

## Case Report

# Late-onset riboflavin-responsive multiple acyl-coenzyme A dehydrogenase deficiency after syphilis infection

Teng Zhao\*, Jiguo Gao\*, Xuemin Feng\*, Hui Zhu, Chunkui Zhou

Department of Neurology, First Hospital, Jilin University, Changchun, China. \*Equal contributors.

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**Abstract:** In this report, we describe a woman patient who presented with general fatigue and gradual weakness of the limbs. Her husband was diagnosed with syphilis. We performed a serological examination for syphilis and muscle biopsy. Her serological examination was TPPA (treponema pallidum particle agglutination assay)-positive and RPR (rapid plasma reagin)-positive with a titer of 1:16. Muscle biopsy showed abnormal lipid accumulation in myofibers. The genetic test revealed homozygous mutation at c.770A > G (p.Y257C) of the ETFDH (electron transferring-flavoprotein dehydrogenase) gene. We conclude that this woman was infected with syphilis from her husband, and because she was a c.770A > G ETFDH mutant, multiple acyl-CoA dehydrogenase deficiency (MADD) was triggered.

**Keywords:** Riboflavin-responsive multiple acyl-coenzyme A dehydrogenase deficiency, syphilis infection, ETFDH gene, riboflavin

## Introduction

Because of prominent accumulation or metabolism of lipids in muscle fibers, lipid storage myopathy can cause clinical symptoms such as muscle weakness, muscle cramps, muscle pain, and exercise intolerance [1, 2]. Lipid storage myopathy can be categorized genetically as primary carnitine deficiency, neutral lipid storage disease with ichthyosis or myopathy, or multiple acyl-coenzyme A dehydrogenase deficiency (MADD; also called glutaric acidemia type II) [1, 2]. Among these, MADD is an inherited autosomal recessive disease, with defects in electron-transferring flavoprotein (ETF) in the mitochondrial matrix, or its relative ETF-ubiquinone (coenzyme Q) oxidoreductase (ETF-QO) in the inner mitochondrial membrane. The defects are due to mutations in the genes that encode the alpha and beta subunits of ETF (genes ETFA and ETFB, respectively, 15q23-q25 and 19q13.3-q13.4), or the gene ETFDH (electron transferring-flavoprotein dehydrogenase; 4q32-q35) [3].

Riboflavin replacement therapy has proved effective for most late-onset adult MADD patients. There have also been reports of dra-

matic responses to riboflavin in patients with MADD (RR-MADD) that are related to mutations of the ETFDH gene [4-6].

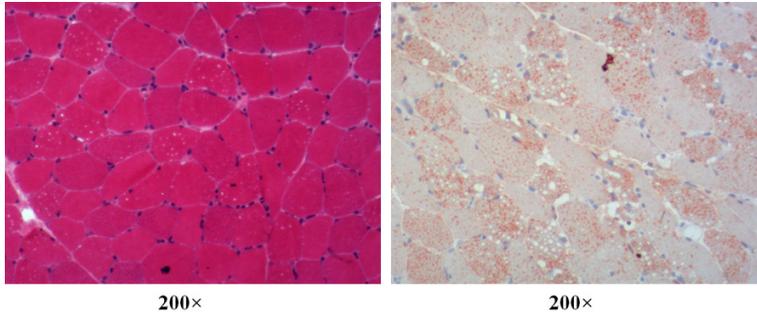
We herein report the case of a 38-year-old woman who received a diagnosis of late-onset MADD associated with syphilis infection, who responded well to riboflavin therapy. She had a homozygous mutation at c.770A > G (p.Y257C) of the ETFDH gene.

## Case report

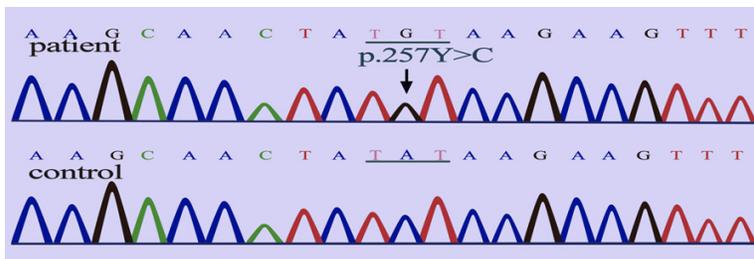
On 25 June 2014, a 38-year-old woman was admitted to Affiliated Hospital of Beihua University, due to abnormal symptoms of general fatigue, dyspnea, nausea, and vomiting. One month before admission, she developed idiopathic weakness of the limbs. Holding or walking required strenuous effort, although she could carry light things and walk independently. Four days before admission, her limb weakness worsened, and she had difficulties eating, holding and walking, and complaining of dyspnea and weak voice.

Upon her arrival at the hospital, the general physical examination revealed spotted pink macules on her chest, back, and the insteps of

## Rare case of late-onset RR-MADD



**Figure 1.** Muscle biopsy finding with (left) hematoxylin and eosin (H&E) staining (200 ×), and (right) oil red O staining (200 ×). H&E staining showed the cytoplasmic vacuoles contained increased numbers of fibers. Oil red O staining revealed prominent lipid accumulation in myofibers of the paravertebral muscles.



**Figure 2.** DNA sequencing identification of a ETFDH 770A > G (p. Y257C) mutation (arrow).

both feet, with body temperature 36.8°C and blood pressure 120/70 mmHg. Although she displayed dysarthria, she was fully conscious and had clear breath sounds and voluntary movement of the eyes with no nystagmus. Both pupils dilated to 3.0 mm diameter, and their reactions to light were normal. She also had pharyngeal reflex with normal tongue position, and no obvious facial dysmorphism.

The neurological examination showed the following: normal muscle tension of the limbs at grade 3; normal sensory system and masonic movements; weak tendon reflex of the arms; weak Achilles tendon reflex; absent patellar tendon reflex of the legs; and negative Chaddock's sign and negative Babinski's sign for the legs.

Blood chemistry results showed aspartate aminotransferase 574.00 U/L; creatine kinase (CK) 1055.68 U/L; CK-MB 97.00 U/L; and myoglobin > 3000 ng/mL. The routine blood test showed a white blood cell count of  $15.64 \times 10^9/L$ , the percentage of neutrophils at 88.00%, alanine aminotransferase 125.00 U/L; and fasting blood-glucose 5.8 mmol/L. The blood gas anal-

ysis showed pH 7.32;  $pO_2$  70 mmHg;  $pCO_2$  42 mmHg; and lactic acid 3.5 mmol/L. The lung CT and full abdomen color Doppler were normal.

Although her syphilis test results were negative before giving birth and 3 months after cesarean section, her serological examination at admission was TPPA (treponema pallidum particle agglutination assay)-positive and RPR (rapid plasma reagin)-positive with a titer of 1:16. The results of the TPPA were also positive for her husband and her husband admitted adulterous sexual behavior during her pregnancy. Based on the above results at her admission, the initial diagnosis was rhabdomyolysis associated with syphilis infection.

After blood filtration performed in the Intensive Care Unit and penicillin treatment for

syphilis infection for one week, the patient's symptoms did not improve. Subsequently, she received a muscle biopsy, which showed abnormal muscular fibers and abnormal lipid accumulation in the myofibers of the paravertebral muscles (**Figure 1**). Using tandem mass spectrometry, the blood acylcarnitine analysis showed a significant elevation of the acylcarnitines C5-1, C6-1, C8-1, C10-1, C12-1, and C16:1-1, indicating possible MADD. Furthermore, the DNA sequencing results of a blood sample revealed a homozygous mutation at c.770A > G (p.Y257C) of the ETFDH gene (**Figure 2**).

Accordingly, she was given riboflavin therapy (300 mg/d) for MADD and penicillin treatment for syphilis infection. The patient did not experience any dyspnea for one week. Two weeks after therapy, the patient was improving, with independent walking, better movements of the limbs, and normal levels of muscle enzymes.

Taken together, the patient was regarded as suffering from RR-MADD associated with syphilis infection. Finally, the patient was discharged from our hospital, with a recommendation for

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**Table 1.** Characteristic comparison of similar cases

	Current patient	Similar cases
The most common mutations in China	c.770A > G	c.250G > A, c.770A > G, c.1227A > C
Inducing factor	Syphilis infections	Infections, fasting, pregnancy, surgery
Simultaneous phenomenon	Vomiting	Vomiting, diarrhea, dysphagia
Therapy	Riboflavin	Riboflavin, glucocorticoid

long-term riboflavin therapy for MADD and penicillin treatment for syphilis infection, and to avoid infections, cold, hunger, or other stressful conditions.

### Discussion

MADD is an inherited autosomal recessive inherited disease that can be roughly classified as early- or late-onset [2]. The clinical manifestations of early-onset MADD in adults mainly include facial dysmorphism and cystic renal dysplasia. In infants, features of early-onset MADD are hypotonia, hepatomegaly, non-ketotic hypoglycemia, metabolic acidosis, and high mortality.

The clinical symptoms of late-onset MADD are variable, consisting of proximal muscle weakness, high CK levels, hepatomegaly, encephalopathy, episodic lethargy, vomiting, hypoglycemia, metabolic acidosis, and lipid storage in muscle [2]. MADD is caused by defects in ETF in the mitochondrial matrix, or its relative ETF-QO in the inner mitochondrial membrane. The defects are due to mutations in the genes that encode the alpha and beta subunits of ETF, or the ETFDH gene [1]. Therefore, serological acyl-carnitine profiles are important biomarkers for MADD, and MADD may be diagnosed on the basis of low free carnitine and elevated serum acyl-carnitines (i.e., all-chain [C4-C18] or medium- and long-chain [C6-C12] acyl-carnitines).

Importantly, RR therapy is of great benefit in improving the clinical and metabolic symptoms in the subgroup of MADD patients who are riboflavin-responsive, especially for adults with late-onset MADD [3]. Cases of RR-MADD have been reported in European countries such as Denmark, Italy, France, and Germany, and RR-MADD is common in Asian countries including mainland China, Hong Kong, Taiwan, Thailand, and Japan. Interestingly, almost all cases of RR-MADD on the mainland of China

have involved mutations in the ETFDH gene [4-6].

To date, more than 80 mutations of the ETFDH gene have been identified worldwide, but the allele frequency for each genotype is variable in different populations. However, the most common mutations of the ETFDH gene in Asian RR-MADD patients are the following: in China, c.770A > G, c.1227A > C, and c.250G > A; in Taiwan, c.250G > A; and in Japan, c.1084G > A and c.1211T > C [4-7] (**Table 1**). This indicates an ethnic-specific link between ETFDH genotypes and RR-MADD. Although the incidence of RR-MADD in mainland China is significantly higher than in other countries, the exact role of riboflavin is unknown.

In the present case, we report a 38-year-old woman who received a diagnosis of late-onset MADD associated with syphilis infection, and who experienced a sensitive response to riboflavin therapy. In addition to the current patient, another was reported to have lipid storage myopathy associated with syphilis infection, although detailed information is lacking [7]. Furthermore, secondary syphilis was reported as an uncommon cause of myositis, which may lead to a delay in diagnosis [8, 9].

In addition to syphilis infection, our patient had a homozygous mutation at c.770A > G (p.Y257C) of the ETFDH gene. Although there are many ETFDH gene mutations that are implicated in MADD, clinical manifestations may be triggered by factors such as infections, fasting, pregnancy, and surgery (**Table 1**). The manifestations of MADD include fluctuating proximal myopathy, premature fatigue, and high CK levels [6, 10].

The current patient had no medical record of syphilis infection, but she and her husband obtained positive TPPA results. Therefore, we may conclude that the woman was infected with syphilis from her husband, and this and

her c.770A > G ETFDH status made her susceptible to MADD. Finally, this patient was discharged from our hospital with complete resolution of all clinical symptoms, after riboflavin therapy for MADD and penicillin treatment for syphilis infection (**Table 1**).

In conclusion, this report describes a rare case of late-onset RR-MADD associated with syphilis infection. The patient had a homozygous mutation at c.770A > G (p. Y257C) of the ETFDH gene.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Chunkui Zhou, Department of Neurology, First Hospital, Jilin University, 71 Xinmin Street, Changchun 130021, China. Tel: +8613844193557; E-mail: shandongzhaoteng@163.com

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