

Case report

Intestinal pseudo-obstruction in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) associated with phenytoin therapy

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Received 28 August 2007; received in revised form 1 December 2007; accepted 4 December 2007

Abstract

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is most commonly associated with a mitochondrial DNA A to G point mutation at nucleotide 3243 (A3243G) and individuals with the disorder present a wide range of multisystemic symptoms. Seizures in MELAS patients are often intractable and require multiple antiepileptic drugs. Here we report a MELAS patient who presented with acute intestinal pseudo-obstruction following the administration of phenytoin (PHT) as an antiepileptic treatment. She presented with the first stroke-like episode at the age of 6 years and mitochondrial DNA analysis revealed A3243G with 94% mutation load in skeletal muscle. Despite treatment with phenobarbital and clobazam at the age of 16 years, she developed status epilepticus which ceased following PHT infusion. Thereafter, she was started on PHT treatment. One month later, however, she was readmitted because of remarkable abdominal distention. Although abdominal CT showed acute ileus with hepatic portal venous gas mimicking surgical emergency, the abdominal distention gradually recovered over several days following the discontinuation of PHT. Our clinical observations suggest the possibility that intestinal pseudo-obstruction in this patient related to PHT therapy. Careful clinical observation including gastrointestinal symptoms is required in the management of epilepsy in MELAS patients.

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Keywords: MELAS; Intestinal pseudo-obstruction; Phenytoin

1. Introduction

Mitochondrial disorders are a heterogeneous group of diseases that affect mitochondrial energy metabolism and result in a wide range of multisystemic symptoms.

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) is typically characterized by childhood-onset neurological deficits, lactic acidosis, seizures, and ragged-red fibers (RRF) in striated muscle biopsy specimens. A heteroplasmic A to G mutation in the transfer RNA (tRNA)^{Leu(UUR)} gene at position 3243 of the mtDNA (A3243G) accounts for most MELAS cases, and the percentage of the mutant

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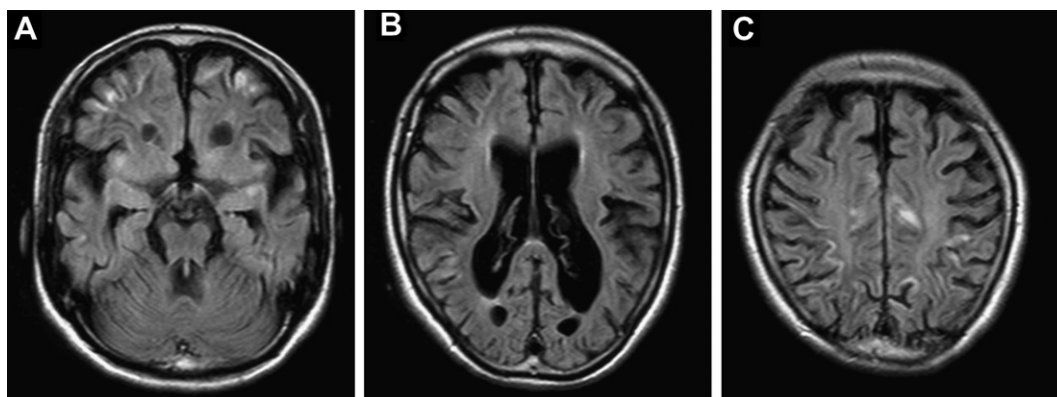


Fig. 1. Axial brain magnetic resonance imaging by fluid-attenuated inversion-recovery obtained at the age of 15 years. Atrophy of the cerebrum and a multifocal gyral pattern of hyperintensity over the frontal and parietal lobes were evident (A–C).

form determines disease expression [1]. Patients also may have short stature, hearing loss, progressive dementia, and migraine-like headache.

Gastrointestinal manifestations in patients with mitochondrial encephalomyopathies are highly variable. Several mitochondrial encephalomyopathies with severe gastrointestinal dysmotility have been reported, and it has been proposed that these variations should be subclassified as mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) [2]. With the advance of molecular genetics, it has been demonstrated that MNGIE is an autosomal recessive disorder caused by nuclear DNA mutations in the thymidine phosphorylase (TP) gene [3]. Here, we report a MELAS patient harboring the A3243G mutation, who presented acute intestinal pseudo-obstruction following the administration of phenytoin (PHT) as an antiepileptic treatment. After discontinuation of PHT, intestinal distention resolved with conservative management.

2. Case report

This female patient was born at full term after an uneventful pregnancy to healthy, nonconsanguineous parents. Although early development was normal, she presented with the first stroke-like episode at the age of 6 years. Laboratory evaluation demonstrated significant elevations of lactate (42.9 mg/dl) and pyruvate (2.10 mg/dl) in venous blood, and marked elevations of lactate (25.2 mg/dl) and pyruvate (1.22 mg/dl) in the cerebrospinal fluid. A muscle biopsy showed abundant RRF. Genetic analysis of mtDNA demonstrated the presence of the A3243G mutation in muscle and lymphocytes from the patient, which confirmed the diagnosis of MELAS. This mutation was detected in a heteroplasmic status in the patient's skeletal muscle at a level of 94%. She was treated with L-carnitine, coenzyme Q10, B-complex vitamins, and dichloroacetate. The patient repeatedly experienced seizures despite treatment with phenobarbital (PB) and carbamazepine

(CBZ), and her psychomotor development gradually declined. At the age of 11 years, her seizures were intractable, and CBZ was replaced by zonisamide (ZNS). Two weeks later, however, poor appetite and vomiting were observed. After discontinuation of ZNS, gastrointestinal symptoms soon improved. Thereafter, she was treated with PB (90 mg/day) and clobazam (CLB) (10 mg/day), and the frequency of seizures decreased. She experienced no obvious gastrointestinal symptoms thereafter. At age 15 years, a fluid-attenuated inversion-recovery brain magnetic resonance imaging demonstrated atrophy of the cerebrum and a multifocal gyral pattern of hyperintensity over the frontal and parietal lobes (Fig. 1).

At age 16 years, she was admitted to the emergency room with status epilepticus. Intravenous midazolam (MDL) was ineffective, but status epilepticus ceased after a loading dose of PHT (20 mg/kg) infusion. Following this episode, she was treated with PB (90 mg/day) and PHT (140 mg/day) for seizure control. Twenty days after that episode, complex partial seizures recurred and her serum PHT concentration was 7.54 $\mu\text{g/ml}$. Therefore, she was administered an additional dose of PHT, a total of 180 mg/day. Two weeks after the dose of PHT was increased, the patient was readmitted because of remarkable abdominal distention. On physical examination, she was found to have a grossly distended abdomen which was tympanitic and without bowel sounds. An abdominal X-ray demonstrated remarkably dilated intestinal loops (Fig. 2). Abdomino-pelvic CT did not demonstrate signs indicating either a definite obstructive level or bowel wall thickening, although the presence of hepatic portal venous gas, which is usually associated with a poor prognostic condition requiring urgent surgical intervention, was noted (Fig. 3). Results of laboratory tests were as follows: white blood cell count 7400/ μl , hemoglobin 13.7 g/dl, C-reactive protein 20.7 mg/dl, total protein 8.2 g/dl, albumin 4.4 g/dl, aspartate aminotransferase 65 IU/l, alanine aminotransferase 48 IU/l, lactate dehydrogenase



Fig. 2. Plain abdominal X-ray demonstrated remarkably increased duodenum–ileum gas.

493 IU/l, and creatine kinase 295 IU/l. Serum PHT concentration was 9.13 $\mu\text{g}/\text{ml}$. Serum free T3, free T4, and TSH were 0.98 pg/ml , 0.63 ng/dl , and 2.64 $\mu\text{U}/\text{ml}$, respectively. A nasogastric tube was inserted to achieve gastrointestinal decompression, and lactate-free fluid and antibiotics were administered intravenously. Next day, however, abdominal distention persisted. Although the serum concentration of PHT was not within a toxic range, we suspected that the abdominal complication related to PHT administration because of the clinical time course. We discontinued PHT administration, and her abdominal distention gradually recovered over the next several days. Radiological enteroclysis demonstrated intestinal dysmotility, but there was no

mechanical obstruction. One week after the discontinuation of PHT, her serum free T3, free T4, and TSH were 2.72 pg/ml , 1.03 ng/dl , and 3.01 $\mu\text{U}/\text{ml}$, respectively.

After resolution of intestinal pseudo-obstruction, she was treated with PB (90 mg/day), L-carnitine, co-enzyme Q10, B-complex vitamins, dichloroacetate, and mosapride citrate. Two weeks after the discontinuation of PHT, however, she developed epilepsy partialis continua (EPC) on her right leg. EPC disappeared after administration of an additional dose of CLB (15 mg/day).

3. Discussion

Epilepsy is one of the most difficult problems of patients with MELAS. Seizures in MELAS patients are often intractable and require multiple antiepileptic drugs (AED). It remains unclear which AED is most appropriate to treat seizures in MELAS. Valproate, which causes a reduction of serum carnitine and inhibition of β -oxidation, is thought to be inappropriate for mitochondrial disease. In addition, individuals with mitochondrial diseases may be at high risk for valproate-induced fulminant liver failure [4]. Despite treatment with PB and CLB, our case developed status epilepticus which ceased after PHT infusion. CLB was then replaced by PHT. However, the patient developed abdominal distention thereafter. Although she presented with acute ileus with hepatic portal venous gas mimicking surgical emergency, the abdominal symptom gradually recovered several days after discontinuation of PHT. Furthermore, since she has not developed a recurrence of such severe abdominal symptoms to date, the intestinal pseudo-obstruction in this patient probably related to PHT therapy.

Gastrointestinal manifestations in patients with mitochondrial encephalomyopathies are highly variable. Gastrointestinal dysmotility is a cardinal feature of MNGIE, which is a unique autosomal recessive multisystem disorder with mtDNA alterations, such as partial depletion, multiple deletions or both. Recent investigations

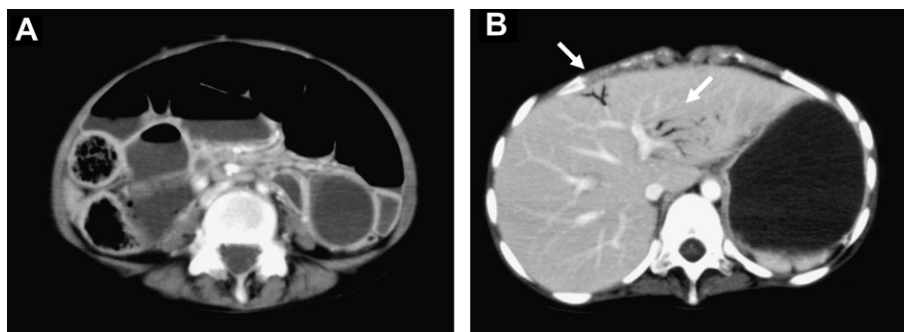


Fig. 3. Abdomino-pelvic CT demonstrated remarkably increased duodenum–ileum gas with air-fluid levels (A). Arrows indicate hepatic portal venous gas, which is usually associated with a poor prognosis (B).

demonstrated that MNGIE is caused by loss-of-function mutations in the nuclear-encoded TP gene, and increased thymidine causes a mitochondrial nucleotide pool imbalance that leads to mtDNA alterations in MNGIE [3]. On the other hand, severe gastrointestinal complications occasionally occur also in MELAS patients harboring the A3243G mutation. There are some case reports describing MELAS patients harboring the A3243G mutation presenting with ileus [5–7]. Previous reports suggest that the mechanism of ileus in MELAS is intestinal pseudo-obstruction due to intestinal dysmotility rather than mechanical obstruction, although only one case was diagnosed with intestinal strangulation [5]. Although the exact pathogenesis of intestinal dysmotility in MELAS patients has yet to be determined, previous reports described similar electron microscopic findings, particularly accumulation of numerous enlarged, abnormal mitochondria that are observed not only in the intestinal smooth muscle cells but also in the intestinal ganglionic neurons [6]. These electrosopic findings of abnormal mitochondria indicate that an energy metabolism defect is responsible for intestinal dysmotility in MELAS. The wide variation in the severity of intestinal dysmotility among individuals of MELAS may be due to the effects of heteroplasmy. Furthermore, subclinical intestinal dysmotility may have been present in our case, although there were no obvious gastrointestinal symptoms before PHT administration.

The mechanism by which phenytoin induced severe intestinal dysmotility in this patient remains unclear. Normal gastrointestinal motility requires the tight regulation of ion channels expressed in smooth muscle cells and interstitial cells of Cajal (ICC). Sodium channels are indeed expressed on gastrointestinal smooth muscle cells and ICC, and can regulate contractile activity [8]. PHT exerts its anticonvulsant action through blockade of the sodium channel, so administration of PHT might have altered her gastrointestinal motility. Although other AED, including CBZ or ZNS, may alter gastrointestinal motility from this point of view, she had not developed intestinal pseudo-obstruction when she had been administered CBZ or ZNS. Considering the progressive nature of MELAS, her gastrointestinal motility might have decreased subclinically with age and be worsen by PHT therapy, resulting in severe intestinal pseudo-obstruction. In addition, abnormality of the thyroid hormones is commonly associated with alterations of bowel function. Hypothyroidism decreases intestinal motility, whereas hyperthyroidism increases intestinal

motility [9]. Serum thyroid hormone levels are decreased in patients receiving some AED, including PHT or CBZ, although most patients appear clinically euthyroid and have normal serum TSH concentrations [10]. In our case, serum free T3 and free T4 levels were low when she developed intestinal pseudo-obstruction and normalized after discontinuation of PHT. Therefore, decreased levels of thyroid hormones might have partly influenced intestinal dysmotility in this case.

Our clinical observations suggest the possibility that intestinal pseudo-obstruction in this patient related to PHT therapy. Since intestinal pseudo-obstruction in MELAS patients may have a fatal outcome, careful clinical observations including gastrointestinal symptoms should be paid for the management of epilepsy in MELAS patients.

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