Case report

Lactate peak in muscle disclosed by magnetic resonance spectroscopy in a patient with CPEO-plus syndrome

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ABSTRACT

A 25-year-old man complained of progressive diplopia and limb weakness for 3 years. Mitochondrial myopathy was suspected according to clinical presentation, elevated serum lactate concentration, and muscle histopathology. However, next-generation mtDNA sequencing (mtDNA NGS) of the blood only revealed a likely benign variant in the MT-CO1 gene (m.6510G > A). An mtDNA NGS study on the muscle sample revealed a large mtDNA deletion (m.5788–m.16071). The patient was diagnosed as having CPEO-plus syndrome related to the large mtDNA deletion. Notably, magnetic resonance spectroscopy revealed a doublet peak at 1–2 ppm in his edematous right vastus lateralis, which indicated lactate accumulation. Thus, muscle imaging and appropriate genetic tests facilitated the diagnosis of mitochondrial myopathy.

1. Introduction

Mitochondrial DNA (mtDNA) deletion syndromes predominantly manifest as three phenotypes: Kearns–Sayer syndrome (KSS), Pearson syndrome, and chronic progressive external ophthalmoplegia (CPEO). The diagnosis is confirmed by the identification of a single large mtDNA deletion in blood or tissues. In the present article, we report a patient with CPEO-plus syndrome whose pathological variant was discovered in the muscles but not in the blood. Muscle magnetic resonance (MR) spectroscopy disclosed a lactate accumulation in edematous right vastus lateralis.

2. Case report

A 25-year-old man complained of progressive diplopia and limb weakness for 3 years. He was the first-born child of a non-consanguineous couple, and the early development milestones were unremarkable. He was diagnosed as having minimal change disease of the kidneys in his childhood and had been receiving cyclosporine and prednisolone medications. His athletic performance had been poor compared with his peers. His family noted the patient’s hoarseness and mild dysarthria when he was in junior high school. No known family members had similar symptoms. He had been treated with pyridostigmine 60 mg 3 times/day but the benefit was equivocal. Due to worsening hoarseness and nasal sounds when speaking, he was referred to our clinic.

The neurologic examination revealed marked ophthalmoplegia, especially when attempting adduction. The patient also had bilateral ptosis and facial diplegia. Both proximal and distal weakness were detected, as evidenced by the following Medical Research Council grades: hip flexion 4, wrist flexion 4, and plantar flexion 4+. Examiners also observed atrophy of the intrinsic muscles of the hands and feet.

Laboratory examinations revealed an elevated creatine kinase (977 U/L) concentration and mildly increased serum lactic acid concentration (2.4 mmol/L) at rest, which increased to 3.8 mmol/L after the patient climbed two flights of stairs, up and down. Normal results were noted in complete blood cell counts, autoimmune profile, and thyroid function. Acetylcholine receptor antibody and muscle-specific kinase antibody tests returned negative results. Moreover, nerve conduction studi...
unremarkable. The needle electromyography revealed spontaneous activities and short and small amplitude motor unit action potentials in the first dorsal interosseous muscle, tibialis anterior muscle, and rectus femoris muscle on the patient’s right side. A repetitive stimulation test of the trapezius muscle revealed no wasting of the muscle. A targeted exome sequencing panel, which included 131 nuclear DNA genes related to hereditary myopathy and congenital myasthenic syndrome, did not reveal pathogenic variants in the blood. A biopsy of the left biceps brachii revealed increased variation of muscle fiber sizes, a moderate number of atrophic fibers with rimmed vacuoles and coarse blue staining in the sarcoplasm, and mild endomysial fibrosis (Fig. 1). Additionally, MR spectroscopy revealed a doublet peak at 1–2 ppm in his edematous right vastus lateralis, which indicated lactate accumulation (Fig. 2A & B). Therefore, mitochondrial myopathy was suspected. The fundoscopy revealed no retinitis pigmentosa. A cardiac sonography and Holter study were both unremarkable. Next-generation mtDNA sequencing of the blood revealed a likely benign variant in the MT-CO1 gene (m.6510G > A). Electron transport chain activity assays revealed decreased activities in all complexes. (Table 1) An mtDNA next-generation sequencing study was conducted on the muscle sample, revealing a large mtDNA deletion (m.5788–m.16071; Fig. 2C). The patient was finally diagnosed as having CPEO-plus syndrome related to the large mtDNA deletion.

3. Discussion

The presentation of mitochondrial disease varies, ranging from the involvement of multiple systems to a mild laboratory abnormality; the variation has been suggested to be related to the different variants of the disease and its heteroplasmy [1]. Due to improvements in genetic examination techniques, next-generation sequencing of the mtDNA genome should be considered in a case where mitochondrial disease is highly suspected [2]. However, the source of examined samples also affects the result due to heteroplasmy. As for the case presented herein, the diagnosis was made after the completion of mtDNA sequencing of the patient’s muscle tissue. We recommend that an extra muscle specimen be preserved when performing the muscle biopsy, and muscle-specific mtDNA sequencing should be performed for patients suspected of having mitochondrial myopathy, even if the genetic study of the blood sample is negative.

MRI has been used extensively to evaluate muscle edema and fatty infiltration. MR spectroscopy could evaluate the biochemical changes in the tissue non-invasively. Lipid and creatine metabolism in muscle had been explored in previous MR spectroscopy study [3]. Notably, we demonstrated the MR spectroscopy could detect the lactate accumulation, and which was more prominent in the edematous muscle. There was no double peak at 1–2 ppm in his less-edematous muscle, and this suggest the lactate accumulation was correlated to the severity of muscle edema. There was also no double peak at 1–2 ppm in our inflammatory myopathy patients with significant muscle edema, suggesting the lactate peak may be a specific finding to mitochondrial myopathy or metabolic myopathy. However, the lactate peak could be covered by the lipid peak (at 1.3 ppm). Further MR spectroscopy study is needed to differentiate lactate peak from lipid peak for precise quantification [4]. In summary,
an MR spectroscopy of affected muscles is valuable for monitoring the severity of mitochondrial disorders [5,6].

4. Conclusion

Mitochondrial DNA deletion could only be detected in affected tissue in mitochondrial depletion syndrome. Muscle imaging and appropriate genetic tests facilitated the diagnosis.

Data availability

The datasets generated during analysis and during the current study are available from the corresponding author upon reasonable request.

Author contributions

All authors contributed to data acquisition and analysis. S.-P. F. and H.-W.H. wrote the manuscript with input from all authors.

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Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.
Informed consent

Informed consent was obtained from all individual participants included in the study.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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