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Case report

Late-onset Leigh syndrome with myoclonic epilepsy with ragged-red fibers

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Abstract

We report the case of a boy with myoclonic epilepsy with ragged-red fibers (MERRF) who had astatic seizures since 2 years of age and later developed ataxia, absence seizures, and myoclonus. Almost homoplasmic A8344G mutation of mitochondrial DNA (m.8344A>G mutation) was detected in lymphocytes. He developed late-onset Leigh syndrome (LS) when he contracted pneumonia at 6 years. He developed bulbar palsy and deep coma. MRI demonstrated lesions in the brainstem, basal ganglia, and cerebral cortex. Three similar cases have been reported; two carried the almost-homoplasmic m.8344A>G mutation in muscle tissue. These suggested that almost homoplastic m.8344A>G mutation developed clinical phenotype of MERRF in the early stage and late-onset Leigh syndrome in the late course of the disease.

Keywords: Leigh syndrome; MERRF; m.8344A>G

1. Introduction

Slowly progressive myoclonic epilepsy, ataxia, and myopathy are the main clinical features of myoclonic epilepsy with ragged-red fibers (MERRF) (OMIM #545000) [1]. MERRF onset varies from childhood to adulthood, after normal early development. The A → G mutation at nucleotide 8344 of mitochondrial DNA (m.8344A>G mutation) accounts for 80–90% of MERRF cases [2]. Biochemically, enzyme complexes of the respiratory chain, mainly NADH-CoQ reductase (complex I) and cytochrome c oxidase (complex IV), are deficient [3].

Leigh syndrome (LS; OMIM #256000) is a rapidly progressive neurodegenerative disorder characterized by necrotizing changes in the basal ganglia and brainstem. Psychomotor retardation, seizures, nystagmus, ophthalmoplegia, optic atrophy, ataxia, dystonia, and respiratory failure are the main clinical features [4]. Most patients developed LS until 2 years of life and diseased in several days to months after the onset. LS has a heterogeneous genetic background, and mitochondrial and nuclear genes coding respiratory chain complexes or the pyruvate dehydrogenase complex are responsible for this disease [5].

The m.8344A>G mutation may rarely be a cause for LS [6]. The development of LS in a patient with the MERRF phenotype is very rare. To our knowledge, only three cases have been reported [1,2,7]. We report the case of a boy diagnosed with LS at 6 years who showed the MERRF phenotype from 2 years of age.

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2. Case report (Fig. 1)

The patient was born at term by normal delivery from nonconsanguineous parents. There was no family history of neurological disorders. Developmental milestones were normal until 1 year of age, when he could walk on his own. At 2 years, he developed astatic seizures well-controlled by valproic acid (VPA). At 3 years, he developed cerebellar ataxia with dysarthria and wide-based gait. At 4 years, he presented with atypical absence and myoclonic seizures, well-controlled with ethosuximide and clonazepam in addition to VPA.

Laboratory data at 5 years were as follows: Blood gas analysis (in vein revealed the following: pH, 7.405; pCO_2, 41.0 mmHg; pO_2, 87.7 mmHg; HCO_3^- 19.1 mmol/l; and base excess, −4.7 mmol/l. Lactate and pyruvate levels in serum were elevated to 33.2 mg/dl and 1.89 mg/dl, respectively. In the cerebrospinal fluid (CSF), lactate and pyruvate levels were 22.3 mg/dl and 1.33 mg/dl, respectively. Ictal EEG during astatic seizures at 2 years showed bilateral occipital-dominant, 3–4 Hz diffuse spike and wave complexes (Fig. 2). Visual evoked potentials (VEPs) demonstrated high amplitude. Somatosensory evoked potentials were normal. MRI revealed cerebral and cerebellar cortex atrophy. Molecular genetic analysis examined the A → G transition at position 8344 in the $tRNA^{Lys}$ gene of mtDNA. The mtDNA mutation in the investigated lymphocytes were demonstrated by the method of Yoneda et al. [8] (Fig. 4). PCR products were digested by Nae 1. The RELP analysis of PCR products generated from wild type and mutant mtDNAs. The mutation band was evaluated by measuring scanned photographs in NIH image J software (available at http://rsb.info.nih.gov/nihimage/Default.html) to determine the relative intensity. The wild type mutation was not detected in the bands, which was considered to be almost homoplasmic in this case.

After MERRF diagnosis at 4 years, VPA was discontinued and CoQ_{10} and Vit B1 were administered. At

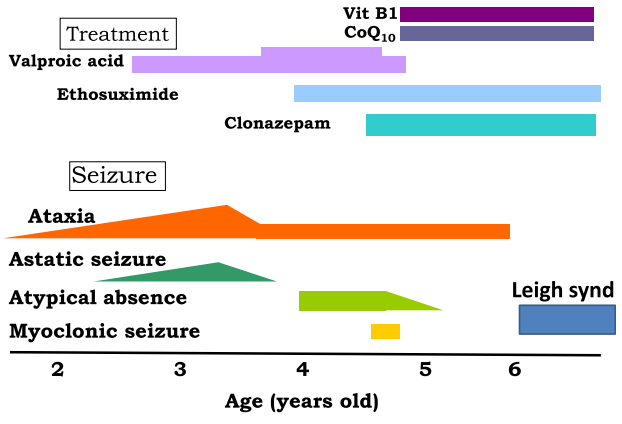

Fig. 1. Clinical course.

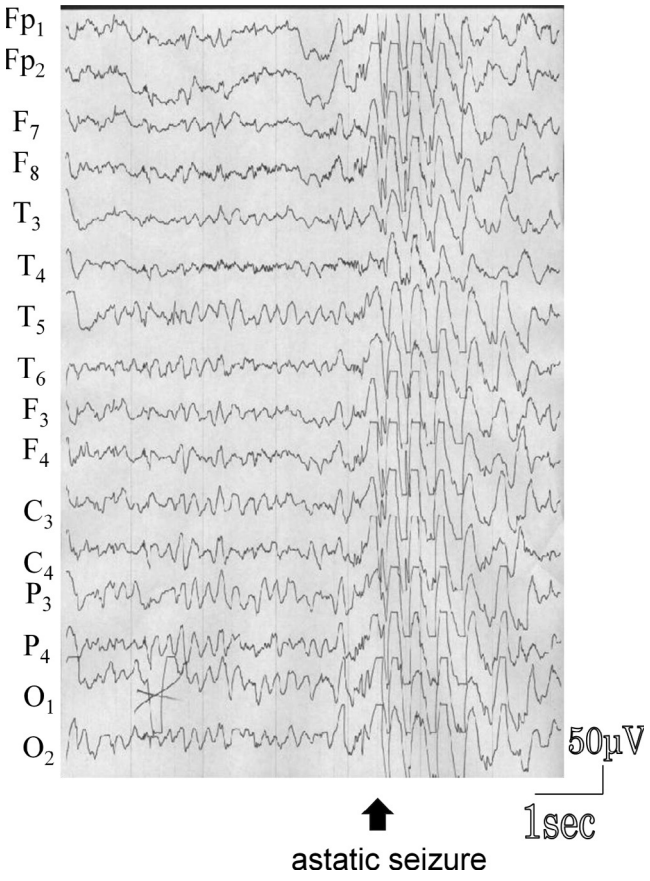

Fig. 2. Ictal EEG in astatic seizure.

6 years, he developed bacterial pneumonia with slight fever (from 98 to 100 °F) for 10 days. He did not have any neurological disturbance at that time. However, he suddenly presented with progressive bulbar palsy and marked generalized hypotonia two days after the body temperature was elevated above 102 °F. Brain T2-weighted MRI demonstrated high-signal bilateral lesions from the pons to the medulla. His consciousness slowly deteriorated, and lesions extending to the thalamus and bilateral cerebral hemispheres were noted on MRI (Fig. 3 (A)–(C)) 4–6 weeks after the initial episode. Within 6 weeks, he went into deep coma without spontaneous movements and was placed on permanent mechanical ventilation.

3. Discussion

Age of onset was 2 years; the male patient had astatic seizures with 3–4 Hz diffuse spike and wave complexes on EEG. The initial differential diagnosis was myoclonic astatic epilepsy, Dravet syndrome and Lennox–Gastaut syndrome. At 4 years, he had absences and myoclonic seizures with elevated lactate and pyruvate levels in serum and CSF and high-amplitude VEPs, and the patient was diagnosed with MERRF with almost