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Adolescent Hyperuricemia with Lipid Storage Myopathy: A Clinical Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABEF 1 Jingzhe Han
AFG 2,3,4 Xueqin Song
CD 2 Shan Lu
DF 2 Guang Ji
ACD 5 Yanan Xie
CD 2,3,4 Hongran Wu

1 Department of Neurology, Harrison International Peace Hospital, Hengshui, Hebei, P.R. China
2 Department of Neurology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, P.R. China
3 Institute of Cardiocerebrovascular Disease, Shijiazhuang, Hebei, P.R. China
4 Neurological Laboratory of Hebei Province, Shijiazhuang, Hebei, P.R. China
5 Department of Cardiology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei, P.R. China

Corresponding Author: Xueqin Song, e-mail: sxq5679@126.com
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Background: In this study, we investigated the clinical and pathological features of patients with lipid storage myopathy (LSM) complicated with hyperuricemia, to improve clinicians' understanding of metabolic multi-muscular disorder with metabolic disorders, and to reduce the risk of missed diagnosis of LSM.

Material/Methods: From January 2005 to December 2017, 8 patients underwent muscle biopsy and diagnosed by muscle pathology and genetic testing in our hospital. All 8 patients were in compliance with LSM diagnosis. We collected data on the patient's clinical performance, adjuvant examination, treatment, and outcomes to provide a comprehensive report and description of LSM patients with hyperuricemia.

Results: All patients were diagnosed as having ETFDH gene mutations. The main clinical manifestations of patients were chronic limb and trunk weakness, limb numbness, and muscle pain. The serum creatine kinase (CK) values in all patients were higher than normal values. Electromyography showed 3 cases of simple myogenic damage and 3 cases of neurogenic injury. Hematuria metabolic screening showed that 2 patients had elevated glutaric aciduria, and 1 patient had elevated fatty acyl carnitine in the blood. All patients were given riboflavin treatment, and the clinical symptoms were significantly improved, and 3 patients returned to normal uric acid levels after treatment. Pathological staining showed an abnormal deposition of lipid droplets in muscle fibers.

Conclusions: If an adolescent hyperuricemia patient has abnormal limb weakness, exercise intolerance, and elevated serum CK values, clinicians need to be highly alert to the possibility of LSM. Early diagnosis and treatment of LSM should improve the clinical symptoms and quality of life and reduce complications.

MeSH Keywords: Adolescent • Hyperuricemia • Lipid Metabolism

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Background

Hyperuricemia (HUA) is defined as fasting serum uric acid levels in men higher than 420 μmol/L and higher than 360 μmol/L in women, detected on any 2 days after normal diet [1]. Uric acid (UA) is the terminal metabolite of purine compounds in humans, and metabolic disorders of purine can lead to hyperuricemia. The prevalence of HUA is affected by a variety of factors, which include heredity, sex, age, lifestyle, eating habits, drug treatment, and economic development. HUA is divided into primary hyperuricemia and secondary hyperuricemia. HUA is inseparable from gout and is an independent risk factor for metabolic diseases, diabetes, metabolic syndrome (MS), hyperlipidemia, chronic kidney disease, cardiovascular disease, and stroke [2,3].

Lipid storage myopathy (LSM) is a group of autosomal recessive hereditary myopathies caused by abnormal fat metabolism, with abnormal deposition of intramuscular fat as the main pathological feature [4]. In 1969, Bradley et al. [5] first used the term "lipid storage myopathy" to describe a young female patient with a proximal myopathy and a large number of lipid droplets deposited in the muscle fibers. The leading causes of LSM include primary carnitine deficiency (PCD), multiple acyl-CoA dehydrogenase deficiency (MADD), neutral lipid storage disease with ichthyosis (NLSDI), and neutral lipid storage disease with myopathy (NLSDM) [6–10]. Depending on the etiology, LSM is caused by mutations in genes such as SLC22A5, ETFA/B, ETFDH, ABHD5, and PNPLA2, which encode the corresponding proteins [4,11–13]. The clinical signs of LSM are complex and diverse. The main clinical manifestations are volatility or progressive proximal limb muscle weakness and exercise intolerance, which may be associated with multiple systemic involvement of the heart muscle, liver, kidney, peripheral nerves, skin, and eyes, causing numerous systems to be compromised [10]. Infants or severely ill patients may progress to central nervous system involvement, respiratory failure, and recurrent non-ketotic or low-ketose hypoglycemia, metabolic acidosis, and other metabolic disorders [14–16]. Our clinical experience has shown that some patients with LSM have first-episode symptoms of hyperuricemia and have been treated at the departments of immunology and rheumatology. However, there are still reports of LSM with hyperuricemia. This study aimed to investigate the clinical and pathological features of LSM patients with hyperuricemia and to improve clinicians' understanding of the complex and diverse myopathy of the multi-system metabolic disorder, to enhance the diagnostic awareness of myogenic hyperuricemia, and to discuss the potential causes of hyperuricemia that develop during LSM.

Material and Methods

Research patients

From January 2005 to December 2017, 8 patients underwent muscle biopsy in the Department of Neurology, Second Hospital of Hebei Medical University, and LSM patients with hyperuricemia were diagnosed by muscle pathology and genetic testing.

Clinical data collection

We collected clinical data on patients, including sex, age at onset, age at visit, first symptom, course of disease, location of muscle weakness, muscle strength, other system involvement, muscle enzymes, liver and kidney function (uric acid), electromyogram, electrocardiogram, clinical transfer, and prognosis.

Acquisition and processing of blood and urine biochemical analysis specimens

Morning urine collection

We collected an appropriate amount of fresh morning urine in a clean container, immersed a special filter paper into the specimen, and when the whole filter paper was full without any excess urine droplets, put it in a special packaging bag for urine organic acid analysis.

Blood test

We collected 3 drops of blood from the ring finger, dropped directly from the fingertip onto the special filter paper, dried it thoroughly at room temperature for 2–3 h, and then put it into a special packaging bag for the analysis of amino acid and acylcarnitine of genetic metabolic disease.

Acquisition and treatment of muscle specimens

After obtaining the consent of the patient and family and signing the informed consent form, an open muscle biopsy was performed under local anesthesia. The surgical sites included the biceps, deltoid, quadriceps, and gastrocnemius. The removed fresh muscle specimens were embedded as soon as possible and quickly frozen in liquid nitrogen with pre-cooled isopentane. The frozen muscle specimens were placed in a frozen slicer at –22°C, and rewarmed for about 30 min to make 8-μm-thick frozen sections, and the remaining specimens were stored in a –80°C ultra-low temperature freezer.

Genetic testing

All LSM patients received 2 ml of peripheral venous blood, and the muscle disease package was selected for high-throughput

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Table 1. Summary of mutations detected in genes associated with LSM.

N.	Gene	Exon	Nucleotide change	Amino acid change	Homozygous/ heterozygous
1	ETFDH	Exon3	c.250G>A	p. A84T	Het
	ETFDH	Exon12	c.1531G>A	p. D511N	Het
2	ETFDH	Exon7	c.770A>G	p. Y257C	Het
	ETFDH*	Exon12	c.1534G>A	p. G512R	Het
	ETFDH*	Exon12	c.1552C>G	p. L518V	Het
3	ETFDH	Exon10	c.1227A>C	p. L409F	Het
	ETFDH	Exon11	c.1395T>G	p. Y465X	Het
4	ETFDH	Exon2	–	–	Het
	ETFDH	Exon10	c.1227A>C	p. L409F	Het
	ETFDH	Exon10	c.1281-1282delAA		Het
5	ETFDH	Exon3	c.389A>T	p. D130V	Het
	ETFDH*	Exon10	c.1285+2T>C	splicing	Het
6	ETFDH	Exon10	c.1211T>C	p.M404T	Het
	ETFDH*	Exon1–5	–	–	Het
7	ETFDH	Exon1	c.67G>A	p. A23T	Het
	ETFDH	Exon5	c.587A>G	p. Y196C	Het
	ETFDH*	Exon10	c.1351G>A	p. G451R	Het
8	ETFDH	Exon3	c.250G>A	p. A84T	Het
	ETFDH*	Exon5	c.511A>G	p. N171D	Het

Het – heterozygous; * – new mutation; bold – indicate novel mutations.

sequencing technology. The muscle disease gene package mainly includes mitochondrial diseases (related to nuclear gene), lipid storage myopathy (LSM), glycogen storage disease (GSD), dystonia, peripheral neuropathy, congenital fibrosis of the extraocular muscles (CFEOM), distal arthrogryposis (DA), and Duchenne muscular dystrophy or Becker muscular dystrophy (DMD/BMD).

Conventional pathological staining of muscle specimens

The frozen sections were subjected to hematoxylin-eosin (HE) staining, Oil-Red-O (ORO) staining, modified Gomori trichrome (MGT) staining, nicotinamide adenine dinucleotide tetrazolium oxidoreductase (NADH-TR) staining, nonspecific esterase (NSE) staining, succinate dehydrogenase (SDH) staining, ATPase staining (pH 4.5, pH 10.2), and periodic Acid-Schiff (PAS) staining, and morphological changes of muscle fibers were observed under a light microscope.

Statistical methods

The processed data were analyzed using SPSS 21.0 statistical software. Measurement data are expressed as mean±standard deviation ($\bar{\chi}$±SD), and differences were considered statistically significant at $P<0.05$.

Results

Genetic test

The patients were confirmed by genetic testing to have LSM, and all of them had ETFDH gene complex heterozygous mutations (Table 1), including 1 family (Figure 1). A family test was performed on a patient with heterozygous mutations in the ETFDH gene. The results showed that the ETFDH gene mutations came from both parents, and the genetic pattern was consistent with autosomal recessive inheritance; the ETFDH

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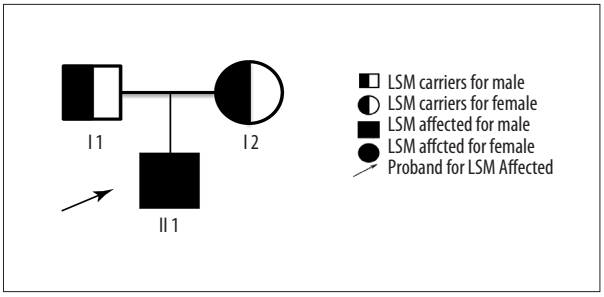

Figure 1. Family map.

gene exon10, c.1227A>C was from the patient's mother and the ETFDH gene exon11, c.1395T>G was from the patient's father (the patient had LSM, the parents were carriers, and none of them had LSM). The most common mutations in the ETFDH gene are c.770A>G and c.1227A>C, and at least 1 mutation site in the patient is located in the FAD domain. Six were discovered to be new mutations, including ETFDH gene c.1534G>A, c.1552C>G, c.1285+2T>C, exon1-5 deletion, c.1351G>A, and c.511A>G. To the best of our knowledge, this is the first such study to be published.

Clinical characteristics

Eight patients were enrolled in this study (6 males and 2 females, sex ratio 3: 1). The average age of the patients was 19.75 years old (range 9–30). Six patients were diagnosed with idiopathic hyperuricemia (75%) before the diagnosis of LSM. More details are shown in Tables 2–4.

Course and family history

All of the patients with LSM in this study were occult onset, with a chronic course of disease ranging from 4 months to 7 years. Among the patients, 1 patient had a family medical history (accounting for 12.5%) and 7 were sporadic cases (87.5%).

Symptoms and signs

The important symptoms of LSM diagnosis were mainly 6 cases of exercise intolerance (6/8, 75%), 1 case of bilateral lower limb weakness (1/8, 12.5%), 1 case of dysphagia (1/8, 12.5%), 2 cases of masticatory muscle weakness (2/8, 25%), 1 case of respiratory muscle weakness (1/8, 12.5%), 3 cases of myalgia (3/8, 37.5%), and 2 cases of nausea and vomiting (2/8, 25%). Additional details are shown in Table 3. The main signs of 7 patients (7/8, 87.5%) were a decrease in limb strength and 2 cases (2/8, 25%) had head weakness. Among the included patients, the symmetrical muscle strength decreased in 7 cases (7/8, 87.5%), the proximal end was heavier than the distal end, and the muscle strength was normal in 1 case. Two patients have symptoms of muscle atrophy (2/8, 25%), 1 case had shoulder girdle muscle and paraspinal muscle atrophy (1/8, 12.5%), and tongue muscle atrophy was present in 1 case (1/8, 12.5%). Three patients had clear predisposing factors that could cause or aggravate muscle weakness, and 3 of them were overworked or hyperactive.

Three patients (3/8, 37.5%) had cardiac involvement, mainly in 2 cases (2/8, 25%) with sinus tachycardia and 1 case presented the highest PR interval (1/8, 12.5%). Two patients (2/8, 25%) had digestive system involvement, which was characterized by nausea and vomiting.

Table 2. First symptoms, predisposing factors, and muscle strength of LSM patients.

N.	Gender	Onset age (year)	Course (year)	Initial symptom	Predisposing factor	Limb weakness				
						Symmetry (yes/no)	Upper limb		Lower limb	
							Proximal	Distal	Proximal	Distal
1	M	16	0.58	Hyp	–	Y	5	5	5–	5
2	M	21	1	Hyp	–	Y	4	5	4	5
3	M	13	1	B-WLL	Exercise	Y	4	5	3	5
4	M	19	7	Hyp	–	Y	4	5	4	5–
5	M	25	1	Hyp	Tired and cold	Y	5	5	5	5
6	M	25	0.33	Hyp	Exercise	Y	4	5	4	5
7	F	9	0.5	WLL	–	Y	3	4	3	4
8	F	30	0.25	Hyp	–	Y	4–	5	4	5

M – Male; F – Female; Hyp – hyperuricemia; WLL – weakness of lower limbs; B-WLL – bilateral weakness of lower limbs; Y – yes; N – no; '–' – not provided.

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Table 3. Main symptoms and signs of LSM patients.

N.	Neck muscle weakness	Chewing weakness	Dysphagia	Respiratory muscle weakness	Exercise intolerance	Muscle atrophy	Gastrointestinal symptom	Myalgia	Paresthesia
1	–	–	–	–	+	–	–	–	–
2	–	–	–	–	–	–	–	–	–
3	–	–	–	+	+	–	Emesis	+	–
4	+	–	–	–	+	–	–	–	–
5	–	–	–	–	+	–	–	+	–
6	–	+	–	–	+	Paraspinal muscles, Shoulder muscle	–	–	–
7	+	–	+	–	+	Tongue muscle	Emesis, Poor diet	–	–
8	–	+	–	–	–	–	–	+	–

Table 4. Laboratory results of LSM patients.

N.	CK (U/L) (0–310 U/L)	ALT (U/L) (9–50 U/L)	AST (U/L) (15–40 U/L)	GLU (mmol/L) (3.9–6.1 mmol/L)	UA (μmol/L) (208–428 U/L)	ECG	EMG		RNS
1	1192	89	160	Unidentified	523	Unidentified	MD	NCAG	–
2	2250	Unidentified	312	Unidentified	587	Unidentified	MD	NCAG	–
3	15050	247	2415	7.64	1516.2	Sinus tachycardia	MD	ND	–
4	1024	70	81	4.8	600	Unidentified	NCAG	NCAG	NA
5	620	64	80	4.24	537	Sinus tachycardia	MD	ND	NA
6	108	20	1.2	4.85	554.2	Unidentified	NCAG	NCAG	NA
7	410	48	107	3.18	436	Sinus tachycardia, P-R	MD	NCAG	–
8	375	29.9	74	Unidentified	489	Unidentified	MD	ND	–

CK – creatine kinase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GLU – urine glucose; UA – uric acid; ECG – electrocardiogram; P-R – P-R maximum of P-R interval; EMG – electromyography; MD – myogenic damage; ND – neurogenic damage; RNS – repetitive nerve stimulation; NA – no abnormality; NCAG – nothing abnormal detected.

Laboratory testing

All of the patients had elevated levels of muscle enzymes (108-15050U/L, Table 4). Uric acid was elevated, with an average of 655.30±351.80U/L. One patient had below normal fasting blood glucose during the period of onset. EMG results showed simple myogenic damage in 3 cases (3/8, 37.5%), neurogenic damage in 3 cases (3/8, 37.5%), and 2 normal patients (2/8, 25%). Three patients underwent hematuria metabolism screening. Two patients presented with urinary 2-hydroxyglutaric acid and 3-hydroxyglutaric acid-induced glutaric aciduria. One patient had increased fatty acyl carnitine of C8–C16 in the blood.

Histopathological staining

The pathological results of muscle biopsy in 8 patients showed that 3 patients had hyperplasia of adipose tissue in the muscle coat. In these patients, fine vacuoles were observed in the muscle fibers, and some of them formed fissures. Normal tissue

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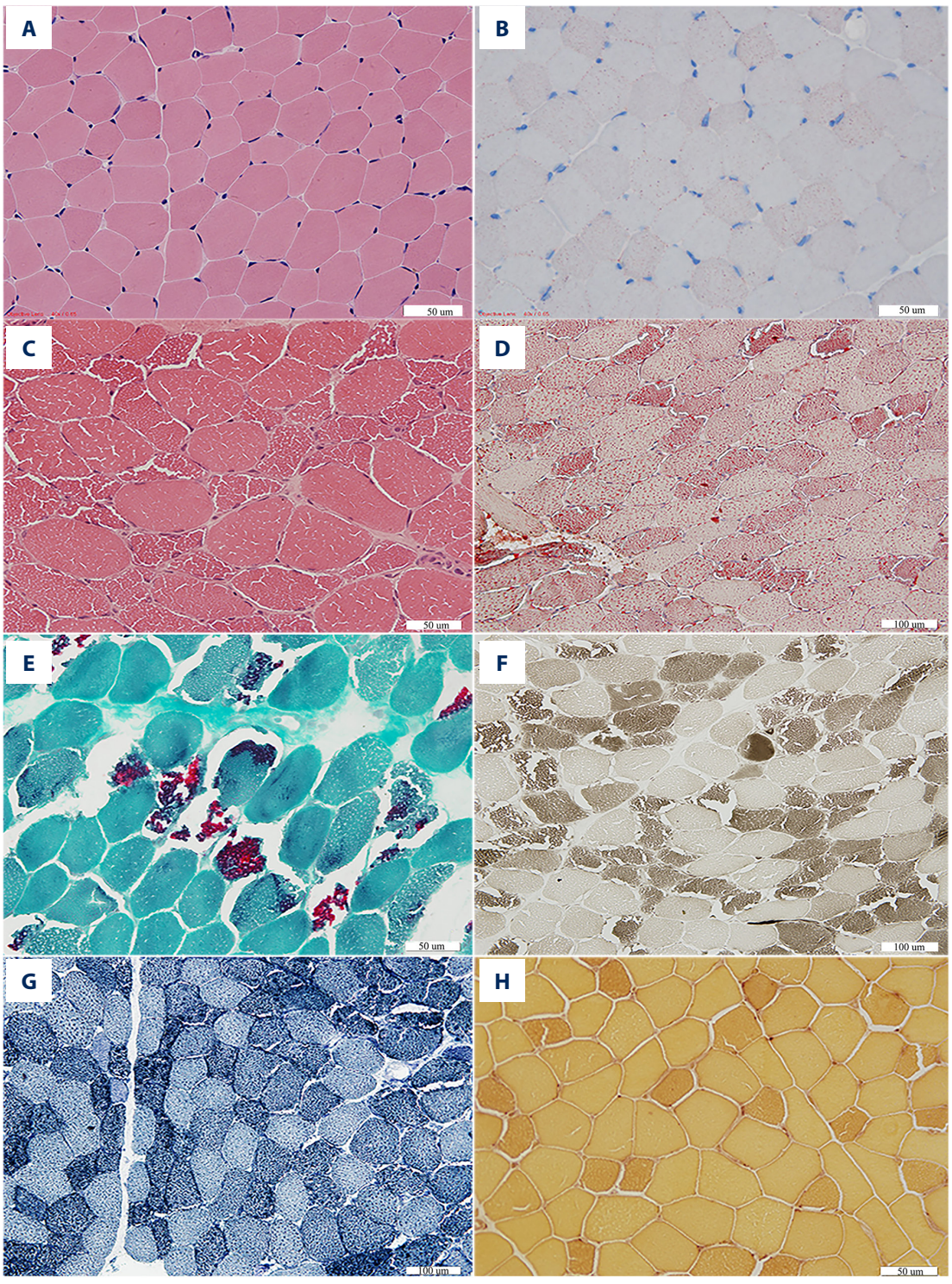

Figure 2. Characteristic histologic results. (**A**) HE staining in normal control (400×); (**B**) ORO staining in normal control (400×); (**C**) HE staining in vacuolar muscle fibers and many atrophic fibers (400×); (**D**) ORO staining in lipid droplets deposition in the myofibers (400×); (**E**) MGT staining in ragged red fiber (RRF, 400×); (**F**) ATPase staining in vacuolated appearance of predominantly type 1 muscle fibers (PH 4.5, 200×); (**G**) NADH-TR staining of deeply stained in atrophic and degenerative muscle fibers (400×); (**H**) NSE staining in deeply stained in atrophic and degenerative muscle fibers (400×).

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was used as a control group for hematoxylin-eosin (HE) staining and ORO staining (Figure 2A, 2B). HE staining (Figure 2C) showed fissures and/or fine vacuoles, and the ORO staining (Figure 2D) showed a marked increase in lipid droplets. Two patients had muscle fiber atrophy, 1 patient had mild nuclear internal migration, and 1 patient had non-finished red fiber (RRF, Figure 2E). ATPase staining (Figure 2F) showed that the 2 types of fibers showed mosaic distribution, type II fibers were dominant in 1 case, and 4 cases of vacuolar-like muscle fibers were mainly type I muscle fibers. The SDH staining of 4 patients showed an uneven distribution of some muscle fiber oxidase, which was deeply stained at the edge or partially stained with atrophic muscle fibers. NADH-TR staining (Figure 2G) in 4 patients showed an uneven distribution of some muscle fiber oxidase, which was deeply stained at the edge or partially stained with atrophic muscle fibers. NSE staining (Figure 2H) of 4 patients showed deep staining of individual atrophic muscle fibers. In 5 cases, both types of muscle fibers showed an abnormal increase in lipid droplets. In patients with type I fibrous atrophy, 1 patient had atrophy involving both types (Figure 2).

Treatment and outcome

All patients were treated with L-carnitine, riboflavin, energy support, and uric acid-lowering drugs. The response of LSM patients was good, and the clinical symptoms were significantly improved. The total effective rate was 100%. Some patients had reviewed muscle pathology, showing that the lipid droplets in the muscle fibers decreased or even disappeared. In addition, uric acid levels decreased in 8 patients after treatment, and uric acid returned to normal in 3 patients (37.5%).

Discussion

Hyperuricemia is caused by excessive uric acid production and/or little excretion in the body, which can be divided into primary and secondary. The cause of hyperuricemia in 90% of patients with primary gout is related to decreased uric acid excretion, and the mechanisms that may be involved are: 1) reduction of glomerular filtration; 2) increased renal tubular reabsorption; and 3) decreased renal tubular secretion [17,18]. The cause of hyperuricemia in 10% of patients with primary gout is related to excessive uric acid production [19–21]. The mechanism may be related to increased amounts and activity of some enzymes in the process of uric acid production and/or decreased amount and activity of some enzymes that inhibit uric acid production. Studies have shown that deficiency of enzymes is mostly related to genetic variation [22]. Reduced renal uric acid excretion and excessive production of uric acid due to bone marrow and lymphoproliferative diseases can lead to secondary hyperuricemia [23,24]. Due to the uricosuric effects of estrogen, the prevalence of gout in females is very low in the premenopausal period [25,26]. In this study, we found that male patients are more likely than women to have LSM with hyperuricemia, and the incidence rate was much higher than in female patients; this is related to the protective effect of estrogen. HUA is predominantly encountered in males and postmenopausal females [27]. HUA that develops at an early age usually indicates an underlying genetic disease. Genetic disorders of purine metabolism must be investigated in young premenopausal female patients with HUA who have no hypertension or renal insufficiency [28]. In this study, patients who had LSM combined with HUA were mainly young, in line with the above guidelines. Therefore, in young patients with HUA, clinicians should be alert to the possibility of genetic metabolic diseases comprising LSM.

The leading causes of LSM include PCD, MADD, NLSDI, and NLSDM. Depending on the cause of the disease, LSM is caused by mutations in genes such as SLC22A5, ETFA/B, ETFDH, ABHD5, and PNPLA2, which encode the corresponding proteins. The ETFDH gene consists of 13 exons that can encode 617 amino acids, including FAD domain, 4Fe-4S cluster, and ubiquinone domain [29]. So far, most of the mutations were found to be located in the FAD domain [10]. The clinical symptoms of the majority of MADD patients can be significantly improved after treatment with riboflavin. All patients in this group were riboflavin-responsive MADD (RR-MADD) with mutations occurring in the FAD domain and responded well to riboflavin.

The clinical manifestations of LSM are complex and diverse, with the main clinical manifestations being volatility or progressive proximal muscle weakness and exercise intolerance [30]. Although the first symptom of HUA combined with LSM is hyperuricemia, we found that the most common reason for which patients seek medical care is limb weakness and exercise intolerance. The characteristics of the patient in this study were consistent with the other reports [31]. Most patients had seizures or fluctuating limb weakness, intolerance of fatigue, proximal limb weakness, weakness of the neck muscles and masticatory muscles, and muscle weakness symptoms in the stress state of infection, fatigue, cold, and hunger. LSM patients may have gastrointestinal symptoms caused by gastrointestinal mucosal lipid deposition, such as vomiting and diarrhea.

In addition to muscle involvement, severe LSM patients may have multiple systemic manifestations such as dilated cardiomyopathy, recurrent rhabdomyolysis, myoglobinuria, and ketohypoglycemia, and accompanied by elevated levels of aminotransferase, blood ammonia, and urinary amino acids [32–35]. In the present study, some patients had multiple system involvement; cardiac involvement was predominantly sinus tachycardia. The patient's muscle enzyme levels were mildly or moderately elevated and increased with CK. In addition, some patients had hypoglycemia during the attack, suggesting

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metabolic abnormalities. Serum CK was elevated in all patients in this group, and EMG was mainly caused by myogenic damage, neurogenic damage, or both, and this is consistent with previous reports. In addition, the rate of abnormal electromyography was 75%. In 2 patients with no abnormal electromyogram, the enzymatic index was higher than average, suggesting that the increase of muscle enzyme sometimes appears earlier than the change in EMG. The muscle pathology of LSM patients showed abnormal deposition of lipid droplets in muscle fibers, which is consistent with previous reports.

We found that hyperuricemia had developed in patients with LSM, and no similar reports have been published in the past. Before the diagnosis of LSM in 6 patients, the typical manifestations of no muscle weakness were only pure hyperuricemia, suggesting that hyperuricemia may be the first manifestation of LSM. In addition, 6 patients had long been diagnosed with idiopathic hyperuricemia, indicating that clinicians have insufficient understanding of hyperuricemia combined with LSM. The effects of LSM and HUA may arise because muscle exercise causes elevated purine metabolite concentrations in the plasma by increasing the flow of purine nucleotides from muscle tissue to plasma, thus leading to hyperuricemia due to increased uric acid synthesis (myogenic hyperuricemia), while other organic acids such as lactic acid and pyruvic acid in the body inhibit the secretion of uric acid by the renal tubules, resulting in a decrease in uric acid excretion. The blood organic acid test results of 3 patients in this group showed that 2 patients had urinary 2-hydroxyglutaric acid, 3-hydroxyglutaric acid increased glutaric aciduria, and 1 patient had high blood fatty acylcarnitine level. In addition, early detection of the cause of adolescent HUA and clear diagnosis of LSM are essential to improve the prognosis of these patients. Firstly, this type of patients can develop gout during puberty, and continuous HUA can cause damage to the kidney, heart, central nervous system, and other parts of the body. Secondly, RR-MADD has a significant therapeutic effect. Early diagnosis can help avoid damage of lipid deposits to various target organs. Some patients in this group were treated with HUA alone but the effect was poor and the uric acid decrease was not obvious.

All our patients were treated with riboflavin-based and uric acid-lowering drugs, and the clinical symptoms were significantly improved. Some patients have returned to normal uric acid levels. Two patients were reviewed for muscle pathology after treatment, showing that the lipid droplets in the muscle fibers decreased or even disappeared. Unfortunately, the urine organic acid content after treatment was not reviewed. There is currently no standard treatment for LSM combined with HUA, and there is no consensus on the treatment of this type of patients. However, for adolescent HUA patients, clinicians should be alert to the possibility of LSM and initiate early application of riboflavin to avoid simple uric acid treatment, but because of the small number of cases, further research is needed. Therefore, although LSM is a hereditary disease, after the diagnosis of RR-MADD, drug treatment can significantly improve the clinical symptoms and improve the quality of life.

Conclusions

Because the clinical manifestations of LSM are complex and diverse, simple assessment of hyperuricemia should be first performed. LSM combined with HUA is most common in adolescent male patients; LSM combined with HUA gene mutation is mainly due to MADD caused by mutation of ETFDH gene, and the correlation between HUA and gene mutation types needs further study. In the present study, the main clinical features, auxiliary examination, and muscle pathology of patients with LSM combined with HUA were consistent with findings of previous reports. Clinicians should pay attention to adolescent patients with simple hyperuricemia and be alert to the possibility of genetic metabolic diseases, especially LSM. The treatment plan for LSM patients with HUA still needs further study.

Conflict of interest

None.

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