Case report

Adult-onset of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome with hypothyroidism and psychiatric disorders

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1. Introduction

Mitochondrial disorders (MIDs), presenting as multi-system affected, such as the central and peripheral nervous system, eyes, ears, endocrine glands, heart, kidney etc., single or multiple combination, are clinically, biochemically and genetically highly variable [1]. MIDs may onset at any age since birth until adulthood with acute or progressively chronic manifestation [2]. Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a subtype of MIDs. Approximately 80% of patients with MELAS carry the A3243G mutation in the mitochondrial DNA [3,4]. An adult MELAS patient with a mutation at A3243G point, characterized by hypothyroidism and psychiatric disorders simultaneously is presented in this article.

2. Case report

The patient was a 37-year-old female, of 157 cm in height and 45 kg in weight. She was transferred to our department from a local hospital due to psychiatric features (both agitated behavior and auditory hallucinations), alexia and apraxia that had begun 10 days ago, followed by disorientation and generalized tonic-clonic seizures. She had a long history of episodic migraine-like headaches and progressive bilateral hearing loss for 3 years. However, she did not take any medication.

Her vital signs showed a normal body temperature of 36.8 °C, a hypotension of 90/56 mm Hg and pulse at 72 beats per minute. Because of the patient’s psychiatric symptoms and application of sedative after seizure attacks, she could not cooperate with physical examination.

The laboratory data showed high anion gap metabolic acidosis with elevated levels of lactate and pyruvate. Serum levels of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) were decreased. Her FT4 concentration was 7.56 pmol/L (normal range 10.2–31 pmol/L). Moreover, elevated titers of serum anti-thyroglobulin and anti-thyroid microsomal antibodies were detected. Cerebral spinal fluid (CSF) studies were normal for cell counts and biochemistry, and negative for culture. CSF IgG index was 0.48 (normal range ≤ 0.7), and oligoclonal bands (OB) was negative.

Computed tomography (CT) scan showed lesions of hypodense in the left temporal and parietal lobe, with brainstem and cerebellar atrophy (Fig. 1A). No evidence of subarachnoid or intracerebral hemorrhage. Vascular imaging of the cervical and cerebral arteries by CT angiography excluded the possibility of cerebrovascular disease (Fig. 1B). However, CT images were not conclusive to differentiate between the infectious or metabolic lesion. On day 5, brain magnetic resonance imaging; ROI, region of interest; CSF, Cerebral spinal fluid; ATP, adenosine triphosphate; CT, Computed tomography; MRI, magnetic resonance imaging; DWI, diffusion-weighted image; ADC, apparent diffusion coefficient; FLAIR, fluid-attenuated inversion recovery; DNA, deoxyribonucleic acid; RFLP, restriction fragment length polymorphism.

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Abbreviations: MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MIDs, mitochondrial disorders; MRC, mitochondrial respiratory chain; ATP, adenosine triphosphate; CT, Computed tomography; MRI, magnetic resonance imaging; ROI, region of interest; CSF, Cerebral spinal fluid; OB, oligoclonal bands; NAA, N-acetyl aspartic acid; Ct, creatine; BAEP, Brainstem auditory evoked potential; DWL, diffusion-weighted image; ADC, apparent diffusion coefficient; FLAIR, fluid-attenuated inversion recovery; DNA, deoxyribonucleic acid; RFLP, restriction fragment length polymorphism.

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imaging MRI (3.0 T) revealed a hypointensity lesion in the left temporal-parietal lobe on T1 weighted image (Fig. 2A), and increased signal intensity in the same region on FLAIR sequences (Fig. 2B) with a clearly restricted diffusion (Fig. 2C). The signal intensity on ADC sequence was mildly reduced (Fig. 2D). No obvious enhancement was found on Gd-DTPA enhanced images (Fig. 2E). MR spectroscopy was carried out as well. Compared to the ipsilateral normally appearing area (Fig. 2F), there was a significantly elevated lactate peak at 1.3 ppm in region of interest (ROI) with decreased NAA spectrum and reduced NAA/Cr ratio (Fig. 2G). The change of the spectrum reflected the severity of metabolic disorders, suggesting the local accumulation of lactic acid and disturbance of hypoxic processes.

Fig. 1. CT scan showed lesions of hypodense in the left temporal and parietal lobe (Panel A). Three-dimensional reconstruction of CT vessel images (Panel B).

Fig. 2. Brain MRI (3.0 T) revealed a hypointense lesion in the left temporal and parietal lobe on T1 (Panel A), and increased signal intensity in the same region on Flair (Panel A) image with a clearly restricted diffusion (Panel C). The signal intensity on ADC sequence is mildly reduced (Panel D). No obvious enhancement was found on Gd-DTPA enhanced images (Panel E). Compared to the ipsilateral normally appearing area (Panel F), MR spectroscopy presented a significantly elevated lactate peak at 1.3 ppm in region of interest (ROI) (Panel G). Panels f and g are the molecular findings of metabolites respectively.
An electroencephalogram was performed on day 7 and displayed bilateral slow wave activities. Brainstem auditory evoked potential (BAEP) showed the bilateral sensorineural hearing loss. All the clinical and radiological findings were suggestive of mitochondrial disease. The final diagnosis of MELAS syndrome was confirmed by genetic analysis. The patient’s peripheral blood leukocytes was detected by restriction fragment length polymorphism (RFLP) and revealed a mitochondrial DNA (mtDNA) mutation at A3242G point (Fig. 3).

Her medications included L-arginine, phenobarbital, co-enzyme Q and levothyroxine substitution therapy. The patient’s condition continuously improved, and was discharged on day 23. Six months following discharge, this patient had no further seizure.

3. Discussion

Mitochondria are intracellular organelles responsible for the production of adenosine triphosphate (ATP) by the process called oxidative phosphorylation [5,6]. In this process, the energy is released by the breakdown of fuels such as glucose and fatty acids through the mitochondrial respiratory chain (MRC) [7].

Mitochondrial disorders usually involve multisystem. Tissues with a greater requirement for energy supply are more susceptible to MRC dysfunction, such as the central nervous system, muscles, myocardium, and endocrine glands. Therefore, the variety of clinical manifestation is extremely broad, including myopathy, myalgia following exercise, epilepsy, repeated stroke-like episodes, ataxia, hearing loss, retinopathy, migraine and cardiomyopathy. Endocrine problems such as diabetes mellitus, growth hormone deficiency and hypoparathyroidism are often described [8–10]. Thyroid involvement is distinctly rare, both hyperthyroidism and hypothyroidism have only been reported in single case [11,12].

In this report, hypothyroidism was observed as a unique feature. Considering the decreased TSH level, it is proposed that the pituitary or hypothalamic dysfunction and the deficiency in growth hormone (GH) may be the contributing factors. Whether mtDNA mutation was involved in the pathogenesis of thyroid gland itself is unknown. It is supposed that the mtDNA mutation was engaged in the development of hypothyroidism for the following reasons. Firstly, the mutant mtDNA may be widely but unequally distributed throughout the body of the MELAS patient and some proportion of mutant mtDNA had...
been reported in the thyroid tissue [13]. Therefore, thyroid dysfunction may occur while the amount of the mutant mtDNA attains the certain threshold. Secondly, we found the obviously elevated titer of serum anti-thyroglobulin and anti-microsomal antibodies without morphological abnormality on ultrasonic examination. This observation suggested that mutant mtDNA may produce some antigens which in turn induced autoimmune response that result in the dysfunction of target gland. Thus, clinicians should be aware of the possibility of endocrine insufficiency accompanied by MIDs.

Psychiatric disorder was another feature of this patient. It has been increasingly recognized that mitochondrial dysfunction may be associated with neuropsychiatric abnormalities [14–16]. Patients with MELAS syndrome have a prevalence of depression, bipolar disorder, delusions of persecution or erratic behaviors. Some patients carrying the A3243G mutation in the MTTL1 gene have developed schizophrenia [17]. Others with the G3274A or C3256T mutation also have been reported to associate with psychosis [18,19]. The underlying mechanism remains unknown. As is known, adenosine triphosphate (ATP) is a high-energy compound utilized for the metabolic processes of neurons, which mostly occurs in mitochondria as products of oxidative phosphorylation. Therefore, mitochondria dysfunction results in a severely lowered ATP production. Previously studies have suggested that ATP depletion and the consequent deficiency of the Na⁺/K⁺-ATPase and Ca²⁺-ATPase leads to increased Na⁺ and Ca²⁺ concentration, which impairs plasma membrane potential [20–22]. The augmentation of intracellular Ca²⁺ may also induce the demyelination [23,24], dysregulate the apoptosis [25,26], and affect the storage, release or uptake mechanisms of neurotransmitters including dopamine, glutamate and GABA, etc. [27–30]. All these would result in structural and functional remodeling in synapses, and alter the intracellular signaling transductions and axonal projection. It is thus proposed that chronic MRC dysfunction and ATP deficiency are probably related to the etiology and pathogenesis of psychiatric disorders in MIDs. In addition, the site and scope of lesions may contribute to the psychiatric problems. As is known, each domain of cerebral cortex receives inputs respectively, further connects each other, and performs their functions precisely [31–33]. For example, the left temporal lobe holds the primary auditory cortex, which is important for processing of semantics in both speech and vision in humans. The patient with temporal and occipital lobes lesion undergoes severe hyperanxiety, visual and auditory hallucinations [34]. As detected by brain MRI (fig.2), our patient’s lesions were located in the left temporal and parietal lobes, which may account for her obvious auditory hallucinations [34]. A definite diagnosis can be made by genes detection.

4. Conclusion

The case of our patient shows that MELAS may present with hypothyroidism and psychiatric disorders. It broadens the clinical manifestation spectrum of the MELAS syndrome. Elevation of serum lactate and typical features with MR spectroscopy provide clues to diagnose the underlying mitochondrial disorder. Definite diagnosis can be made by genes detection.

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