

An Infant With a Mitochondrial A3243G Mutation Demonstrating the MELAS Phenotype

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Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is a syndrome associated with mitochondrial DNA mutations such as A3243G, the most common mutation. Ragged-red fibers and strongly succinate dehydrogenase-reactive blood vessels in the muscle are diagnostic pathologic features of MELAS. In general, the first typical attack of MELAS occurs in children at school age; it is rare for stroke-like episodes to occur in early infancy. This report describes a 4-month-old male harboring A3243G, whose phenotype at onset was consistent with that of MELAS in infancy. The patient was admitted because of disturbances of consciousness and ventilatory insufficiency. Remarkable lactic acidosis was observed. MRI revealed several bilateral lesions. Periodic lateralized epileptic discharges on the EEG suggested regional lesions. Biopsied muscle displayed scattered ragged-red fibers and succinate dehydrogenase-reactive blood vessels; over 90% of muscle mitochondrial DNA had A3243G. This case suggests that MELAS can develop in early infancy with its typical clinical presentation. The high percentage of A3243G may contribute to the early onset of the MELAS phenotype in this patient. © 2006 by Elsevier Inc. All rights reserved.

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Introduction

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is clinically characterized by recurrent seizures and headache followed by dementia and psychomotor retardation. Seizures are considered as one of the manifestations of stroke-like episodes and thus focal seizures indicate focal lesions resulting from attacks. Periodic lateralized epileptic discharges may thus appear on the electroencephalogram, indicating such focal lesions.

Several mitochondrial DNA mutations have been identified as a cause of MELAS. Approximately 80% of individuals with the clinical characteristics of MELAS have a heteroplasmic A to G point mutation in the dihydrouridine loop of the tRNA^{Leu (UUR)} gene at position 3243 (A3243G) [1-3]. Nevertheless, A3243G was also recently found to be associated with various other types of mitochondrial multisystemic disease [4] such as diabetes mellitus and Leigh encephalopathy.

Muscle pathology manifests the diagnostic features of MELAS. The combination of both ragged-red fiber and strongly succinate-dehydrogenase-reactive blood vessels in the muscle are diagnostic for MELAS. Strongly succinate-dehydrogenase-reactive blood vessels represent mitochondrial abnormalities of smooth muscle cells of blood vessels, resulting in mitochondrial angiopathy, which may cause the stroke-like episodes of MELAS.

In general, MELAS affects children at 5-15 years of age, and includes the presence of mitochondrial abnormalities. On the other hand, stroke-like episodes seldom occur in early infancy whereas various atypical manifestations are observed in infants with A3243G. Hence, it is rare to find typical clinical manifestations of MELAS in infants. This report describes a 4-month-old male infant harboring A3243G, whose phenotype and pathologic findings in a muscle biopsy specimen at the onset were consistent with those of MELAS.

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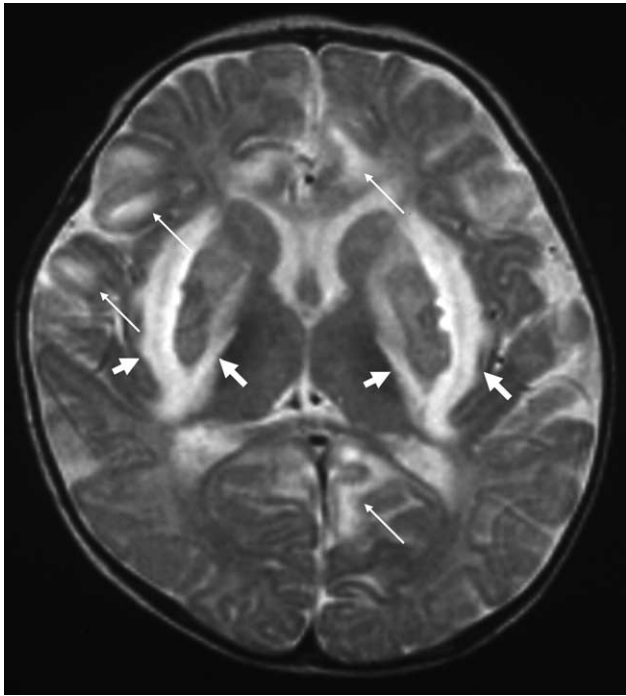


Figure 1. Magnetic resonance imaging taken on the eighth day of admission. Symmetrical lesions in the internal and external capsules (bold arrows) indicating high intensity on T₂-weighted images (TR: 3600, TE: 100 ms). Similar but asymmetric findings on magnetic resonance images were observed in the white matter of the cerebrum and cerebellum (thin arrows).

Case Report

The 4-month-old male was born by normal spontaneous delivery after an uneventful gestation at term weighing 3310 gm. No abnormal findings were recorded in the perinatal period. The mother was 30 years old and healthy. He grew normally, and weight at 3 months of age was 5480 gm. At 4 months of age, he developed a common

cold followed by several episodes of vomiting, disturbance of consciousness, and respiratory distress. On admission, the patient was in a coma and required ventilatory support. Muscle tone and the deep tendon reflexes were normal, and no muscle atrophy was observed.

Laboratory evaluation revealed a normal blood count, serum electrolytes, C-reactive protein, but marked lactic acidosis of the arterial blood [pH 7.097, base excess -25.1, serum lactate 210 mg/dL, (normal values 5-18 mg/dL); pyruvate 5.2 mg/dL, (normal values 0.3-0.9 mg/dL)]. The cerebrospinal fluid exhibited marked increase in lactate and pyruvate (192 mg/dL and 5.9 mg/dL, respectively) with a lactate/pyruvate rate of >20. This remarkable lactic acidosis could not be ameliorated with sodium bicarbonate.

A brain magnetic resonance imaging study on the eighth day of admission revealed symmetric lesions in the internal and external capsules with a low-intensity on T₁-weighted images and high intensity on T₂-weighted images. Similar but asymmetric findings on magnetic resonance imaging were observed in the white matter of the cerebrum and cerebellum (Fig 1). Diffusion-weighted images yielded scattered cortical high signals in the cerebrum and cerebellum. The electroencephalogram on admission revealed continuous diffuse irregular slow waves with arrhythmic high-voltage sharp waves in the left central area. Muscle biopsy was performed for histologic, biochemical, and DNA analyses. A specimen was obtained by a biopsy of the biceps brachii muscle at 4 months of age. Serial frozen sections were stained with hematoxylin and eosin and by a battery of histochemical methods, including a modified Gomori trichrome method. Hematoxylin and eosin-stained muscle sections revealed a mild variation in muscle fiber size, measuring from 5 to 10 μm in diameter, but no necrotic or regenerating fibers. The

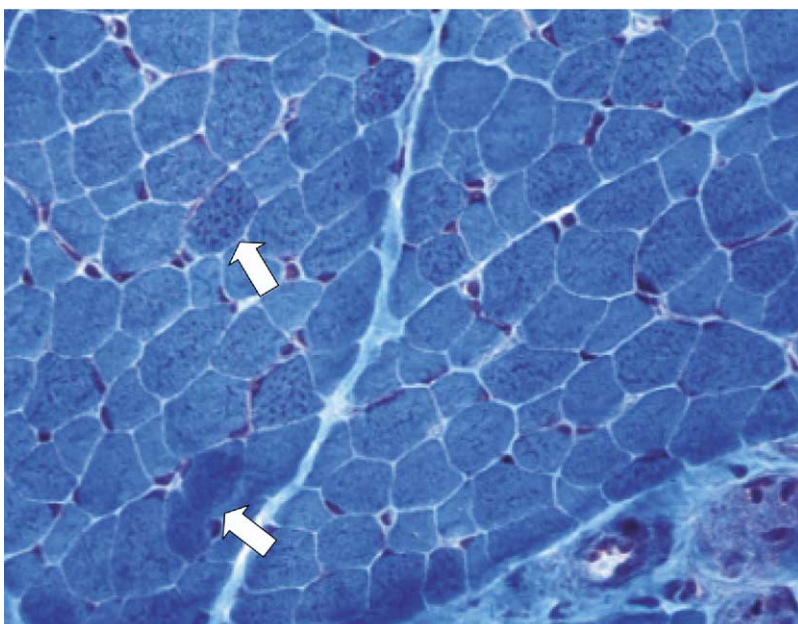


Figure 2. Diagnostic histologic features for MELAS in muscle specimens. Modified Gomori trichrome staining highlights ragged-red fiber-like appearance (arrows). Magnification: ×200.

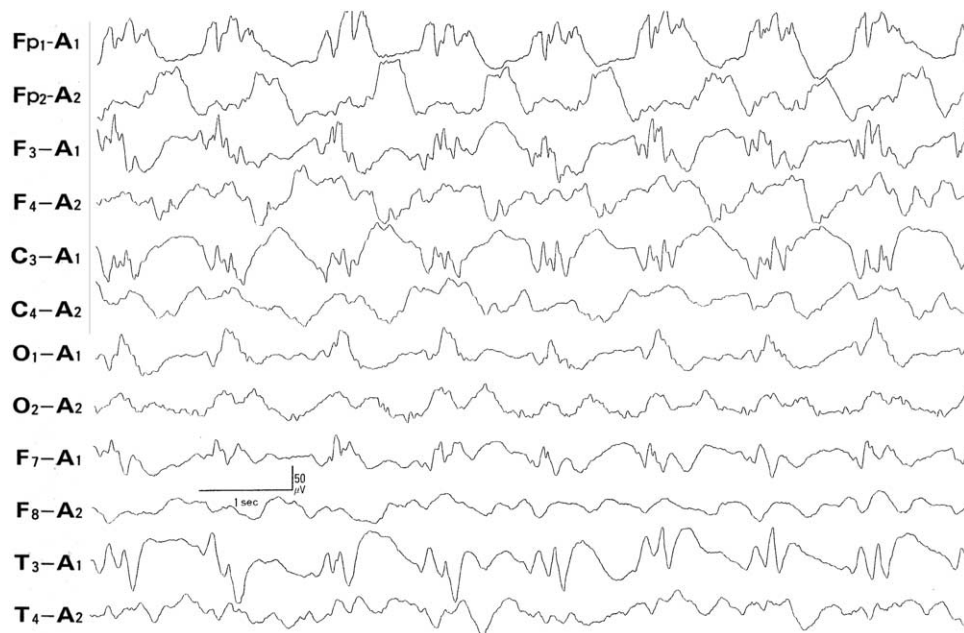


Figure 3. Electroencephalogram recorded on the second day of admission. The electroencephalogram documents periodic lateralized epileptic discharges in the left hemisphere.

sections stained by modified Gomori trichrome method (Fig 2) manifested several fibers with increased di-formazan granules and ragged-red fiber-like appearance. Oxidative enzyme-stained sections manifested slight disorganization of the intermyofibrillar networks in scattered fibers. Many fibers contained excessive numbers of mitochondria highlighted by succinate dehydrogenase staining. Scattered strongly succinate-dehydrogenase-reactive blood vessels were also found, and cytochrome c oxidase staining revealed well-preserved enzymatic activities. Type 2 fiber atrophy was also observed.

Mitochondrial DNA analysis revealed A3243G with approximately 90% mutation load in muscle cells. No other known mutations in mitochondrial DNA were present. The respiratory chain enzyme activity of complex I was considerably low; however, the activities of other respiratory chain enzymes were normal.

Lactate level was controlled with dichloroacetic acid and thiamin. From the second day of admission, the patient developed right-side dominant partial seizures. At that time, electroencephalogram disclosed periodic lateralized epileptic discharges on the left side (Fig 3). The general condition improved gradually but the patient continued to develop seizures and exhibited severe psychomotor retardation.

Discussion

This report presents an infant with A3243G, who demonstrated the MELAS phenotype at onset. Both periodic lateralized epileptic discharges on electroencephalogram and magnetic resonance imaging findings of the brain suggested that the clinical findings (including con-

sciousness disturbance and right side hemiconvulsions) represented the first attack of stroke-like episodes of MELAS. Muscle biopsy accordingly [2] revealed strongly succinate-dehydrogenase-reactive blood vessels, a characteristic pathologic feature of MELAS.

Further tests demonstrated that more than 90% of muscle mitochondrial DNA had A3243G. Approximately 80% of the reported patients with MELAS had A3243G [2,3] although symptoms in infants who harbor A3243G are known to be nonspecific, such as motor developmental delay, failure to thrive, hypotonia, and seizures. Thus, clear MELAS symptoms including stroke-like episodes are rare in infancy [2]. Furthermore, A3243G can be also found in individuals with non-MELAS phenotypes such as diabetes mellitus and deafness [5]. The phenotypic presentation of the A3243G mutation, originally described as MELAS mutation, is extremely heterogeneous [4]. A3243G is therefore highly associated with MELAS while not diagnostic for MELAS per se [6].

Periodic lateralized epileptic discharges are nonspecific unilateral periodic abnormal discharges on electroencephalogram [7,8] and can be recorded in MELAS. Although the exact mechanism of periodic lateralized epileptic discharges remains obscure, they may be observed also in central nervous disorders with focal lesions such as apoplexy, anoxic encephalopathy, subarachnoid hemorrhage, and craniocerebral trauma [9]. In MELAS, periodic lateralized epileptic discharges appear transiently during the acute phase but rarely in the chronic phase [10]. The presence of periodic lateralized epileptic discharges in the patient reported herein implied recurrent stroke-like episodes of MELAS [11].

Because of their putative nature, periodic lateralized epileptic discharges are often associated with partial seizures, which were observed in this patient. Epileptic seizures may occur in many mitochondrial disorders involving the central nervous system and are thus frequent in MELAS. In fact, seizures are often observed as an early symptom of infantile mitochondrial encephalopathies and recognized as the first unequivocal neurologic sign in almost half of such cases [12].

Typical magnetic resonance imaging findings in MELAS include focal lesions in the occipital regions mimicking those of cerebral infarction. However, the lesions do not follow a vascular distribution. The magnetic resonance imaging in the present case revealed multifocal high-intensity areas on T₂-weighted images. In contrast to the magnetic resonance imaging findings indicative of bilateral lesions, the patient had only right-side dominant partial seizure and corresponding left-side periodic lateralized epileptic discharges on the electroencephalogram.

Certain findings on the magnetic resonance imaging may seem different from the typical findings of MELAS such as white matter involvement. However, mitochondrial respiratory chain deficiency is known to cause severe white matter involvement [13]. Although Leigh syndrome is sometimes associated with mitochondrial respiratory chain deficiency, the magnetic resonance imaging in our patient revealed no abnormal lesions of the basal ganglia (except for internal and external capsules) or brainstem, which are typical findings in Leigh syndrome.

In conclusion, this case suggests that MELAS can develop in early infancy and exhibit typical clinical presentation. The high percentage of A3243G may contribute to the early onset of the MELAS phenotype in this patient.

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