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MELAS: A nationwide prospective cohort study of 96 patients in Japan ☆

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ABSTRACT

Background: MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) (OMIM 540000) is the most dominant subtype of mitochondrial myopathy. The aim of this study was to determine the prevalence, natural course, and severity of MELAS.
Methods: A prospective cohort study of 96 Japanese patients with MELAS was followed between June 2003 and April 2008. Patients with MELAS were identified and enrolled based on questionnaires administered to neurologists in Japan. MELAS was defined using the Japanese diagnostic criteria for MELAS. Two follow-up questionnaires were administered to neurologists managing MELAS patients at an interval of 5 years.
Results: A prevalence of at least 0.58 (95% confidential interval (CI), 0.54–0.62)/100,000 was calculated for mitochondrial myopathy, whereas the prevalence of MELAS was 0.18 (95%CI, 0.02–0.34)/100,000 in the total population. MELAS patients were divided into two sub-groups: juvenile form and adult form. Stroke-like episodes, seizure and headache were the most frequent symptoms seen in both forms of MELAS. Short stature was significantly more frequent in the juvenile form, whereas hearing loss, cortical blindness and diabetes mellitus were significantly more frequent in the adult form. According to the Japanese mitochondrial disease rating scale, MELAS patients showed rapidly increasing scores (mean ± standard deviation, 12.8 ± 8.7) within 5 years from onset of the disease. According to a Kaplan–Meier analysis, the juvenile form was associated with a higher risk of death than the adult form (hazard ratio, 3.29; 95%CI, 1.32–8.20; $p = 0.0105$).
Conclusions and General Significance: We confirmed that MELAS shows a rapid degenerative progression within a 5-year interval and that this occurs in both the juvenile and the adult forms of MELAS and follows different natural courses. This article is part of a Special Issue entitled: Biochemistry of Mitochondria.

1. Introduction

Mitochondrial dysfunction increases the risk of developing various human diseases, including degenerative neuromuscular disorders, diabetic or metabolic conditions, and cancer; it also affects the aging process [1]. The classical clinical entity in this category is the so-called mitochondrial myopathy, in which mitochondrial dysfunction is caused by mitochondrial or nuclear genetic abnormalities. The disease, which encompasses mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) (OMIM 540000), is characterized by the early onset of stroke-like episodes and was first described by Pavlakis and colleagues in 1984 [2]; it is thought to be the most dominant subtype of mitochondrial dysfunction. At least 39 distinct mitochondrial DNA mutations have been associated with MELAS [3]; however, approximately 80% of MELAS patients have an A3243G mutation in the mitochondrial $tRNA^{Leu(UUR)}$ gene (OMIM 590050) [4] and [5]. Because this mutation was also found to be a major genetic abnormality in diabetes mellitus, it may be a particularly common genetic variant in human populations [6]. Although more than 26 years have passed since the clinical and pathological definition of MELAS, there are few reports on its prevalence and epidemiology, and no reports exist on the natural course, survival rate or severity of the disease in a cohort study, meta-analysis, or nationwide survey [7] and [8]. In this study, we determined the prevalence, clinical symptoms, natural course, severity, and survival rate of MELAS patients in a nationwide Japanese

Abbreviations: JMDRS, Japanese mitochondrial disease rating scale; NPMDS, Newcastle pediatric mitochondrial disease scale; NMDAS, Newcastle mitochondrial disease adult scale

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cohort study. Additionally, we also evaluated the clinical rating scale that may be a very useful tool for the assessment of efficacy of therapeutic approach for mitochondrial myopathy.

2. Materials and methods

2.1. Study design, patients, and data collection for the Japanese cohort study

The cohort study was performed using questionnaires. To determine the prevalence of mitochondrial myopathies throughout the country, the first questionnaire was mailed in 2001 to 2236 neurology departments within Japan (1474 departments with pediatric neurologists and 762 departments with adult neurologists, including governmental, public, private and university hospitals with 50 beds or more). Patients' medical records were evaluated using MELAS diagnostic criteria (Table 1) and adequately screened. In 2003, after compiling the results of the first questionnaire, we mailed a second questionnaire to the neurologists who had examined MELAS patients in 2001. In 2008, we mailed a third questionnaire to the same group of neurologists. The second and third questionnaires included a Japanese mitochondrial disease rating scale (JMDRS) (Supplemental Table 1). Relevant information from the medical records of eligible patients was transcribed onto case report forms by neurologists, who were later interviewed by telephone if ambiguous data or unsatisfactory descriptions were found in the case report forms. Detailed documentation of the patients' clinical status was compiled by the same neurologists. The case report form was originally constructed according to the JMDRS and was updated whenever the scores were altered. Written informed consent was obtained from the patients or their legal guardians. The study protocol was approved by the Institutional Review Board (Kurume University #9715).

2.2. Diagnostic criteria for MELAS

The nationwide survey of MELAS in this study is based on the definitive diagnosis of MELAS presented in Table 1.

Table 1
Diagnostic criteria for MELAS (MELAS study committee in Japan).

Category A. Clinical findings of stroke-like episodes
1. Headache with vomiting
2. Seizure
3. Hemiplegia
4. Cortical blindness or hemianopsia
5. Acute focal lesion observed via brain imaging[a]
Category B. Evidence of mitochondrial dysfunction
1. High lactate levels in plasma and/or cerebral spinal fluid or deficiency of mitochondrial-related enzyme activities[b]
2. Mitochondrial abnormalities in muscle biopsy[c]
3. Definitive gene mutation related to MELAS[d]
Definitive MELAS
Two items of Category A and two items of Category B (four items or more)
Suspicion of MELAS
One item of Category A and two items of Category B (at least three items)

[a] Focal brain abnormalities in CT and/or MRI.
[b] 2 mmol/L (18mg/dl) or more lactate in plasma at rest or in cerebral spinal fluid and/or deficiency of electron transport chain enzyme, pyruvate-related, TCA cycle-related enzymes or lipid metabolism-related enzymes in somatic cells (desirable for muscle cells).
[c] RRF (ragged-red fiber) in modified Gomori's trichrome stain and/or SSV (strongly SDH-reactive blood vessels) in succinate dehydrogenase stain, cytochrome *c* oxidase-deficient fibers or abnormal mitochondria in electron microscopy.
[d] Definitive mitochondrial gene mutations reported in the literature (G583A, G1642A, G1644A, A3243G, A3243T, A3252G, C3256T, A3260G, T3271C, T3291C, G3481A, G3697A, T3949C, G4332A, G5521A, A5814G, G7023A, T7512C, A8296G, T8316C, T9957C, A12299C, A12770G, G13042A, A13084T, G13513A, A13514G, A13528G, and G14453A) as of 2010 [3].

2.3. Japanese Mitochondrial Disease Rating Scale (JMDRS)

We prospectively analyzed the clinical progress of MELAS using the JMDRS (Supplementary Table 1), which was revised following the European NeuroMuscular Conference (ENMC) in 2003 [9]. The second and the third questionnaires were also based on the JMDRS and enabled longitudinal analysis of disease progression. We established a rating score for each patient in 2003 and 2008, and these values were used to analyze the clinical severity of MELAS.

2.4. Statistical analysis

Demographic and clinical data for the juvenile and adult forms of MELAS were summarized using descriptive statistics. An unpaired *t*-test was used to test for any differences in the death rates of juvenile and adult forms. Differences between the juvenile and adult forms in the symptoms at onset and throughout the entire follow-up period were evaluated by chi-square tests or Fisher's exacts test when the criteria for the chi-square test were not fulfilled. Alterations in the JMDRS scores between 2003 and 2008 were evaluated using unpaired *t*-tests alone or combined with a Welch correction when variances were significantly different. Survival rates were compared between juvenile and adult forms using the log-rank test. Statistical analyses were performed with the SPSS 11.0 J software package for Windows. $p<0.05$ was considered statistically significant.

3. Results

3.1. Questionnaire responses from the Japanese cohort

We received 1051 responses to the first questionnaire (total 47.0% response rate, 1051/2236); among them, 756 were from pediatric neurology departments(51.3% of responses) and 295 were from adult neurology departments(38.7% of responses). We identified 741 patients with mitochondrial myopathies and of these, 233 were MELAS patients (31.4% of total mitochondrial myopathy patients, 233/741), as described by 105 pediatric neurologists and 29 adult neurologists. We received 64 responses to the second questionnaire (total 47.8% response rate, 64/134): 36 from pediatric neurologists (34.3% response rate, 36/105) and 28 from adult neurologists (96.6% response rate, 28/29). We received 64 responses to the third questionnaire (100% response rate, 64/64); only 96 MELAS patients completed the 5-year cohort study.

3.2. Prevalence of MELAS in Japan

We found 741 cases of mitochondrial myopathy in our cohort study. Based on the MELAS diagnostic criteria (Table 1), we found 233 MELAS patients (juvenile/adult = 111/122) among the Japanese population of approximately 127,434,000 (approximately 22,275,000 under 18 years of age and approximately 105,159,000 over 18 years of age, adult form, according to census data from 2001). The prevalence of mitochondrial myopathy in Japan is therefore at least 0.58 (95% confidence interval (CI), 0.54–0.62)/100,000 in the total population. The prevalence of MELAS is at least 0.18 (95%CI, 0.17–0.19)/100,000 in the total population, 0.50 (95%CI, 0.41–0.59)/100,000 in children under 18 years of age, and 0.12 (95%CI, 0.10–0.14)/100,000 in the population over 18 years of age.

3.3. Demographic and pathological findings of MELAS in the cohort study

Our cohort study included 96 MELAS patients who were followed prospectively for 5 years. A histogram and a density plot showing the various ages of onset in MELAS in these patients indicate an approximately bimodal distribution (Fig. 1). We therefore divided the MELAS patients into two sub-groups to determine whether MELAS