

Mitochondrial Encephalomyopathy Lactic Acidosis and Strokelike Episodes Mimicking Occipital Idiopathic Epilepsy

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We report on a 19-year-old man with a 9-year history of occipital seizures characterized by deviation of the eyes and tonic ipsilateral turning of the head during sleep, initially diagnosed as idiopathic childhood occipital epilepsy, Gastaut type. The eventual development of status epilepticus, associated with a T₁ hypointense as well as T₂, fluid-attenuated inversion recovery, and diffusion-weighted hyperintense brain lesion led to pathologic and genetic testing that identified a A3243G mitochondrial DNA point mutation associated with mitochondrial, encephalomyopathy, lactic acidosis, and strokelike episodes. This case emphasizes that occipital epileptic seizures can be the only presenting and long-lasting sign in patients with mitochondrial, encephalomyopathy, lactic acidosis, and strokelike episodes. © 2009 by Elsevier Inc. All rights reserved.

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Introduction

Benign childhood epilepsy with occipital paroxysms, initially described by Gastaut, is presently recognized as two distinct syndromes: early-onset benign childhood epilepsy with occipital paroxysms (Panayiotopoulos type), and late-onset benign childhood epilepsy with occipital paroxysms (Gastaut type). The two syndromes differ in terms of age of onset, clinical manifestations, and seizure frequency, while sharing similar interictal electroencephalograms. In late-onset benign childhood epilepsy with occipital paroxysms, signs begin between ages 3-16 years (mean age, 8 years), with diurnal seizures characterized by visual hallucinations that may be followed by hemi-clonic convulsions or automatism. Ictal blindness and postictal migrainous headaches are common. The interictal electroencephalogram pattern reveals runs of nearly continuous high-amplitude, rhythmic, unilateral, or bilateral posterior sharp-and-slow-wave complexes with “fixation-off” sensitivity. Psychomotor development, laboratory testing, and neuroimaging produce normal results. In more than 50% of patients, remission occurs during the late teen years [1].

Late-onset benign childhood epilepsy with occipital paroxysms must be differentiated from symptomatic occipital-lobe epilepsy associated with malformations of cortical development, tumors, vascular disease, and mitochondrial encephalomyopathies [2]. Mitochondrial, encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS), probably the most common of mitochondrial encephalomyopathies, usually presents as a multisystem disorder with a number of characteristic clinical features, including severe headache associated with episodes of vomiting, strokes, and epileptic seizures [3]. Seizures are usually partial, with a prominence of posterior interictal discharges and the presence of a photoparoxysmal response [4]. In the absence of classical clinical signs and with negative laboratory test results, the diagnosis of MELAS can be difficult.

We report on a patient who presented in infancy with occipital paroxysms and clinical findings consistent with benign childhood epilepsy, for whom a diagnosis of MELAS was established only 9 years later. Our case emphasizes that occipital epileptic seizures can be the only presenting and long-lasting sign in patients with MELAS.

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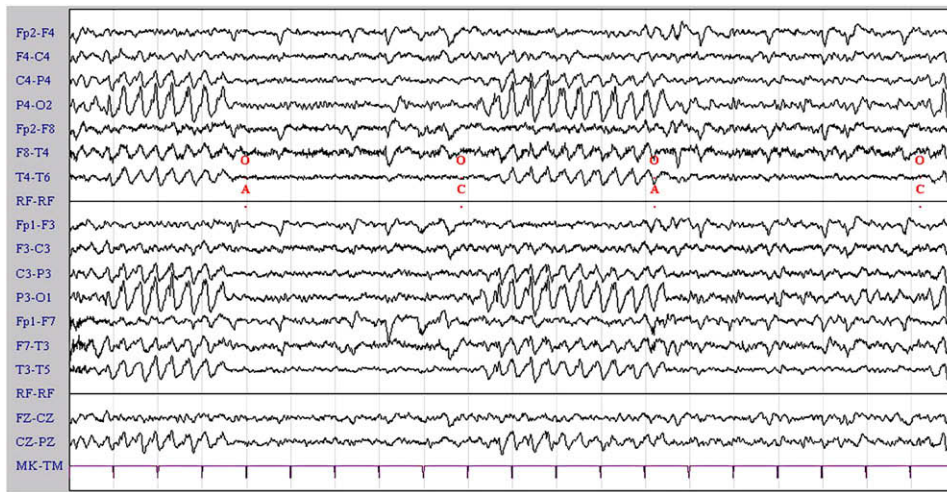


Figure 1. Interictal electroencephalogram (sensitivity, 10 $\mu\text{V}/\text{mm}$; speed, 15 mm/second). Occipital paroxysms occurred immediately after closing the eyes, and lasted as long as the eyes were closed. The electroencephalogram normalized immediately after opening the eyes, for as long as the eyes were open.

Case Report

The patient presented for the first time when he was 10 years old because of three occipital seizures, characterized by deviation of the eyes and tonic ipsilateral turning of the head during sleep. An electroencephalogram, recorded when the patient was awake, revealed frequent occipital paroxysms, as long as fixation and central vision were eliminated by closing his eyes (Fig 1). The electroencephalogram recorded during brief sleep showed a rhythmic, 2–3-Hz, high-amplitude, sharp-and-slow-wave complex that ran nearly continuously, unilaterally or bilaterally in the occipital lobe. Neurosensory evaluation, mental ability, laboratory tests including lactic acid and magnetic resonance imaging, all produced results within normal range. The patient was diagnosed with idiopathic childhood occipital epilepsy, Gastaut type. Treatment with carbamazepine resulted in complete control of his signs during the next 4 years, and then seizures with the previous characteristics reappeared. Good control was achieved with carbamazepine plus acetazolamide, and was maintained in subsequent years, allowing for a progressive reduction of therapy. Five years later, when the patient was 19 years old, seizures with the previous characteristics recurred. An extensive number of clinical and laboratory tests were performed, including measurement of the level of venous lactate, neurophysiologic examinations, hearing tests, and visual ability and cognitive

evaluation, but all results were within normal range. Carbamazepine was reintroduced, but a few months later the patient developed status epilepticus with multiple brief, partial, unilateral, left tonic seizures, and severe frontal and ocular headaches. The patient referred to elementary visual hallucinations consisting of small, multicolored circular patterns moving horizontally from the periphery to the center of his visual field that stopped when his eyes were closed. Electroencephalogram video telemetry revealed a slightly decreased amplitude of background activity, with bilateral occipital spikes and spikes-waves. Epileptiform discharges from the right occipital lobe, sometimes associated with evident clinical manifestations of leftward eye and head tonic deviation, were frequent (Fig 2). The status epilepticus persisted for 5 days, despite treatment with valproic acid, diazepam, and phenytoin, as did the migraines, that diminished only after 6 days. Magnetic resonance imaging was performed in the immediate post-seizure phase and at intervals of 1 week, 3 weeks, and 6 months.

Magnetic resonance imaging scans during the immediate postseizure phase showed a T_1 hypointense as well as T_2 , fluid-attenuated inversion recovery, and diffusion-weighted hyperintense lesion without contrast enhancement in the right occipital-polar region, involving the cortex and subcortical white matter. One week later, the lesion was significantly reduced, and after 6 months, it was barely detectable (Fig 3). Because of the atypical course of the epilepsy and the results of magnetic resonance

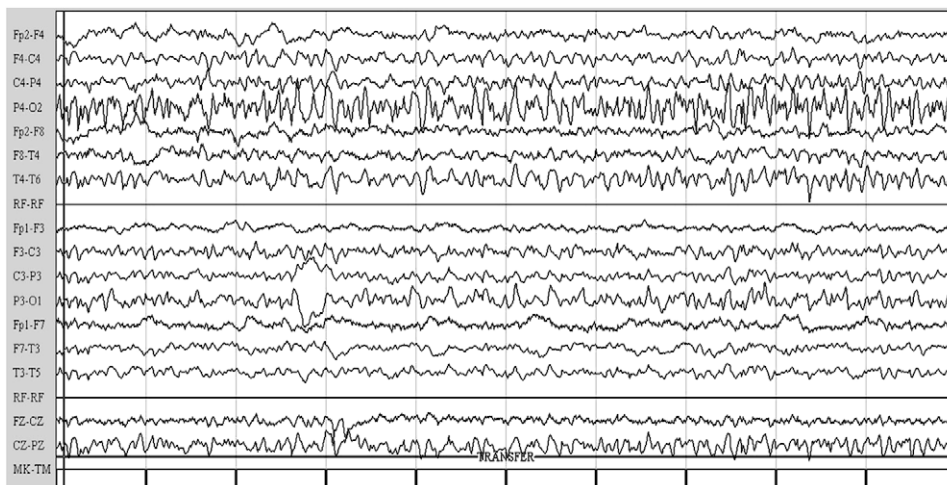


Figure 2. Ictal video electroencephalogram (sensitivity, 7 $\mu\text{V}/\text{mm}$; speed, 30 mm/second) recording depicting subcontinuous seizure discharges from the parietal-occipital region in the right hemisphere, with frontal and ocular headaches, elementary visual hallucinations, and frequent leftward eye and head tonic deviation.

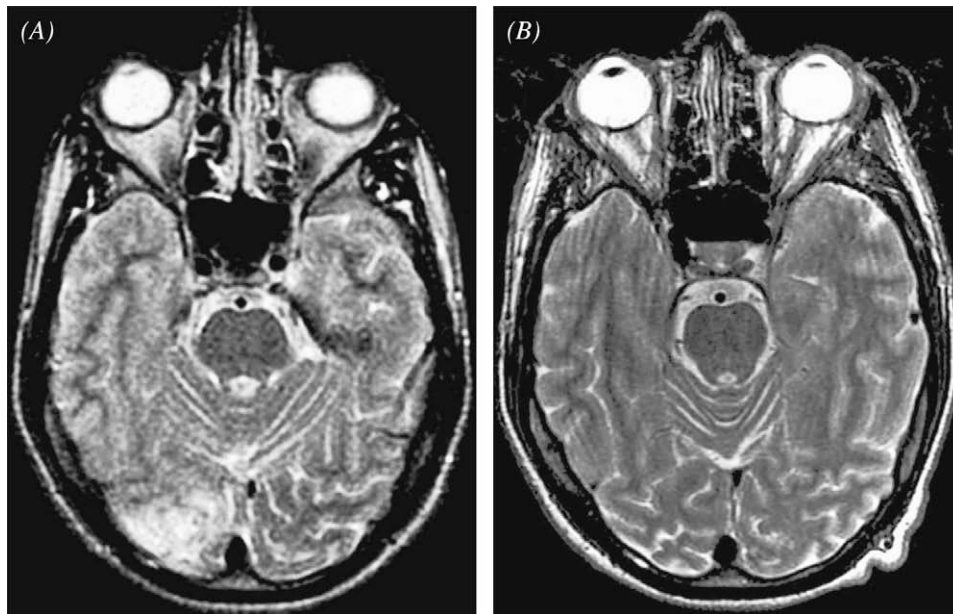


Figure 3. Magnetic strength, 1.5 T. (A) T_2 -weighted turbo spin-echo axial scan (TR/TE = 3720/85.5 ms). (B) T_2 -weighted turbo spin-echo axial scan (TR/TE = 5420/87.6 ms).

imaging, the initial diagnosis was reconsidered. In particular, an alternative hypothesis of mitochondrial encephalopathy was taken into consideration.

A muscle biopsy from the left lateral vastus muscle indicated mild variation in fiber size, scattered angular atrophic fibers intensely stained with nicotinamide-adenine-dinucleotide-tetrazolium reductase, and a single blood vessel in the perimysium whose wall was strongly stained with succinate dehydrogenase. No ragged red fibers were identified with modified Gomori trichrome, and less than 1% of the fibers were cytochrome c oxidase-negative.

Biochemical analyses, performed on frozen muscle tissue, revealed a normal pattern of respiratory-chain enzymes. Using polymerase chain reaction fragment-length polymorphism analysis, a heteroplasmic mutation was found in 40% of the mitochondrial genome of muscular fragments and in 20% of lymphocytes from peripheral blood. A A3243 G mitochondrial DNA point mutation was identified, and the patient was diagnosed with MELAS.

The family history was negative for headaches and epilepsy. The brother developed partial occipital epilepsy when he was 5 years old. Magnetic resonance imaging and neurophysiologic examinations produced normal results. Mild language delay was recognized via neurocognitive tests. An electroencephalogram revealed multifocal spikes in different brain locations (mainly in the right occipital lobe), as described in one third of patients with idiopathic childhood occipital epilepsy, Panayiotopoulos type [1]. Carbamazepine was administered, and partial good control was achieved.

The mother was free of clinical signs. A muscle biopsy obtained from her vastus lateralis produced normal results. In particular, ragged red fibers or defects of oxidative enzymes were not identified, and the expression of cytochrome c oxidase was normal. Both the mother and brother harbored the same mutation as the patient.

Discussion

The initial diagnosis of benign occipital epilepsy was based on characteristics of the seizures, i.e., visual signs, often followed by hemiclonic manifestations or automatisms. Electroencephalograms indicated high-voltage repetitive occipital spike/sharp and slow waves suppressed by eye-opening, and good control of the seizures was achieved with two drugs for a long time. The clinical diagnosis was substanti-

ated by the absence of signs of multisystemic involvement and normal results of laboratory tests and brain imaging.

Childhood occipital epilepsy, as described by Gastaut (1982) [1], is rare, of uncertain boundaries, and often of unpredictable prognosis. This “Gastaut type” of childhood occipital epilepsy is characterized by brief seizures with mainly visual signs, such as elementary visual hallucinations, illusions, or amaurosis, followed by hemiclonic convulsions. Postictal migraine headaches occur in half of the patients, and the age at onset is around 8-9 years. Electroencephalograms indicate occipital spike-wave paroxysms that attenuate when the eyes are open, and these paroxysms are called “fixation-off-sensitivity” [5]. Gastaut and Zifkin hypothesized that the occipital paroxysms are attributable to a subclinical thalamocortical mechanism, thus explaining the rhythmic spike-and-wave complexes arising with eye closure or intermittent photic stimulation over an intact occipital lobe [6].

Initially, fixation-off-sensitivity was described only in idiopathic occipital childhood epilepsy [5,7], but it has also been reported also in cryptogenic generalized epilepsies [5], and in exceptional symptomatic cases. It was suggested that in symptomatic cases, damage in the occipital cortical area might result in an increased instability of neuronal membranes, and the activation of neurons for central vision may be an important inhibitory factor in the suppression of epileptic discharges [8].

Seizures are common in MELAS. Partial seizures from the occipital lobe are most common, but generalized myoclonic, tonic-clonic manifestations were also reported [4]. Seizures are often associated with strokelike episodes and usually follow them. Specific electroencephalographic features are absent.

Although MELAS has been described with diverse clinical presentations, it usually presents during childhood or adolescence with severe headache, vomiting, and deafness,

and it is unresponsive to conventional anticonvulsive drugs. Status epilepticus is associated with strokelike episodes. Magnetic resonance imaging reveals infarct-like lesions that are commonly parieto-occipital, and not confined to the vascular territories [2,9].

Diagnostic muscle biopsy in patients with MELAS exhibits a combination of ragged-red fibers and strongly succinate-dehydrogenase-reactive blood vessels. However, these changes are evident only in a minority of patients. Most commonly, a biopsy demonstrates a number of modifications that can be misleading, such as small angulated and nicotinamide-adenine-dinucleotide-tetrazolium reductase hyperactive fibers, suggesting neurogenic atrophy [10]. In our patient, the only significant histologic finding was of a single blood vessel with a succinic dehydrogenase hyperactive wall, and this finding was considered sufficiently suspicious to prompt additional tests, to confirm a mitochondrial disease. Ragged-red fibers and cytochrome c oxidase hyperactive fibers were notably absent.

The absence of abnormalities on muscle biopsy is rather common in children [11], and reinforces the idea that biochemical and genetic testing should be performed in the presence of suspicious clinical findings, even in the absence of abnormalities on muscle biopsy. It is worth considering that the mother of the patient, harboring the same mutation, was completely free of signs, and her muscle biopsy produced results within normal range, without abnormalities in the structure of fibers, and no succinic dehydrogenase hyperactive blood vessels.

A diagnosis of MELAS can be suspected according to three invariant criteria: strokelike episodes before age 40 years; encephalopathy characterized by seizure, dementia, or both; and lactic acidosis, ragged red fibers, or both [12]. Our patient was only 19 years old, and thus the full repertoire of signs were not completely manifest, but the absence of multisystemic involvement led to a diagnosis of idiopathic occipital epilepsy.

In conclusion, the slow course of the disease (which is unusual in this mutation), the absence of typical strokelike episodes, and the benign course of the epilepsy all contributed to delaying the final diagnosis of MELAS in our patient.

Conclusions

Mitochondrial respiratory-chain disorders represent a challenge to clinicians, because the clinical presentation

and course demonstrate enormous variation [11,13]. We described a patient with genetically proved MELAS whose clinical signs were represented exclusively for many years by occipital epilepsy, with electroencephalogram and clinical findings consistent with idiopathic benign occipital epilepsy. The evolution of epilepsy into status epilepticus, modifications of the type of seizures, and the detection of a lesion on magnetic resonance imaging were the main clues that led to the final diagnosis 9 years later. Mitochondrial disorders should be taken into account in patients with clinical and electroencephalogram features of idiopathic epilepsy, even in the absence of multisystem involvement.

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