Transient Postictal Hyperglycemia as a Diagnostic Clue of Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes

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Abstract

Purpose: To propose that transient postictal hyperglycemia as a diagnostic clue of mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS).

Case Report: We reported two non-diabetic patients presenting with generalized seizure and transient postictal hyperglycemia. At the acute stage, both patients had hyperglycemia with serum glucose levels >400 mg/dl, normal glycated hemoglobin (HbA1C) levels, normal ketone body levels, and no infection signs. Within three days of the seizure event, both patients were euglycemic and did not require any diabetes treatment. Brain MRI examination revealed gyriform restricted diffusion at bilateral superior temporal gyri in one patient, and diffuse cerebral and cerebellar atrophy without restricted diffusion lesions in the other. Polymerase chain reaction and restriction fragment length polymorphism (RFLP) analysis confirmed that both patients harbored the m.3243A>G mutation.

Conclusion: Seizure-induced stress hyperglycemia is uncommon in normal individuals, but such kind of energy crisis may be pronounced in patients with mitochondrial dysfunction. Early diagnosis of mitochondrial diseases-related epilepsy and hyperglycemia is crucial since certain antiepileptic drugs (ex. Valproic acid) and antihyperglycemic agents (ex. Metformin) are contraindicated in patients with mitochondrial diseases. Our findings support that transient postictal hyperglycemia may be a red flag to consider the diagnosis of MELAS.

Keywords: m.3243A>G; MELAS; mitochondrial disease; transient postictal hyperglycemia.

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INTRODUCTION

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) (MIM #540000) is a mitochondrial disorder that manifests with various neurological manifestations, including seizure, stroke-

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like episode, cognitive impairment, headache, myopathy, exercise intolerance, visual disturbance and gait disturbance[1]. Approximately 80% of MELAS cases are caused by the m.3243A>G mutation in the mitochondrially encoded tRNA leucine 1 (UUA/G) gene (MT-TL1)[2]. Individuals with m.3243A>G mutation may also develop diabetes mellitus (DM), hearing loss, short stature and heart diseases[3]. Despite both seizure and hyperglycemia are common manifestations of MELAS, the reports focusing on the phenomenon of postictal hyperglycemia in non-diabetic MELAS subjects are still sparse[4,5]. Here, we reported two patients with m.3243A>G mutation suffering from first-time seizure and transient postictal hyperglycemia.

CASE REPORTS

Patient A was a 38-year-old woman called at the emergent room for sudden onset consciousness change and generalized convulsion. She had headache and dizziness for a few days and developed clusters of generalized tonic-clonic seizure suddenly. Blood examination showed marked leukocytosis (WBC = 30600, Seg/Lym = 77/16), lactic acidosis (lactate = 84.8 mg/dl; arterial blood gas: pH = 7.14, pCO_2 = 44, HCO_3 = 13.9), hyperglycemia (serum glucose = 498 mg/dl), but normal glycated hemoglobin (HbA1C 5.3%). The patient was afebrile and her serum C-reactive protein value was 0.85 mg/dl. Brain CT showed mild calcification in bilateral globus pallidi. Fluid-attenuated inversion recovery (FLAIR) images of brain revealed hyperintensity over bilateral anterior temporal regions and diffusion weight images (DWI) showed gyriform hyperintensity at the cortex of corresponding regions (Fig. 1a-c). After insulin infusion and anti-epileptic agent treatment, she was free of seizure on day three. Fasting sugar levels were 122 mg/dl on day three and 99 mg/dl on day five without any antihyperglycemic agent. She was clear of diabetes medication after discharge, and remained diabetes-free until seven years after the first seizure event (last HbA1c = 5.4%). Tracing back the patient's personal and family histories, she had short stature and several of her maternal relatives suffered from diabetes and short stature. The patient developed progressive hearing loss after the seizure event and had been admitted twice at age 45 for stroke-like episodes. Status epilepticus with cluster attacks of generalized tonic-clonic seizure occurred repeatedly at age 46 and the patient died of pneumonia later. Polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) assay[6] confirmed the patient carried the m.3243A>G mutation with 25% heteroplasmy of the mutation in the peripheral blood leukocytes (Fig. 2).

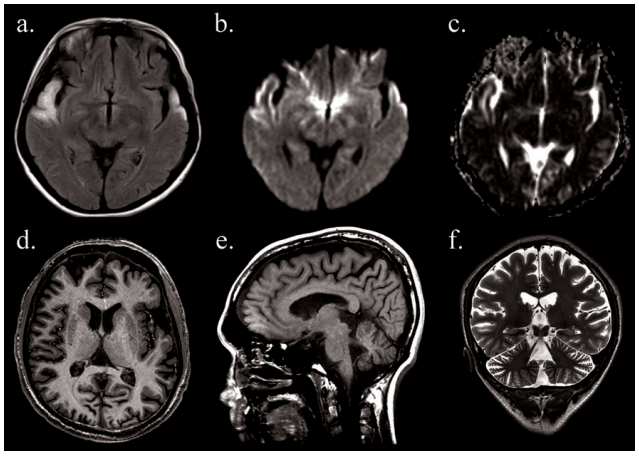

Fig. 1. Brain MRI of the two patients with m.3243A>G mutations in this study.
Representative brain MRI images of Patient A revealed (a) white matter hyperintensity lesions at the axial T2 and fluid-attenuated inversion recovery (FLAIR) images, and (b, c) diffusion restriction lesions at the diffusion weight images/apparent diffusion coefficient map (DWI/ADC). (d-f) Representative brain MRI images of Patient B showed generalized atrophy over cerebral and cerebellar hemispheres in the axial and, sagittal T1-weighted images and coronal T2-weighted images.

Patient B was a 26-year-old man with short stature and exercise intolerance since childhood. He had tinnitus and progressive hearing loss since age 23 years. At age 26, he experienced sudden onset vertigo followed by generalized tonic-clonic seizure. Upon arrival at the emergent room, he was comatose with Glasgow coma scale of E1V2M5 and regained conscious gradually within 40 minutes. Blood examination showed prominent lactic acidosis (lactate = 80.8 mg/dl; arterial blood gas: pH = 6.81, pCO_2 = 40, HCO_3 = 6.4) and leukocytosis (WBC = 47620, Band/Seg/Lym = 6/70/11). Serum glucose level was above the testing limit of the glucose meter (>400 mg/dl), but his HbA1c was 5.8% and serum ketone body showed negative finding. After insulin pump and anti-epileptic treatment, he was free of seizure and fasting glucose level was 78 mg/dl on day three without any diabetes medication. CRP was 0.35 mg/dl and the infection survey including CSF analysis yielded no remarkable findings. Brain CT revealed bilateral moderate globus pallidi calcification, and brain MRI showed generalized cerebral and cerebellar atrophy without hyperintensity lesions on FLAIR or DWI (Fig. 1d-1f). The patient suffered from poor appetite with body mass index (BMI) of 14.4 kg/m^2. His maternal grandmother had hearing impairment, but his mother and siblings did not have any neurological symptoms, diabetes or hearing impairment. PCR-RFLP assay confirmed the patient harboring the m.3243A>G mutation with 46% heteroplasmy of the mutation in the peripheral blood leukocyte (Fig. 2). The patient's fasting glucose level was 86 mg/dl without antihyperglycemic agent three years later. He was never diagnosed with diabetes and deceased suddenly at age 32.

DISCUSSION

In this report, two unrelated patients carrying the MELAS mutation, m.3243A>G, presented with generalized seizures and transient severe postictal hyperglycemia before their molecular diagnoses were confirmed. Similarly, Liou reported a 35-year-old female with m.3243A>G mutation and Toki described a 4-year-old girl with MELAS-Leigh syndrome developed hyperglycemia after seizure[4,5]. Unlike our cases were free from diabetes for years, both their patients continued to use diabetes medication for the new-onset DM. Although seizure events could provoke the release of stress hormones such as catecholamines[7,8] and corticosteroids[9-11], which subsequently aggravate gluconeogenesis and glycogenolysis, the averaged increase of serum glucose in postictal state comparing with baseline serum glucose is only 14% in general populations with epilepsy[12]. However, in our patients and

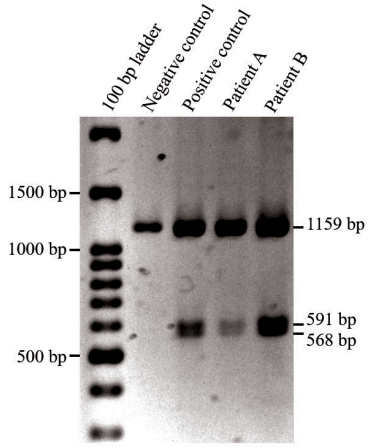

Fig. 2. Polymerase chain reaction and Restriction fragment length polymorphism (PCR-RFLP) analysis
Total DNA was prepared from blood cells of two patients and control individuals. The PCR products amplified from each DNA sample were digested with Apa I and electrophoresed on an agarose gel. Bands of 1159 bp and 591/568 bp denote DNA bands from wild type and mutant mtDNA, respectively. The heteroplasmy rates of m.3243A>G mutation in the peripheral blood leukocyte were 25% and 46 % in patient A and patient B as measured by the ImageJ software (https://imagej.nih.gov/).

the two historical cases, the postictal glucose levels (498 – 623 mg/dl) increased by fourfold to fivefold, suggesting that mitochondrial DNA mutation may play a role in the severe postictal hyperglycemia.

Mitochondrial dysfunction could impair glucose homeostasis through insulin deficiency and insulin resistance, both leading to increased susceptibility to stress hyperglycemia. First, patients with mitochondrial disease had impaired pancreatic beta cell insulin secretion at oral glucose tolerance test, glucagon test and hyperglycemic clamp test[13-18], as well as decreased beta cell mass[19, 20]. Second, positron emission tomography[15] and magnetic resonance spectroscopy[21] studies revealed a decreased skeletal muscle glucose uptake in patients with m.3243A>G mutation, suggesting insulin resistance in these subjects. These studies demonstrated how mitochondrial dysfunction causes derangement of glucose metabolism, which in terms makes patients vulnerable to glucose fluctuations.

Regarding m.3243A>G MELAS patients, diabetes and first-time seizures are both common presentations before age 40[3]. By the time of the first seizure event, asymptomatic individuals with m.3243A>G mutation may be already in the prediabetes status. Therefore, postictal hyperglycemia is induced by gluconeogenesis under the stress of the seizure, combined with underlying insulin insufficiency and insulin resistance. Although less preferred, the alternative hypothesis is that seizure is the consequence of hyperglycemia in patients with m.3243A>G MELAS. Overt diabetes is commonly observed in m.3243A>G MELAS patients, but several reports have shown that m.3243A>G carriers usually present with hyperglycemic crises but rarely with concomitant seizure attacks[5,22]. Considering both our patients having normal HbA1c values, negative serum ketone levels, no dehydrated status or infection, we favored both cases had transient postictal hyperglycemia rather than hyperglycemic crises-induced seizure.

In conclusion, we reported two unrelated patients with MELAS presenting with transient severe postictal hyperglycemia. These findings suggest that for adults with unprovoked seizure and severe transient hyperglycemia, measuring lactate levels in serum or CSF, analyzing blood gas, and querying for family history of diabetes, short statue, or hearing impairment are important to identify clues for early diagnosis of MELAS. Accurate diagnosis of mitochondrial diseases-related epilepsy and hyperglycemia is crucial since certain antiepileptic drugs (ex. Valproic acid) and antihyperglycemic agents (ex. Metformin) are contraindicated. Our report also underscores that transient postictal hyperglycemia may be a red flag to consider the diagnosis of MELAS.

Conflicts of Interest Statement

The authors have no conflicts of interest to disclose.

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