

A Historical Cohort Study on the Efficacy of Glucocorticoids and Riboflavin Among Patients with Late-onset Multiple Acyl-CoA Dehydrogenase Deficiency

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Abstract

Background: Late-onset multiple acyl-CoA dehydrogenase deficiency (MADD) is the most common type of lipid storage myopathies in China. Most patients with late-onset MADD are well responsive to riboflavin. Up to now, these patients are often treated with glucocorticoids as the first-line drug because they are misdiagnosed as polymyositis without muscle biopsy or gene analysis. Although glucocorticoids seem to improve the fatty acid metabolism of late-onset MADD, the objective evaluation of their rationalization on this disorder and comparison with riboflavin treatment are unknown.

Methods: We performed a historical cohort study on the efficacy of the two drugs among 45 patients with late-onset MADD, who were divided into glucocorticoids group and riboflavin group. Detailed clinical information of baseline and 1-month follow-up were collected.

Results: After 1-month treatment, a dramatic improvement of muscle strength was found in riboflavin group ($P < 0.05$). There was no significant difference in muscle enzymes between the two groups. Significantly, the number of patients with full recovery in glucocorticoids group was less than the number in riboflavin group ($P < 0.05$). On the other hand, almost half of the patients in riboflavin group still presented high-level muscle enzymes and weak muscle strength after 1-month riboflavin treatment, meaning that 1-month treatment duration maybe insufficient and patients should keep on riboflavin supplement for a longer time.

Conclusions: Our results provide credible evidences that the overall efficacy of riboflavin is superior to glucocorticoids, and a longer duration of riboflavin treatment is necessary for patients with late-onset MADD.

Key words: Glucocorticoids; Historical Cohort Study; Late-onset Multiple Acyl-CoA Dehydrogenase Deficiency; Lipid Storage Myopathy; Riboflavin

INTRODUCTION

Multiple acyl-CoA dehydrogenase deficiency (MADD) is an autosomal recessive inherited disease that is caused by mutations in the electron transfer flavoprotein A (*ETF A*), electron transfer flavoprotein B (*ETF B*), or electron transfer flavoprotein dehydrogenase (*ETF DH*) genes.^[1,2] Based on different phenotypes, MADD is classified as neonatal-onset forms with or without congenital anomalies and late-onset MADD. The latter is the most common form of lipid storage myopathy in China.^[3] Late-onset MADD is mainly caused by *ETF DH* mutation that results in misfolding and instability of *ETF DH* protein.^[4,5]

Late-onset MADD patient with *ETF DH* mutation shows a dramatic response to riboflavin, which is known as riboflavin-responsive MADD (RR-MADD), and riboflavin is recommended for treating this disorder since the 1980s.^[6] However, in China,

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late-onset MADD patients are usually misdiagnosed as polymyositis and treated by glucocorticoids due to lack of muscle biopsy and gene detection in many hospitals. Late-onset MADD patients exhibited symmetrical proximal upper limbs weakness and difficulty in lifting the neck as major clinical manifestations. Some patients also performed myalgia, mastication deficits, or dysphagia.^[7,8] Amyotrophy was also observed.^[8] These clinical features are easily confused with polymyositis without muscle biopsy and genetic analysis. Moreover, increased muscle enzymes and myopathic changes on electromyography (EMG) are common in both diseases. The treatments for these two diseases are quite different. Late-onset MADD patients with *ETFDH* mutations show a dramatic response to riboflavin, whereas glucocorticoids are generally the first-line drugs for polymyositis. Therefore, the similarity of clinical symptoms leads to the misuse of glucocorticoids for late-onset MADD patients. Recently, cases with effective glucocorticoids treatment on late-onset MADD have been reported,^[9] and a study showed that RR-MADD patients exhibited clinical remission after a short-term glucocorticoids treatment.^[10] Even though riboflavin is recommended for late-onset MADD, we do not know whether glucocorticoids have the same effect as riboflavin or not. It is of importance to find out the efficacy of glucocorticoids on late-onset MADD patients.

To date, there is no longitudinal study about the efficacy of glucocorticoids on late-onset MADD, not to mention the comparison of glucocorticoids and riboflavin on muscle strength and laboratory data during treatment. Therefore, we performed a historical cohort study to objectively assess the efficacy of glucocorticoids and riboflavin on late-onset MADD patients and compared the changes in muscle strength and muscle enzymes between these two therapies.

METHODS

Study population and design

This study included 45 late-onset MADD patients from the Han ethnic group in Southern China who visited the First Affiliated Hospital of Fujian Medical University from January 2006 to June 2015. All the included patients have been clinically, pathologically, and genetically diagnosed as late-onset MADD. Patients presenting lipid storage abnormalities secondary to steroids and mitochondrial diseases were excluded. Based on medication history, patients were divided into riboflavin group and glucocorticoids group. In glucocorticoids group, 18 patients who were misdiagnosed as polymyositis without muscle biopsy and genes sequencing in primary hospitals were administered glucocorticoids initially at least 1 month (1.0 mg/kg weight per day). The remaining 27 patients in riboflavin group took riboflavin (90–120 mg/d) and coenzyme Q10 (60 mg/d) as initial treatment for at least 1 month in the First Affiliated Hospital of Fujian Medical University. The study was approved by the Ethical Committees of the First Affiliated Hospital of Fujian Medical University.

Clinical information

Baseline and 1-month follow-up information were collected in detail, including age, sex, onset age, physical examinations, and

muscle enzymes. Clinical presentations and genotype of the patients were summarized in Supplemental Table 1. The manual muscle testing (MMT) with a 0–5 scale was used to evaluate muscle strength and performed by two neurologists who are long engaged in neuromuscular disorders in our hospital.^[11] The strength of the following 14 muscle groups were examined: neck flexion, neck extensor, deltoid, biceps, triceps, iliopsoas, gluteus medius, gluteus maximus, hamstrings, quadriceps femoris, wrist flexion, wrist extension, ankle dorsiflexion, and ankle plantarflexion. Muscle strength grade in MMT scoring was converted to Kendall 0–10 point scale and described as previous reported.^[12,13] Muscle strength of neck was the average of the neck flexor and extensor. Muscle strength of proximal upper limb was the average strength of the deltoid, biceps, and triceps. The proximal lower limb muscle strength was the average strength of the iliopsoas, gluteus medius, and gluteus maximus.

Muscle enzymes test included serum creatinine kinase (CK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH). Blood acylcarnitine spectrum and urine organic acids spectrum were measured by tandem mass spectrometry (MS/MS) and gas chromatography-MS, respectively (ABI 2000, Applied Biosystems; Foster City, CA, USA). EMG, abdominal ultrasound, and pathologic examination including hematoxylin-eosin and oil red O (ORO) staining were performed before treatment.

Polymerase chain reaction and Sanger sequencing

DNA was extracted from peripheral blood samples (Qiagene, Hilden, Germany). Exons and intron-exon boundaries of *ETFA*, *ETFB*, and *ETFDH* were amplified by polymerase chain reaction (PCR), and the products were sequenced using an ABI 3730XL Automated DNA Sequencer (PE Applied Biosystems, Foster City, CA). The primers and amplifying conditions were based on our previously published literature.^[14]

Statistical analysis

Data were summarized using descriptive statistics including median, range, frequency, and percentage. As the data did not follow the normal distribution, Mann–Whitney *U*-test, and Chi-square test were used. We calculated the difference value before and after treatment between glucocorticoids and riboflavin groups, respectively. Then we compared the difference value between these two groups using Mann–Whitney *U*-test. The percent of patients whose muscle strength and enzymes returned to normal level after treatment between the two groups were compared by Chi-square test. Patients with incomplete data on certain items were eliminated when analyzed. Analysis was applied by SPSS 19.0 software (SPSS Inc., Chicago, IL, USA). The value $P < 0.05$ is considered to be significant.

RESULTS

ETFDH mutations

Nine *ETFDH* mutations were detected in the 45 patients, including c.250G>A (p.Ala84Thr), c.380T>A (p.Leu127His), c.1601C>T (p.Pro534Leu), c.524G>A (p.Arg175His), c.998A>G (p.Tyr333Cys), c.770A>G

(p.Try257Cys), c.409C>T (p.Pro137Ser), c.1395T>G (p.Try465X), and c. 643G>A (p.Ala215Thr). Among the 45 patients, 43 patients carried the hotspot mutation c.250G>A in Southern China, and 30 patients were homozygous. No *ETFA* or *ETFB* mutation was detected.

Baseline features

Of the 45 patients, the median age was 27-year-old. The median onset age was 21-year-old, ranging from 4 to 44-year-old. The disease course lasted from 2 months to 28 years. All patients suffered symmetrical proximal limbs weakness, difficulty in lifting head, and exercise intolerance. MMT revealed the significant weakness in neck flexor, neck extensor, triceps, biceps, deltoid, iliopsoas, gluteus medius, and gluteus maximus. Muscle strength of the distal limbs and quadriceps femoris were normal in all the patients. Twenty-one patients presented with myalgia (46.7%), and 10 patients manifested proximal limbs muscle atrophy (25.0%). Twenty-one patients exhibited difficulty in mastication (46.7%). Twenty-six patients (57.8%) accompanied with gastrointestinal symptoms such as vomiting, diarrhea, or flatulence. EMG was available in 42 patients, which showed myopathic changes in 28 patients, neurogenic changes in two patients, and no obvious abnormality in the remaining 12 patients. Fatty liver was detected in 6 of the 31 patients who underwent ultrasound. In most patients, CK, AST, and LDH were increased to several times above the upper limit of normal. Clinical features of the 45 patients were summarized in Table 1.

Table 1: Clinical features of the 45 patients with late-onset MADD

Clinical features	Numbers of patients
Gender	
Male	27/45 (60.0)
Median age (years), range	28 (6, 44)
Median onset ages (years), range	21 (4, 44)
Muscle weakness	
Proximal limbs	45/45 (100)
Distal limbs	0/45 (0)
Neck	45/45 (100)
Mastication	21/45 (46.7)
Exercise intolerance	45/45 (100)
Myalgia	21/45 (46.7)
Muscle atrophy	10/45 (22.2)
Gastrointestinal symptoms	26/45 (57.8)
Electromyography	
Myopathic changes	28/42 (66.7)
Neurogenic changes	2/42 (4.8)
No obvious abnormality	12/42 (28.6)
Fatty liver	6/31 (19.4)
CK (U/L), mean (range)	888 (168, 2526)
LDH (U/L), mean (range)	962 (253, 3507)
AST (U/L), mean (range)	139 (37, 447)

Values are presented as *n/N* (%). MADD: Multiple acyl-coenzyme A dehydrogenase deficiency; CK: Creatinine kinase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase. Upper limit of normal: CK 140 U/L, LDH 245 U/L, and AST 40 U/L.

The results of blood acylcarnitine and urine organic acids spectrum of 16 patients were showed in Supplemental Table 2. ORO staining of all the patients showed lipid droplets accumulation in the myofibers.

There was no difference between glucocorticoids group and riboflavin group in baseline characteristics including sex, onset age, disease course, genotype, muscle strength, and enzymes [Table 2].

Follow-up changes

After 1-month treatment, compared with glucocorticoids group, riboflavin group showed a significant increase of muscle strength including neck ($P = 0.016$), proximal upper ($P = 0.027$), and lower limbs ($P < 0.001$). The medians of muscle strength after 1-month riboflavin treatment rose to normal level, while the medians of muscle strength after 1-month glucocorticoids treatment were still below the normal level. Even though no significant difference was detected in the muscle enzymes between the two groups, the medians of CK and AST were decreased to normal range in riboflavin group, whereas the medians of CK and AST were still above the upper limit of normal in glucocorticoids group [Table 3]. Compared with glucocorticoids group, patients in riboflavin group were more prone to have complete recovery in proximal limbs muscle strength, CK, and AST ($P < 0.05$) [Table 4]. However, not all patients in riboflavin group had complete recovery after 1-month treatment. In riboflavin group, only 40.7% (11/27) patients, 74.1% (20/27) patients, and 59.3% (16/27) patients had completely recovery in muscle strength of neck, proximal upper limbs, and proximal lower limbs, respectively. The percentages of patients whose muscle enzymes reducing to normal level were 69.6% (16/23) in CK, 39.1% (9/23) in LDH, and 65.2% (15/23) in AST [Table 4].

DISCUSSION

This is the first historical cohort study with quantitative analysis to assess the efficacy and prognosis of riboflavin and glucocorticoids treatment on late-onset MADD patients with objective evaluation. Late-onset MADD and polymyositis are easily confused without target genes sequencing and muscle biopsy. The clinical features of late-onset MADD, such as symmetrical proximal limbs weakness, difficulty in lifting head, and exercise intolerance, also appeared in polymyositis. Moreover, increased muscle enzymes and myopathic changes on EMG are observed in both late-onset MADD and polymyositis patients. In general, glucocorticoids are the first-line drugs for polymyositis. Therefore, the misdiagnosis of late-onset MADD usually leads to the misuse of glucocorticoids for late-onset MADD patients. Even though previously literature reported that some late-onset MADD patients exhibited the mild and short-term clinical remission when treated with glucocorticoids,^[9,10] the rationality of glucocorticoids for late-onset MADD patients remains unclear. In our study, after 1-month treatment, the improvement of limbs muscle

Table 2: Baseline characteristics between glucocorticoids group and riboflavin group among the 45 late-onset MADD patients

Baseline characteristics	Glucocorticoids group (n = 18)	Riboflavin group (n = 27)	Z	P
Demographic characteristics				
Male (n)	10	17	-0.491	0.623
Onset ages (year), median (range)	22 (6, 38)	20 (4, 44)	-0.290	0.772
Disease course (year), median (range)	6 (4 m, 19 y)	1 (2 m, 28 y)	-1.300	0.194
c. 250G <A homozygote (n)	10	20	-1.277	0.202
Muscle strength and enzymes, median (range)				
Neck muscle*	8 (2, 9)	7 (1, 9)	0.427	0.446
Proximal upper limbs*	9 (2, 10)	9 (6, 10)	-0.492	0.623
Proximal lower limbs*	8 (5, 10)	8 (2, 9)	-1.123	0.261
CK (U/L)	806 (316, 2526)	666 (168, 2302)	-1.367	0.172
LDH (U/L)*	616 (253, 3054)	630 (311, 3507)	-0.795	0.426
AST (U/L)	131 (40, 447)	98 (37, 317)	-0.429	0.668

*Partial data of muscle strength and LDH value in glucocorticoids group were not available. m: Months; y: Years; MADD: Multiple acyl-coenzyme A dehydrogenase deficiency; CK: Creatinine kinase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase.

Table 3: Changes in muscle strength and muscle enzymes of patients with one-month glucocorticoids or riboflavin treatment

Variables	Glucocorticoids group, median (range)			Riboflavin group, median (range)			Z	P
	Baseline	1 month	n	Baseline	1 month	n		
Neck muscle	8 (2, 9)	8 (4, 10)	11	7 (1, 9)	10 (6, 10)	27	-2.400	0.016*
Proximal upper limbs	9 (8, 10)	9 (5, 10)	15	9 (6, 10)	10 (9, 10)	27	-2.206	0.027*
Proximal lower limbs	8 (5, 10)	8 (5, 10)	15	8 (2, 10)	10 (6, 10)	27	-4.318	<0.001*
CK (U/L)	878 (316, 2526)	373 (31, 2729)	15	718 (168, 2231)	112 (27, 5236)	23	-0.164	0.870
LDH (U/L)	861 (253, 3054)	819 (164, 10771)	13	630 (311, 3507)	304 (159, 3085)	23	-1.301	0.193
AST (U/L)	146 (40, 447)	82 (21, 775)	14	109 (37, 317)	35 (8, 138)	23	-0.830	0.407

*P<0.05 is considered to be significant. CK: Creatinine kinase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase.

Table 4: The number of patients whose muscle strength and muscle enzymes returned to normal after glucocorticoids or riboflavin treatment

Variables	Glucocorticoids group	Riboflavin group	χ^2	P
Neck muscle	2/15	11/27	2.228	0.136
Proximal upper limbs	5/16	20/27	7.570	0.006*
Proximal lower limbs	2/16	16/27	9.026	0.003*
CK	4/16	16/23	7.501	0.006*
LDH	2/15	9/23	1.817	0.178
AST	4/15	15/23	5.397	0.020*

Values are presented as n/N. *P<0.05 is considered to be significant. CK: Creatinine kinase; AST: Aspartate aminotransferase; LDH: Lactate dehydrogenase.

strength in glucocorticoids group was significantly lower than riboflavin group. Moreover, the number of patients, who had complete recovery in neck muscle strength or muscle enzymes in glucocorticoids group, was also significantly less than riboflavin group. Therefore, glucocorticoids group did not achieve the same efficacy as the riboflavin group neither on improvement of muscle strength nor reduction of muscle enzymes. Glucocorticoids treatment for late-onset MADD patients not only lacks efficacy, but also brings many adverse effects, such as Cushing syndrome, metabolism disorders, and gastrointestinal ulcers. Thus, riboflavin is the unique treatment for late-onset MADD patients and cannot be replaced by glucocorticoids.

Because a number of patients with late-onset MADD are misdiagnosed as polymyositis, standardization of the diagnosis and treatment procedure of this disease is particularly urgent. For “polymyositis patients” with unsatisfactory glucocorticoids effect and middle-young age patients who exhibit symmetrical proximal limbs weakness, exercise intolerance, and difficulty in lifting head as major clinical manifestations should be highly suspicious of late-onset MADD. Muscle pathology and genes testing should be performed to help the differential diagnosis. In Southern China, the hotspot of *ETFDH* mutation is c. 250G<A. And in this study, 75% (30/45) of patients were homozygous, and 95.6% (43/45) patients carried the hotspot mutation. By the hotspot mutation sequencing or PCR-restriction fragment length polymorphism (PCR-RFLP), most late-onset MADD patients in Southern China could be diagnosed. After diagnosed as late-onset MADD, patients should take a large dose of riboflavin to improve symptom and be followed up regularly.

Our study also observed the efficacy of riboflavin treatment for 1-month follow-up. To date, the period of treatment on late-onset MADD remains controversial. As previously reported, patients treated with riboflavin for months showed a complete recovery.^[15,16] But a rapid symptom recovery also has been reported after 1-month riboflavin treatment.^[10,17,18] It is still confused whether the clinical symptoms and biological indicators would return to normal

after a short-term riboflavin treatment. As observed in our study, a significant increase of muscle strength was detected after 1-month riboflavin treatment. The medians of muscle strength and muscle enzymes (CK and AST) returned to the normal level after 1-month riboflavin treatment. The LDH level was still higher than the normal range. However, not all the patients' muscle strength and muscle enzymes returned back to the normal range. In riboflavin group, almost half of the patients still exhibited high-level muscle enzymes and weak muscle strength after 1-month riboflavin treatment. This may due to the short-term use of riboflavin, which may indicate that 1-month riboflavin using is not long enough for the complete recovery of all the patients. Future studies with longer follow-up are required to assess the long-term efficacy on late-onset MADD. In clinic practice, doctors and patients should keep on riboflavin treatment for a longer period.

In conclusion, the efficacy of glucocorticoids is weaker than riboflavin among late-onset MADD. One-month riboflavin treatment is not long enough for all patients to recover completely. Therefore, standardization and longer period of riboflavin treatment is necessary for the complete recovery of late-onset MADD patients.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

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