# Chapter 14
# A 37-Year-Old Woman with Leg Weakness and CK Elevation


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## History

A 37-year-old woman presented for evaluation of leg weakness. The symptom started about 6 months prior to the office visit and were gradually worsened. She had to rest during household chores. She had great difficulty with stairs, needed to use the hand rail, and felt as if there were weights on her legs. She would sometimes have to push with her arms to get out of chairs. Her arms would get tired when she would fix her hair. She had some minor anterior thigh discomfort but no stiffness, spasms, or cramps. She had mild non-radiating low back pain but no neck pain. She denied ocular or bulbar symptoms. She had very mild shortness of breath with exertion but no orthopnea. She denied constitutional symptoms, skin rashes, or joint swelling. She denied any history of pigmenturia. There was no history of myotoxic drug exposure. Her past medical history included gastro-esophageal reflux disease treated with proton pump inhibitor, vitamin B12 deficiency undergoing supplementation, and a remote episode of polyarthralgia with unclear diagnosis. Family history was negative for neuromuscular diseases, adverse reactions to anesthesia, or autoimmune diseases. She was a non-smoker, and she did not drink alcohol or use illicit drugs.

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## Physical Examination

Her general examination was normal. Neurological examination showed normal mental status and cranial nerve functions. Muscle bulk was notable for bilateral calf hypertrophy. Tone was normal. There was mild weakness detected in the bilateral shoulder abductors, elbow flexors, hip flexors, and hip extensors (MRC 4+/5), as well as subtle weakness in the thigh abductors (5−/5). Sensory examination was normal. Deep tendon reflexes were slightly brisk and symmetric. Hoffmann sign was absent. Toes were downgoing bilaterally. Her gait and coordination were normal.

## Investigations

Blood tests showed elevated creatine kinase (CK) at 1,139 U/L, mildly elevated sedimentation rate at 31 mm/hour (normal: 0–20) and C-reactive protein 6.9 mg/L (normal: < 5), minimally elevated AST 37 U/L (10–30) and ALT 41 U/L (6–29) but normal alkaline phosphatase. Renal function, thyroid function, and lactate level were all normal. Hepatitis B and C, HIV, and HTLV serology was negative. Antinuclear antigen (ANA), extractable nuclear antigen antibody (ENA) panel, rheumatoid factor, and myositis antibody panel were all negative. Acetylcholine receptor and muscle-specific kinase antibodies were negative. Very long chain fatty acid profile was normal. Dried blood spot analysis for acid alpha glucosidase activity was normal. Magnetic resonance imaging (MRI) of the brain and spine was unremarkable. Motor and sensory nerve conduction studies (NCS) were normal. Needle electromyography (EMG) study demonstrated an irritable myopathy, with findings most pronounced in the thoracic paraspinal muscles. A right biceps muscle biopsy was performed.

## Muscle Biopsy Findings

This right biceps muscle biopsy (Fig. 14.1) showed a vacuolar myopathy with many fibers containing multiple small sarcoplasmic vacuoles. These fibers were mainly type 1 fibers, which appeared generally smaller than type 2 fibers. The sarcoplasmic vacuoles were not rimmed or autophagic; they contained excessive neutral lipids but not glycogens as demonstrated by Oil Red O and PAS stains. Some fibers with vacuolar changes also displayed incomplete ragged red appearance. There were no COX-deficient fibers. Electron microscopy (EM) confirmed the presence of abundant accumulations of lipid droplets associated with pleomorphic mitochondria between the myofibrils and less frequently under the sarcolemma. No abnormal cristae pattern or crystalline inclusions were seen. These findings are characteristic of a lipid storage myopathy.

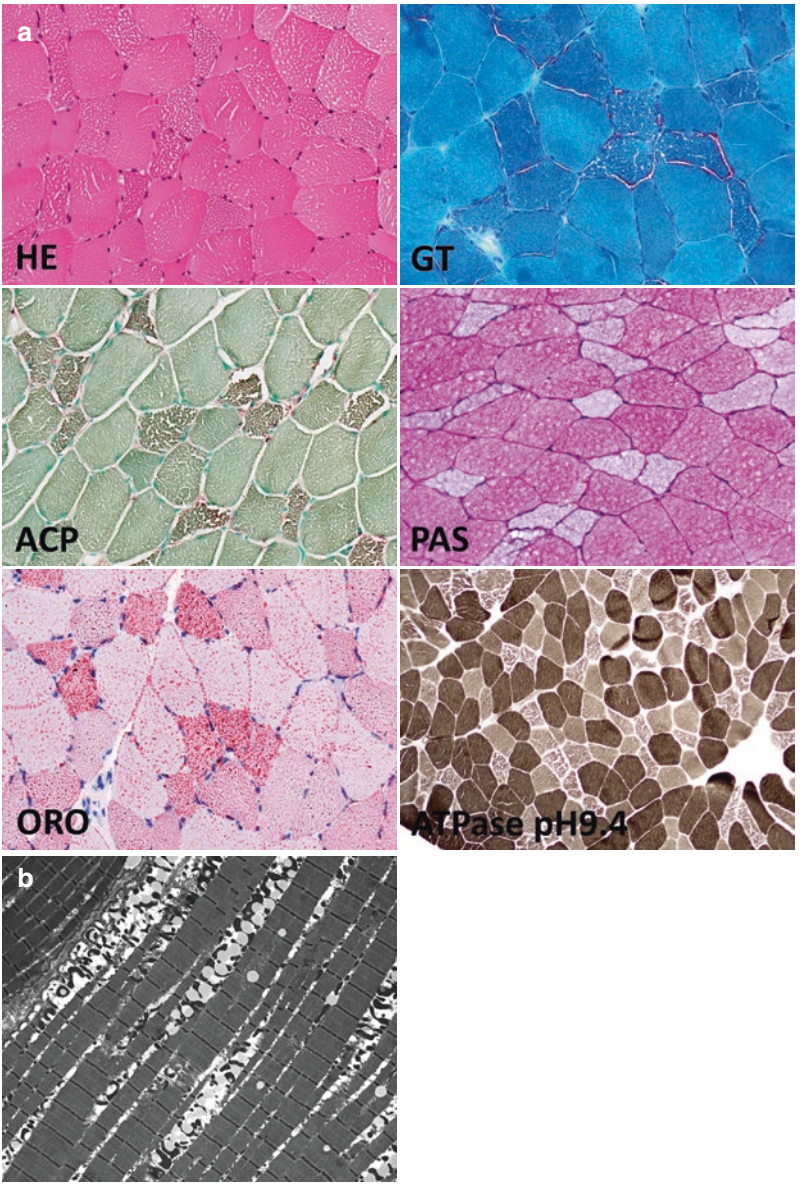


**Fig. 14.1** Lipid storage myopathy. (**a**), HE stain shows many fibers containing multiple small sarcoplasmic vacuoles. Gomori trichrome stain (GT) shows these vacuoles are not red rimmed; a few of these fibers also display incomplete ragged red appearance. Acid phosphatase stain (ACP) shows no increase in acid phosphatase activity. PAS stain shows no abnormal glycogen accumulation. Oil Red O (ORO) stain shows some type 1 fibers containing intense larger red droplets, indicating excessive lipid accumulation. ATPase pH 9.4 stain shows the vacuolar changes are mostly seen in type 1 fibers (pale), and the type 1 fibers are generally smaller than the type 2 fibers (dark). (**b**), EM shows abundant sarcoplasmic accumulations of lipid droplets (round empty spaces with no membranes) associated with pleomorphic mitochondria between the myofibrils and under the sarcolemma

## Additional Investigations After the Muscle Biopsy Diagnosis

After the muscle biopsy diagnosis of a lipid storage myopathy was obtained, the patient had additional laboratory tests. Urine organic acids were normal. Acylcarnitine profile showed low levels of essentially all species. Plasma total and free carnitine levels were very low; the esterified carnitine level was also decreased but to a lesser degree. The total carnitine level was 5 μmol/L (normal: 25–28), free carnitine level was 3 μmol/L (normal: 19–48), and the esterified carnitine level was 2 μmol/L (normal: 4–13). The esterified carnitine/free carnitine ratio was elevated at 0.63 (normal: 0.13–0.42).

## Final Diagnosis

Lipid storage myopathy with carnitine deficiency

## Patient Follow-up

The patient declined genetic testing for more specific characterization of her lipid storage myopathy. She was recommended to take empiric supplementation with L-carnitine and riboflavin. She was also referred for cardiology evaluation.

## Discussion

Lipid storage myopathies (LSM), a type of metabolic myopathies, are genetic disorders caused by defects in the intracellular triacylglycerol catabolism and characterized by excessive lipid accumulation mainly in the muscle fibers. Body triacylglycerol is mostly derived from dietary fat with a small portion synthesized in adipocytes and liver. It is stored in subcutaneous and visceral adipose tissue with minimal amount in muscle, in the form of lipid droplets, to provide energy for muscle activity. Triacylglycerol catabolism takes several key steps. Triacylglycerol is first hydrolysed to fatty acids by lipases. Fatty acids are then transported in circulation and taken up by target cells. Within target cells, non-esterified fatty acids couple with coenzyme A (CoA) to form short-chain (< C8), medium-chain (C8–12), long-chain (C12–24), and very long-chain (> C24) acyl-CoAs by fatty acyl-CoA synthetases. While short- and medium-chain acyl-CoAs can passively diffuse across mitochondrial membranes, long- and very long-chain acyl-CoAs need the

carnitine shuttle system. They bind free carnitine catalyzed by the carnitine palmitoyltransferase I (CPT I) to form acylcarnitines, which then translocate into mitochondrial matrix, where acylcarnitines dissociate back to acyl-CoAs and free carnitine catalyzed by the carnitine palmitoyltransferase II (CPT II). Acyl-CoAs then undergo beta-oxidation catalyzed by acyl-CoA dehydrogenases to generate acetyl-CoA molecules, which subsequently undergo tricarboxylic acid (TCA) cycle and oxidative phosphorylation to generate the energy molecule adenosine triphosphate (ATP) [1].

LSM are genetically and phenotypically heterogeneous. The onset can be early or late, and the disease presentation can be acute or chronic. Clinical presentations of infant-onset are similar across different types and are severe with multisystem involvement. Patients usually present with hypotonia, hypoketotic hypoglycemic encephalopathy, hepatomegaly, and cardiomyopathy. The late-onset presentations can be acute (recurrent rhabdomyolysis) or chronic (fixed slowly progressive muscle weakness), and the disease is relatively mild [2–5].

Recurrent rhabdomyolysis has been associated with defects in mitochondrial fatty acid transport or beta-oxidation, such as deficiencies in CPT II, very-long-chain acyl-CoA dehydrogenase (VLCAD), trifunctional protein, and lipin-1. CPT II deficiency mainly causes recurrent rhabdomyolysis in adults, which is frequently triggered by strenuous exercise and/or fasting [6, 7]. Lipin-1 deficiency is one of the most common causes of severe recurrent rhabdomyolysis in children [8, 9]. Muscle biopsy in these patients usually does not show significant abnormal lipid accumulation. In patients with CPT II deficiency, neurological examination, CK, EMG, and muscle biopsy are usually normal between the rhabdomyolysis attacks. During or shortly after the attacks, muscle biopsy may show a necrotizing myopathy with the presence of necrotic and regenerating muscle fibers. Besides acute management of rhabdomyolysis, these patients should avoid triggers such as fasting, prolonged exercise (> 30 minutes), infection, fever, cold, emotional stress, and high-fat diet. They may change diet to high-carbonhydrate and low-fat diet, take extra carbohydrate before and during exercise, and take frequent meals. They may also take carnitine. Bezafibrate did not improve fatty acid oxidation in patients with CPT II or VLCAD deficiency [10].

There are four types of LSM: neutral lipid storage disease with myopathy (NLSD-M), neutral lipid storage disease with ichthyosis (NLSD-I), primary carnitine deficiency (PCD), and multiple acyl-CoA deficiency (MADD).

NLSD-M is an autosome recessive disease caused by mutations in the patatin-like phospholipase domain containing 2 (*PNPLA2*) gene which encodes adipose triglyceride lipase (ATGL) [11]. NLSD-M may manifest gradually progressive muscle weakness (either distal- or proximal-predominant), exercise intolerance, myalgia, and cardiomyopathy with a disease onset in childhood or early adulthood [12, 13]. NLSD-I is caused by mutations in the comparative gene identification-58 (*CGI-58*) gene which encodes alpha/beta-hydrolase domain-containing protein 5 (ABHD5), a co-activator of ATGL [14]. It tends to cause less muscle weakness but

prominent skin involvement with non-bullous congenital ichthyosiform erythroderma as well as cognitive, ophthalmologic, and hearing deficits, hepatomegaly, and intestinal involvement [15–17]. The disease onset of NLSD-I is earlier than that of NLSD-M. CK is typically elevated in NLSD-M but may be normal in NLSD-I. Lipid accumulation is seen in muscle as well as many other tissues. Lipid accumulation seen in leukocytes on routine peripheral blood smear is called "Jordan's anomaly" [4, 18]. There is no specific treatment for NLSD. Topical application of urea-containing emollients may be used for skin ichthyosis. Dietary changes with high-carbonhydrate and low-fat diet supplemented with medium-chain triacylglycerols are beneficial.

PCD is caused by mutations in the solute carrier family 22 member 5 (*SLC22A5*) gene which encodes organic cation/carnitine transporter 2 (OCTN2) responsible for the cellular uptake of carnitine [19, 20]. The *SLC22A5* mutations impair the carnitine transport into cells and carnitine reuptake by kidneys, thus causing carnitine wasting. As carnitine is required for long-chain and very long-chain fatty acid transport from cytoplasm into mitochondria, carnitine deficiency causes impaired utilization of fatty acids for energy production. PCD has a wide clinical spectrum. Infant- or childhood-onset may manifest progressive limb weakness, cardiomyopathy, hepatomegaly, and recurrent episodes of hepatic encephalopathy, while adult-onset may only show subtle fatigability, mild progressive limb weakness, or no symptoms at all (though cardiac involvement may still be present) [6, 21]. Previously asymptomatic women may decompensate during pregnancy [22]. CK may or may not be elevated, and total carnitine and acylcarnitine levels are extremely low. Urine organic acids are normal. Lipid accumulation is seen in muscle and liver. Treatment with lifelong L-carnitine supplementation, 100–400 mg/kg/day in four daily doses, titrated to normalize plasma carnitine levels, can improve skeletal and cardiac muscle function and yield a favorable prognosis [23–26]. Pivalic acid containing antibiotics should be avoided. Patients should also have regular screening for cardiac involvement with echocardiogram and electrocardiogram [18, 22].

MADD, also known as glutaric acidemia type II, is an autosomal recessive disorder caused by dysfunction of flavoproteins, which normally function to transfer electrons from acyl-coA dehydrogenases to coenzyme Q10 in the electron transport chain [18]. The disease is caused predominantly by mutations in the electron transfer flavoprotein (*ETFA*, *ETFB*) or ETF dehydrogenase (*ETFDH*) genes. It can also be caused by mutations in the other genes associated with riboflavin transport such as *SLC52A1*, *SLC52A2*, and *SLC52A3,* or flavin adenine dinucleotide (FAD) transport or synthesis such as *SLC25A32* and *FLAD1*. Mutations in the *ETFA* and *ETFB* tend to cause the severe neonatal-onset form, while *ETFDH* mutations are linked to the mild adult-onset form [27]. Most late-onset cases present with a gradual onset of muscle weakness, exercise intolerance, and myalgia, although a third present with acute and episodic metabolic decompensation with lethargy, vomiting, hypoglycemia, acidosis, and liver

dysfunction [28]. Cardiomyopathy can be seen in both neonatal- and late-onset forms. Lipid accumulation can be seen in muscle and liver. There may be secondary carnitine deficiency, but blood acylcarnitines of all species are usually increased. Serum CK may be normal or elevated, though note that labs may be normal if not drawn during an episode of metabolic decompensation. A subset of MADD patients respond to riboflavin very well, and all the riboflavin-responsive cases appear associated with *ETFDH* mutations [27–30]. Riboflavin should be initiated at 100–400 mg daily. Carnitine and coenzyme Q10 supplementation may also be considered, particularly if there is evidence of secondary deficiency [4]. The mechanism of riboflavin-responsiveness is still not entirely clear, but supplementation likely increases mitochondrial FAD concentration, which could increase FAD binding and/or increase the chaperone effect of FAD to improve flavoprotein folding [27]. Patients should also avoid fasting [18].

Diagnostic evaluation of LSM should include blood and urine biochemical analyses, muscle biopsy, and genetic testing. Biochemical analyses to measure blood and urine carnitines, plasma acylcarnitine species, and urine organic acids are helpful to distinguish different types of LSM, but the definitive diagnosis relies on the gene tests. In PCD, plasma total and free carnitine levels as well as acylcarnitine species are usually severely reduced. Urine excretion of carnitine is increased. Urine organic acids are normal. In MADD, free carnitine may be normal or low (secondary deficiency), all acylcarnitine species are elevated, and urine C5 to C10 dicarboxylic acids are elevated [4, 18]. It may also show secondary CoQ10 deficiency. In CPT II deficiency, plasma C16 and C18 acylcarnitines are increased, but the free carnitine level is normal. Our patient showed markedly reduced blood free and total carnitines as well as low acylcarnitines but normal urine organic acids. She was well-nourished, had no significant hepatic or renal dysfunction, and was not on any medications which could cause carnitine deficiency. Therefore, she was most likely to have lipid storage myopathy from primary carnitine deficiency. Unfortunately, she refused the gene test to confirm the diagnosis and the genetic cause.

Muscle biopsy plays an essential role in diagnosing LSM as seen in our case, as the clinical presentation with mild, progressive, and proximal limb muscle weakness is quite non-specific, and can be seen with inflammatory myopathies, late-onset Pompe disease, and limb-girdle muscular dystrophies. We initially suspected an inflammatory myopathy given her weakness pattern, moderate CK elevation, and irritable myopathic changes on EMG. Bilateral calf hypertrophy also raised a suspicion for a limb-girdle muscle dystrophy. But her muscle biopsy showed no inflammation or dystrophic changes; it showed prominent sarcoplasmic lipid accumulation in type 1 fibers, characteristic for a LSM.

Muscle biopsy in LSM such as PCD typically shows a vacuolar myopathy with many small vacuoles present in the sarcoplasm of predominantly type 1 fibers. These vacuoles are not red rimmed in the Gomori trichrome stain. They are not of lysosomal origin with increased acid phosphatase activity (autophagic)

as seen in Pompe disease. They are not filled with excessive PAS-positive glycogen as seen in glycogen storage disease. These vacuoles are filled with excessive neutral lipids that can be readily revealed by Oil Red O or Sudan black stain. Oil Red O stain shows intense and larger red lipid droplets in the affected type 1 fibers. EM often shows prominent accumulation of lipid droplets between the myofibrils and under the sarcolemma. The lipid droplets are often adjacent to mitochondria. Mitochondrial abnormalities such as increased proliferation, subsarcolemmal accumulation, and pleomorphism are often present [31].

It is important to obtain a specific diagnosis of LSM, as some of the LSM are treatable. PCD can be successfully treated with a high-dose of L-carnitine supplementation (100–400 mg/kg/day). Early carnitine therapy not only improves muscle strength, but also prevents cardiomyopathy and other irreversible organ damage [23–26]. A subset of MADD patients respond very well to riboflavin, and all riboflavin-responsive cases are associated with *ETFDH* mutations [27]. Riboflavin should be initiated at 100–400 mg daily. There is still no specific effective treatment for NLSD-M or NLSD-I. Besides the specific supplementations, it is critical for patients with LSM to avoid various triggers of rhabdomyolysis and to modify lifestyle and diet.

## Pearls

**Clinical Pearls**

1. Lipid storage myopathies, especially those with late-onset, can present with mild, progressive, proximal limb weakness, mimicking inflammatory myopathy, muscular dystrophy, and late-onset Pompe disease, among others.
2. Although recurrent rhabdomyolysis is a feature of many patients with metabolic myopathies, lack of a history of rhabdomyolysis does not exclude a metabolic myopathy.
3. Muscle biopsy plays an essential role in diagnosing LSM.
4. Once the diagnosis of LSM is made by a muscle biopsy, biochemical analyses of blood and urine carnitine levels, acylcarnitine profile, and urine organic acids can help differentiate different types of LSM to direct gene test.
5. As PCD and some MADD patients respond very well to L-carnitine and riboflavin, respectively, it is important to make a specific genetic diagnosis for a patient with LSM.
6. It is critical for patients with LSM to avoid various triggers of rhabdomyolysis and to modify lifestyle and diet.

**Pathology Pearls**

1. Muscle biopsy in LSM such as PCD typically shows a vacuolar myopathy with many small sarcoplasmic vacuoles mainly in type 1 fibers. These vacuoles are not rimmed; they do not show increased acid phosphatase activity or contain PAS-positive glycogen accumulation. These vacuoles contain excessive neutral lipids which can be revealed by Oil Red O or Sudan black stain. Oil Red O stain shows intense larger red droplets in type 1 fibers.
2. EM is very useful in evaluating LSM, which typically shows prominent accumulation of lipid droplets between myofibrils and under sarcolemma. The lipid droplets are often adjacent to mitochondria. Mitochondrial structural changes such as increased proliferation, subsarcolemmal accumulation, and pleomorphism can be seen in PCD. But crystalline inclusions are absent in contrast to primary mitochondria diseases.
3. Muscle biopsy in LSM does not show dystrophic changes.

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