

Long-term outcomes of a patient with late-onset multiple acyl-CoA dehydrogenase deficiency caused by novel mutations in *ETFDH*

A case report

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Abstract

Rationale: Late-onset multiple acyl-coenzyme A dehydrogenase deficiency (MADD) mainly affects the neck extensor muscle group, which has been confirmed by novel mutations in electron-transferring-flavoprotein dehydrogenase (ETFDH). So far, a few cases have been reported with long-term follow-up. Here we report a case of late-onset MADD where the patient was followed up for 8 years during which time he underwent 2 muscle biopsies and 2 pathological examinations and his symptoms were significantly alleviated after appropriate treatments.

Patient concerns: In September 2009, a 16-year-old male patient was hospitalized due to gradually increasing difficulty in raising his head and weakness in limb muscles over a 6-month period. During the physical examination, the patient's neck extensor muscle strength was grade III–IV. His proximal limb muscle strength was grade IV, and his distal muscle strength was normal. His blood creatine kinase (CK) was 783 U/L.

Diagnosis: Muscle biopsy revealed a large number of vacuolar fibers, which were mainly type I fibers. These findings were consistent with the diagnosis of lipid storage myopathy (LSM). ETFDH gene test detected C.736G > A at exon 7 and C.920C > G at exon 8.

Interventions: Coenzyme Q10 treatment was administered. The first coenzyme Q10 40 mg tid was treated for three months, with the change of coenzyme Q10 20 mg tid for 6 months, followed by the change of coenzyme Q10 10 mg tid for long-term use.

Outcomes: The patient's condition significantly improved after 3 months. At 7th year follow-up the patient's blood CK was normal, and a second muscle biopsy revealed no muscle vacuolar fibers and no increase in lipid droplets. Subsequently, the patient was withdrawn from the coenzyme Q10 treatment, and the condition of the patient remained normal.

Lessons: Muscle biopsy was the main method used to determine LSM. Treatment with riboflavin should be started when the diagnosis of LSM is definitive. Furthermore, ETFDH gene tests should be performed for further classification. Moreover, coenzyme Q10 may be another effective drug for MADD.

Abbreviations: CK = creatine kinase, EMG = electromyogram, ETFDH = electron-transferring-flavoprotein dehydrogenase, H&E = hematoxylin and eosin, LSM = lipid storage myopathy, MADD = multiple acyl-coenzyme A dehydrogenase deficiency, SCV = sensory conduction velocity.

Keywords: coenzyme Q10, electron-transferring flavoprotein dehydrogenase late-onset multiple acyl coenzyme A dehydrogenase deficiency, pathological features

1. Introduction

Lipid storage myopathy (LSM) refers to a group of myopathies caused by the defects of enzymes or prosthetic groups in primary

fat metabolism pathways.^[1] Its main pathological features are lipid deposits in muscle fibers.^[2] In China, the cause of approximately 90% of LSM cases is multiple acyl-coenzyme A dehydrogenase deficiency (MADD).^[3,4] In the present study, we report a case of late-onset MADD. The diagnosis was confirmed by genetic sequencing and typical pathological findings during the muscle biopsy examination. The patient was followed up for 8 years, and his symptoms were significantly alleviated after appropriate treatments.

So far, a few cases have been reported with long-term follow-up. Now we report a case of late-onset MADD. The patient was followed up for 8 years. He underwent 2 muscle biopsies and 2 pathological examinations; and his symptoms were significantly alleviated after appropriate treatments.

2. Case report

In September 2009, a 16-year-old male patient was hospitalized due to gradually increasing difficulty in raising his head and weakness in limb muscles over a 6-month period. The first onset of muscle weakness occurred in March 2009. Limb weakness was

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The authors declare no conflicts of interest.

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obvious when he climbed the stairs or stood up from a squatting position, and these symptoms were progressively exacerbated. In July 2009, it took substantial effort for the patient to raise his head and chew food. In addition, he could only walk up to the second floor of his residence. These symptoms were temporarily relieved after he rested. An electromyogram (EMG) revealed myogenic abnormalities. He had no history of fever or medication use before the onset of this disease. Furthermore, he had no sense of muscle twitching or pain, and his family history was normal.

During the physical examination, the patient's neck extensor muscle strength was grade III–IV, and his flexor muscle strength was normal. His proximal limb muscle strength was grade IV, and his distal muscle strength was normal. His knee tendon reflexes were decreased. His blood creatine kinase (CK) was 783 U/L. Motor conduction velocity sensory conduction velocity (SCV), H reflex, F wave, EMG, and low frequency and high frequency stimulation tests all revealed no abnormalities. In September 2009, the first muscle biopsy revealed a large number of vacuolar fibers, which were mainly type I fibers. The quantity of lipid droplets significantly increased. These findings were consistent with the diagnosis of LSM (Figs. 1A–C). Further classification was not performed.

Subsequently, coenzyme Q10 treatment was administered. The first coenzyme Q10 40 mg tid was treated for 3 months, with the change of coenzyme Q10 20 mg tid for 6 months, followed by the change of coenzyme Q10 10 mg tid for long-term use. The patient's condition significantly improved after 3 months. Then, the patient was asked to complete the long-term clinical follow-up, and condition of the patient was stable. In October 2016, the patient's blood CK was normal, and a second muscle biopsy revealed no muscle vacuolar fibers and no increase in lipid droplets (Figs. 1D–F). Furthermore, the *ETFDH* gene test detected C.736G>A at exon 7 (Fig. 1G) and C.920C>G at

exon 8 (Fig. 1H). Subsequently, the patient was withdrawn from the coenzyme Q10 treatment, and the condition of the patient remained normal.

3. Discussion

The causes of LSM include late-onset MADD.^[5] The most common cause of LSM in China is late-onset MADD, and most patients are responsive to vitamin B2 treatment.^[6,7] Late-onset MADD mainly affects the neck extensor muscle group, which is characterized by muscle weakness. Some patients with severe cases can even have drooped head signs. The definitive diagnosis of LSM depends on the muscle biopsy and pathological examination,^[8] although muscle pathology cannot further classify this disease.^[9] The classical findings for late-onset MADD are characterized by large numbers of small, round and vacuolar fibers observed by hematoxylin and eosin (H&E) staining. In the present patient's case, oil red O staining revealed that the vacuoles in the muscle fibers were lipid deposits. A left biceps muscle biopsy was performed at 6 months after the onset of the disease. The frozen pathological examination was consistent with the typical muscle pathological changes of this disease.

The long-term follow-up study revealed that most patients can withdraw from riboflavin after 3 to 6 months of treatment, and no recurrence occurred.^[3] The present patient received chronic coenzyme Q10 supplementation, and the condition of the patient remained stable during the long-term follow-up. Since the treatment was effective and the cost was low, the patient was treated with chronic coenzyme Q10 supplementation. The second muscle pathology was basically normal. However, it could not be determined when the muscle pathology improved, and whether the pathologic findings were consistent with the recovery of the clinical symptoms. This needs to be confirmed

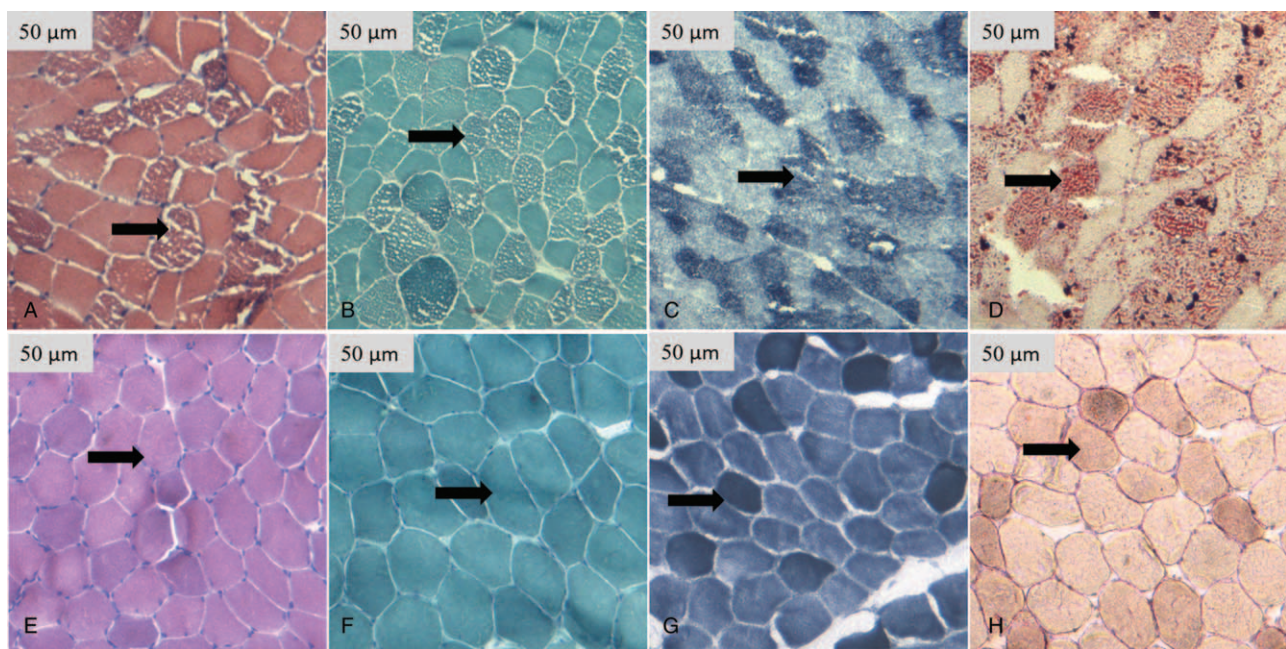


Figure 1. Results of 2 muscle pathology examinations. A, HE staining ($\times 200$) a large number of vacuolar fibers, which were mainly type I fibers; (B) MGT staining ($\times 200$) a large number of vacuolar fibers; (C) NADH staining ($\times 200$) a large number of vacuolar fibers, which were mainly type I fibers; (D) ORO staining ($\times 200$) a large number of lipid storage fibers; (E) HE staining ($\times 200$) normal fibers; (F) MGT staining ($\times 200$) normal fibers; (G) NADH staining ($\times 200$) normal fibers; and (H) ORO staining ($\times 200$) normal fibers (arrow).

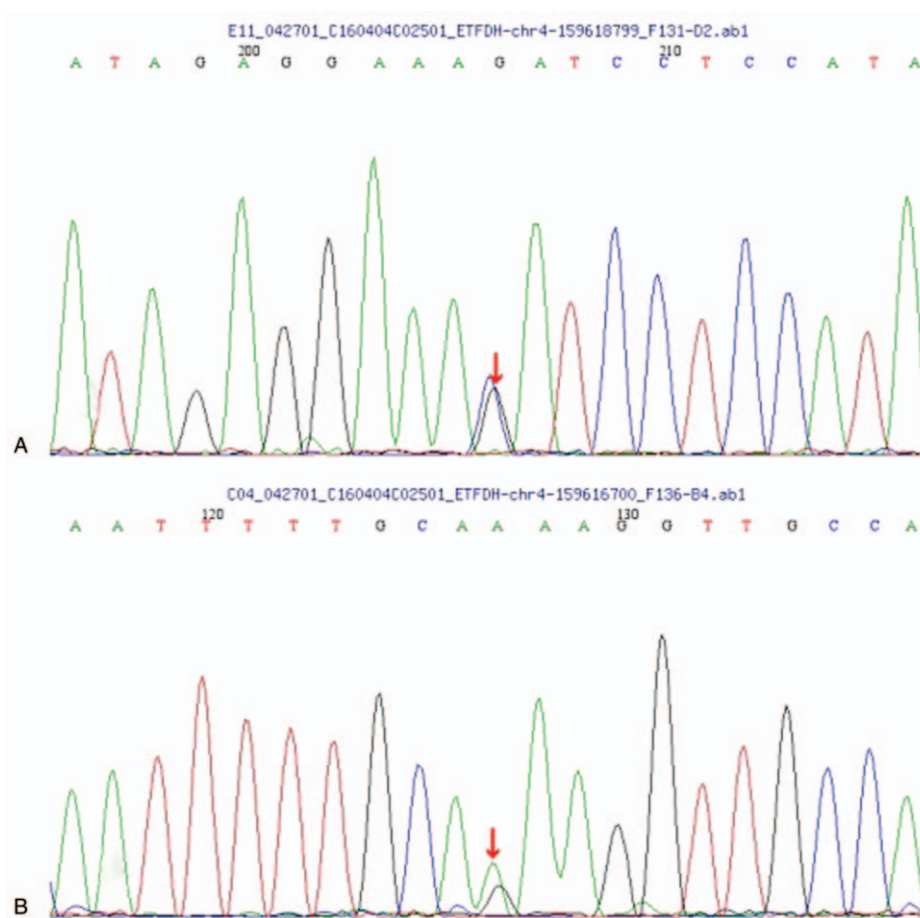


Figure 2. Genetic test results. A, C.736G>A at exon 7; and (B) C.920C>G at exon 8 (arrow).

through more cases. In the present case, the review of the muscle pathology was a reliable indicator for withdrawal. However, biopsy is an invasive test that is not easy to perform, and other simple objective indicators need to be identified as the basis for withdrawal. The present case indicates that MADD may be a coenzyme Q10 without related myopathy, which is subject to more research.

In the present case, the electron-transferring-flavoprotein dehydrogenase (*ETFDH*) gene test detected C.736G>A at exon 7 (Fig. 2A) and C.920C>G at exon 8 (Fig. 2B).^[6] The subtype for the present case was clear, and the diagnosis of late-onset MADD was confirmed. These tests were performed after the diagnosis of LSM, which were conducted based on the pathologic finding of increasing lipid droplets. Therefore, muscle biopsy remains as the most accurate diagnostic test for this disease.

Once the diagnosis of LSM is suspected, muscle biopsy is the main method of examination,^[3] while neck extensor muscle involvement is the specific symptom.^[2] Treatment with riboflavin should be started when the diagnosis of LSM is definitive. Furthermore, *ETFDH* gene testing should be performed for further classification.

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Second People's Hospital of Hefei City. Informed written consent was obtained from the patient for publication of the case details.

4. Conclusions

The patient was followed up for 8 years, and his symptoms were significantly alleviated after appropriate treatments with coenzyme Q10. Muscle biopsy was the main method used to determine LSM. Treatment with riboflavin should be started when the diagnosis of LSM is definitive. Furthermore, *ETFDH* gene tests should be performed for further classification. Moreover, coenzyme Q10 may be another effective drug for MADD.

Author contributions

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