10-12] Several studies report that multiple types of epileptic seizures and associated electroencephalography (EEG) changes occur in individuals with MELAS, although none of the findings is pathognomonic.[13,14] However, previous research has been limited by small numbers of patients and by the analysis of mitochondrial diseases in general and not solely focusing on MELAS. There is a paucity of in-depth systematic review of seizure phenotypes in individuals with MELAS, especially in the pediatric age group.

Therefore we analyzed the clinical features of epileptic seizures associated with MELAS in children and adolescents. We reviewed seizure semiology, EEG changes, treatment and response, and investigated prognostic outcome in terms of development and multiorgan involvement of a mitochondrial nature, which can be improved by interdisciplinary management.

Materials and Methods

Patients and inclusion criteria

Patients who were symptomatic and had clinical features that were compatible with the mitochondrial disease criteria proposed by Bernier et al.[15] were identified from electronic medical records at Gangnam Severance Hospital. From this pool, patients with confirmed MELAS based on the diagnostic criteria of Yatsuga et al.[2] who were less than 18 years of age were selected, with a follow-up period from March 2006 to November 2015. The study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine.

Data collection regarding diagnostic investigations for MELAS

Intensive diagnostic evaluations were performed on these subjects. Laboratory test results were obtained, including serum lactic acid and pyruvic acid levels, serum amino acids, and urine organic acids. All 22 patients were tested for common genetic mutations involved in MELAS, including the A3243G mutation. Muscle biopsies were performed surgically from the quadriceps muscle, and routine histologic, immunohistochemical, and electron microscopic examinations were conducted. Biochemical assays to evaluate mitochondrial respiratory chain enzyme activity were also performed, defining the enzyme to be defective when residual enzyme activity was less than 10% of reference. Brain magnetic resonance imaging and magnetic resonance spectroscopy study data were also collected.

Data collection regarding epileptic conditions in MELAS

Further data including seizure type and epilepsy syndrome, using the International League Against Epilepsy (ILAE) classification,[16] antiepileptic medications and other treatment options used, severity of epilepsy, and response to treatment were also obtained. Seizure types were described as either focal or generalized, according to the ictal semiology in combination with EEG abnormalities, based on the ILAE classification.[16] Drug-resistant epilepsy was defined as epilepsy in which seizures persist despite adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug treatments, according to the ILAE consensus proposal.[17] Clinical seizure reduction rate within the past one year was described as response at the last visit. Serial EEGs were reviewed to analyze interictal EEG features of background abnormalities and epileptiform discharges, as well as ictal EEG changes.

Correlation of clinical features and severity of epileptic condition

We also investigated the correlation of the severity of epileptic conditions in accordance with the severity of the subjects' clinical status, systemic organ involvement, level of lactic acidosis, and level of severity in neuroimaging studies. The severity grade used in this study was built based on our clinical experience.

The severity of epilepsy was defined as follows: 0, no seizure events; 1, having epilepsy, using $\leq$2 antiepileptic drugs, and without recurrent status epilepticus; 2, having epilepsy, using $\leq$2 antiepileptic drugs, and with a history of recurrent status epilepticus; and 3, having epilepsy, using $\geq$3 antiepileptic drugs, and with a history of recurrent status epilepticus. The clinical severity was defined as follows: 0, normal, asymptomatic, or no apparent cognitive or motor disability; 1, mild, the subject is ambulatory on own with or without independence for daily activities; 2, moderate, the subject is full time wheelchair-bound or partially dependent for daily activities, with ability for brief communication; and 3, severe, the subject is bedridden, totally dependent for daily activities, or expired. The severity of multiorgan involvement was defined as follows: 0, normal, no involvement; 1, mild, central nervous system involvement only; 2, moderate, involvement of both central nervous system and musculoskeletal system; and 3, severe, involvement of central nervous system, musculoskeletal system, and other organ systems. The severity of serum lactic acidosis was defined as follows: 0, normal; 1, mild, $\geq$2-fold normal reference; 2, moderate, $\geq$3-fold normal reference; and 3, severe, $\geq$4-fold normal reference value. For the neuroimaging studies, the severity grade was defined as follows: 0, normal; 1, mild, single infarction with or without mild atrophic change; 2, moderate, $\geq$2 infarction with or without mild atrophic change; and 3, severe, multiple infarctions with or without severe atrophic change.

Statistical analysis

All analyses were performed using SPSS version 20.0 (SPSS Inc Chicago, IL, USA). Descriptive statistics were used including the mean, standard deviation, median, and range. Parametric *t* tests and chi-square tests were used to evaluate differences between the groups. *P* values less than 0.05 were considered statistically significant.

Results

Patient characteristics

A total of 22 patients were recruited for the study, including 13 male and 9 female subjects (Table 1 for full details). Every subject's age was less than 18 years at the first clinical presentation (mean age 8.0 $\pm$ 3.9 years, range 0.5 to 16.8 years) and was regularly followed up at our institute, with a mean duration of follow-up of 5.4 $\pm$ 3.8 years. Initial presenting symptoms were variable, with seizure (12/22, 54.5%) being most common. Mean age of first seizure onset was 8.3 $\pm$ 4.0 years (range 0.7 to 18.0 years). The time interval was 1.7 $\pm$ 2.5 years (range 0.2 to 11.5 years) from the first clinical presentation until the confirmative diagnosis of MELAS. The subjects' mean age at the diagnosis of MELAS was 9.6 $\pm$ 4.9 years (range 4.3 to 25.0 years). All 22 patients (100%) had involvement in the central nervous system, and various organs were affected as shown in Table 1.