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MELAS and Kearns–Sayre overlap syndrome due to the mtDNA m. A3243G mutation and large-scale mtDNA deletions

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ABSTRACT

This paper reported an unusual manifestation of a 19-year-old Chinese male patient presented with a complex phenotype of mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome and Kearns–Sayre syndrome (KSS). He was admitted to our hospital with the chief complaint of "acute fever, headache and slow reaction for 21 days". He was initially misdiagnosed as "viral encephalitis". This Chinese man with significant past medical history of intolerating fatigue presented paroxysmal neurobehavioral attacks that started about 10 years ago. During this span, 3 or 4 attack clusters were described during which several attacks occurred over a few days. The further examination found that the hallmark signs of this patient included progressive myoclonus epilepsy, cerebellar ataxia, hearing loss, myopathic weakness, ophthalmoparesis, pigmentary retinopathy and bifascicular heart block (Wolff–Parkinson–White syndrome). By young age the disease progression is characterized by the addition of migraine, vomiting, and stroke-like episodes, symptoms of MELAS expression, which indicated completion of the MELAS/KSS overlap syndrome. The m. A3243G mitochondrial DNA mutation and single large-scale mtDNA deletions were found in this patient. This mutation has been reported with MELAS, KSS, myopathy, deafness and mental disorder with cognitive impairment. This is the first description with a MELAS/KSS syndrome in Chinese.

1. Introduction

Since the identification of the first pathogenic mutations in human mitochondrial DNA (mtDNA) in 1980, hundreds of large-scale mtDNA rearrangements and over 200 mtDNA point mutations have been described [1]. Different mtDNA mutations may demonstrate many presentations. Among the clinical presentations of mitochondrial disorders, there are several merges as distinctive entities: mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), myoclonus epilepsy with ragged-red fibers (MERRF), Kearns–Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO) and Leigh disease.

Point mutations of mtDNA, mostly in transfer RNA (tRNA) genes, have been described in the patients with syndromes of MELAS and MERRF, usually causing a wide spectrum of syndromes [2]. MELAS syndrome is commonly associated with an A to G transition at nt 3243 of the mtDNA. In contrast, KSS is a mitochondrial disorder characterized by the early-aged onset of progressive external ophthalmoplegia or pigmentary retinopathy, together with at least one of a triad of cerebellar ataxia, heart block and elevated cerebrospinal fluid protein [3]. Typically, KSS is due to single large-scale mtDNA deletions and is almost always sporadic.

Although some mtDNA mutations tend to be associated with specific clinical syndromes, genotype–phenotype correlations are imprecise. Reportedly many individuals who harbor a pathogenic mtDNA mutation manifest overlapping features of typical mitochondrial syndromes [4]. Because there is presently no curative treatment to mitochondrial diseases, the early definitive diagnosis is very important.

Here, we report another case of an overlap syndrome with features of MELAS and KSS in which there are correspondingly double mutations of m. A3243G mitochondrial DNA mutation and single large-scale mtDNA deletions.

2. Patients and methods

On Jul. 11th 2013, a 19-year-old man was first admitted to our department with the chief complaint of "acute fever, headache and slow reaction for 3 weeks". Some cold symptoms appeared on Jun. 20th, 2013, followed by obvious eye pain. Subsequently, he manifested fever, headache, malaise, nausea and vomiting. Meanwhile, his family found him unresponsive with cognitive disorders, memory and computing power loss. Past history: patient with significant past medical history of intoleratting fatigue presented paroxysmal neurobehavioral attacks that started about 10 years ago. Patient denies diabetes, drugs

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and food allergies, and infectious hepatitis and tuberculosis. No smoking, alcohol, nor illicit substance abuse. Family history: his mother had migraine headache for over 20 years and his grandmother was diagnosed with diabetes for 35 years. No other family members presented with similar features.

Neurological examination: T 38.6 °C, BP 110/70 mmHg, HR 80 bpm, weight 40 kg, height 139 cm. Awake and alert, fluent to the point, poor calculation. When written down, he is able to read it aloud. Speech is slightly hesitant with apparent word finding difficulties. He seems easily confused, perhaps contributed by hearing deficits. Round bilateral pupillary diameter of 3.0 mm, light responsive. The muscle bulk is small. His motor and sensation may normal.

Brain magnetic resonance imaging showed large abnormal signal on the right temporal lobe and the left temporal lobe, with the impression of viral encephalitis or vascular lesions. Proton MRS showed an elevated lactate level in involved regions of the brain; the lactate peak disappeared in old areas of T2 prolongation (Fig.1). ECG showed WPW syndrome. CSF studies: cranial pressure 180 mm H_2O, protein 0.71 g/L, glucose 3.5 mmol/L, chloro 118.2 mmol/L, IgG 43.6 mg/L. EEG showed atypical irregular 2.5–3.5 Hz spike and wave complexes. Based on the above history, symptoms and lab tests, he was initially misdiagnosed with "viral encephalitis". After 2 days of anti-viral treatment, the patient presented significant psychiatric symptoms, such as the contents of hallucination, soliloquise and emotional irritability with no insight.

In order to further confirm the diagnosis, the min exercise testing of lactic acid was done. The venous blood lactate concentration was detected: 5.6 mmol/L at resting level (normal <1.2), 12.1 mmol/L after 10 min movement (normal <3.6), 11.6 mmol/L after 10 min rest (normal <2.0). Laboratory tests revealed a mildly elevated creatine kinase of 398 U/L (normal <200) with normal glucose, thyroid function tests, parathyroid hormone, and liver function panel.

His mitochondrial gene was tested by bidirectional DNA sequencing analysis (Homo mtDNA No. NC-012920.1 as a control) with High-resolution agarose gel electrophoresis. Total genomic DNA was extracted from whole blood cells, isolated leukocytes and thrombocytes. We also compared the levels of the mtDNA mutation in blood with the level of urinary epithelial cells in this patient, as mutation levels are known to decrease in blood over time, while in some patients it may be absent. About 350 mL of the first morning urine was obtained after a 10 min-exercise, so as to increase the amounts of urinary epithelial cells. The heteroplasmic ratio of the mutant to normal mtDNA results of genetic tests showed the heteroplasmic ratio of the mutant to normal mtDNA: the m. A3243G mitochondrial DNA mutation (15% in leukocytes and 78% in urinary epithelial cells) and single large-scale mtDNA deletions (from 8470 to 13,446, totally 4977 bp, only found in urinary epithelial cells) in this patient (Fig.2).

Then the patient was diagnosed with mitochondrial encephalomyopathy and received nerve nutrition and symptomatic treatment. On Jul. 19th 2013, his family required discharged to outside hospital for further treatment.

On Aug. 24th 2013, the patient was secondly admitted with the complaint of "acute right limb convulsions and weakness for 1 week". He could not walk independently with progressive loss of balance and gait instability with leg weakness. He also suffered transient stroke-like episodes, consisting of initial headache and vomiting. In the ward, he developed myoclonus epilepsy. MRI again showed a large acute-to-subacute lesion over the right parietal–occipital–temporal region (Fig.3).

Neurological examination revealed mild clumsiness of rapid alternating movement and fine finger movements on the left, and a Romberg sign. Further examination showed atypical pigmentary retinopathy with normal optic discs, and abnormal eye movements with right eye

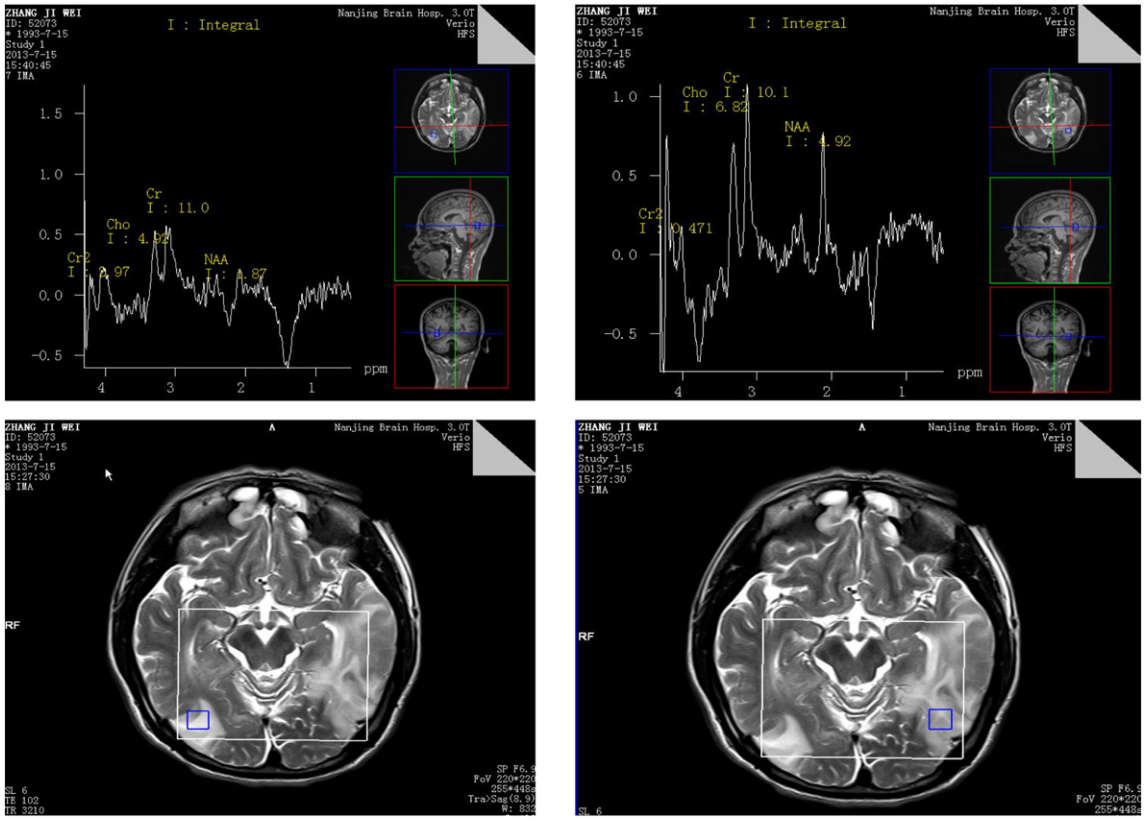

Fig. 1. Large abnormal signal on the right temporal–parietal lobe and the left temporal lobe. Proton magnetic resonance spectroscopic imaging (MRS) showed that (1) the levels of N-acetylaspartate (NAA, a marker of neuronal density) were reduced in bilateral temporal and occipital lobes; (2) the levels of choline-containing compounds (Cho) were not obviously changed between the lesions and normal brain tissue (3) a creatine lactic acid peaks are showing in the lesions.