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A Case of Muscular Dystrophy Simulating Inflammatory Myopathy

Introduction

The diagnosis of patients with clinical myopathy (muscle weakness + elevation of serum muscle enzymes) has become difficult and increasingly complex. A variety of new diseases have been described, with characteristic genetic, clinical, biochemical and histopathologic features. This case report is a good example of the pitfalls to be avoided in clinical practice.

Case Report

An 18-year-old Caucasian female presented to the rheumatology division of Carle Clinic without a specific physical complaint. She had been referred upon advice of her gastroenterologist, who requested a consultation because of abnormal muscle enzymes and elevated serum transaminases.

The patient was an excellent student at a highly competitive university and gave a history of having been rejected as a blood donor because of abnormal liver function tests. She saw her primary care physician who referred her to gastroenterology for a liver biopsy, which was normal. The gastroenterologist requested a creatine phosphokinase (CPK) test that showed initial levels of 9710 IU/L and serum aldolase of 65.4 U/L. These values made clear that the patient was suffering from a muscle disease, responsible for the elevation of CPK, the aldolase and the transaminases. This realization prompted a rheumatology consultation.

At the time of the initial rheumatology visit, the patient gave no history of any significant muscle weakness; in fact she was exercising regularly, including swimming laps 2–3 times per week. The review of systems was negative for any rash, muscle aches and joint pains. Past medical history was positive for infectious mononucleosis at age 16 and an episode of pneumonia as an infant. Family history was negative for neuromuscular disease. Social history was positive for minimal smoking and an occasional alcoholic drink. The only medications the patient was taking were

amoxicillin for acne and fluoxetine for mild depression. She had no known allergies.

Upon physical examination, the patient was a healthy-appearing, overweight Caucasian female with normal vital signs. She had no rashes, no other skin changes, no lymphadenopathy and no abnormalities of the head, eyes, ears, nose, throat, thyroid gland, heart, lungs or abdomen.

The patient had no signs of joint inflammation and the muscular examination showed normal strength of the individual muscle groups in the extremities when checked on the examining table. However, she could not get up after squatting without pushing herself up with her arms and she was not able to walk on her heels. Cervical spine, lumbar spine and neurological examination were unremarkable. She had normal deep tendon reflexes and normal sensation to touch in the hands and feet.

The initial diagnostic impression was probable genetic/metabolic myopathy but an atypical inflammatory myopathy could not be ruled out.

Further blood investigations revealed:

CBC – Normal
Serum myoglobin – 663 (30 or less ug/l)
Creatine phosphokinase – 12,220 (22–269 IU/L)
Serum aldolase – 65 (3–7.5 U/L)
C-reactive protein – 2.6 (≤ 10)
ESR – 14 (0–25 mm/hr)
Serum protein electrophoresis – Normal
Anti Jo-1 antibody – Negative (< 1.00)

An MRI of the thighs was ordered, searching for diagnostic clues and assistance in choosing a biopsy site.

Report of the MRI:

Vague increased signal throughout all of the muscle groups of both thighs. T1 images demonstrated fat streaking through all of the muscle groups in the anterior and posterior thighs. The

signal increase was most evident in the right adductor longus and the right and left vastus medialis muscles.

Impression: Polymyositis involving all muscle groups of both thighs.

Other Imaging:

Chest x-ray – Normal

CT scan of abdomen/pelvis – Normal

Upper/lower GI endoscopy – Hiatal hernia and small rectal arteriovenous malformation. Otherwise these were normal studies.

Course and Treatment

The patient was advised to avoid strenuous exercise and was referred to physical therapy for mild muscle-setting exercises. She was also referred to a specialized neuromuscular unit at a tertiary facility to have the muscle biopsy performed and interpreted using the newest techniques that could elucidate the diagnosis.

The muscle biopsy report described:

1. Prominent variation in muscle fiber size and staining
2. Scattered necrotic muscle fibers with macrophage-like cellularity in many areas
3. Vessels were unremarkable and the endomysial connective tissue was mildly increased
4. Congo red highlighted inflammation associated with numerous necrotic appearing muscle fibers
5. Alkaline phosphatase strongly stained perimysial connective tissue
6. There was no storage material on periodic acid-Schiff (PAS) or Sudan stain
7. Phosphorylase and AMPDA (5'-adenylic acid deaminase) were present

These findings were considered compatible with polymyositis. The neuromuscular consultants recommended high dose intravenous pulses of methyl prednisolone as initial treatment. Instead, and because of the minimal muscle weakness, we decided to recommend the usual rheumatologic protocol and the patient was started on 40mg daily of prednisone po with the plans for addition of methotrexate after assessing the initial response.

Five weeks after the beginning of corticosteroid treatment the patient was definitely worse, including a sudden episode of aggravated weakness with difficulty in getting up from the floor. At this point the patient was started on methotrexate 7.5mg/week with subsequent increases to 10mg/week, 12.5mg/week and eventually 15mg/week.

Follow-up laboratory testing showed increases in all the muscle enzymes and serum myoglobin:

CPK – 23,500 (22–269 IU/L)

Aldose – 178 (3–7.5 IU/L)

AST– 302 (17–59 IU/L)

ALT– 485 (7–40 IU/L)

Serum myoglobin – 1870 (30 or less ug/l)

Because of further deterioration of the muscle function and the appearance of obvious side effects from corticosteroids, such as increased weight and aggravation of her acne, the patient was referred back to the neuromuscular unit with a special request for a review of the muscle histology including histochemical investigation of specific muscle proteins.

The patient was re-examined by the consultants and re-examination of the muscle biopsy showed absence of dysferlin. The diagnosis was changed to a limb girdle muscular dystrophy (LGMD) type 2B, due to a mutation or absence of the dysferlin gene. The methotrexate was discontinued and prednisone tapered off as quickly as possible.

The patient regained her pretreatment muscle strength quickly and was referred for a neurology evaluation and genetic counseling.

Discussion

Limb girdle muscular dystrophy (LGMD) includes a number of disorders with different etiologies. It is a generic term describing patients with a muscular condition of hip and shoulder distribution; in other words, patients with a muscular dystrophy with predominantly proximal distribution of weakness, which early in the course spares the distal muscles and muscles of the face and extraocular muscles.

As the diagnosis of LGMD really describes a group of several different disorders it is not surprising that the genetics are varied. Most cases are inherited as an autosomal recessive disease and are sporadic; however, families with an autosomal dominant pattern have also been described.^{1,2}

Mutations within the same gene may result in different phenotypes. For example, mutations in the gene encoding for lamin A/C may result in phenotypes of the autosomal dominant Emery-Dreifuss muscular dystrophy, LGMD 1B or the phenotype of cardiomyopathy with conduction system disease. LGMD 2B and the Miyoshi distal myopathy are caused by mutations of the dysferlin gene. In experimental mice, deficiency of dysferlin interferes with the ability of the sarcolemma to reseal injuries, resulting in

muscular degeneration.^{3,4} Sarcoglycanopathies are early onset autosomal recessive LGMDs caused by mutations in the sarcoglycan genes. Other genetic disorders in LGMD include mutations in the dystrophin gene, calpain 3 gene, fukutin related proteins, myotilin, telethonin, caveolin and O-mannosyl transferase.^{5,6}

The clinical features of LGMD are variable with different age of onset and different degrees of disability. In some cases, particularly those inherited as autosomal dominant disease, weakness may not appear in early or even in late adult life. The course is usually slowly progressive, with some exceptions. The muscular weakness may affect the shoulder girdle, pelvic girdle or both. Most childhood onset cases have pelvifemoral distribution. By comparison, adult onset disease involves both shoulder and pelvic girdle with increasing proximal limb weakness, sometimes leading to severe restriction of mobility and eventually wheelchair confinement

Neck flexor and extensor weaknesses can also occur. Facial weakness is usually mild or absent. Extraocular muscles are completely spared in LGMDs. Distal muscle strength is usually preserved. In this regard, our patient was atypical since she had demonstrated weakness of extensors of the feet. Low back pain may be prominent in LGMD. Intellect is usually normal and cardiac involvement unusual. The LGMDs secondary to abnormalities in the dysferlin gene are peculiar because the muscle biopsies often show evidence of inflammation. This is particularly true in the Miyoshi myopathy.

The treatment is supportive. It is aimed primarily at the prevention of contractures, which may result in substantial disability. A passive stretching physical therapy program should be instituted early. Later in the course of the disease, cardiorespiratory status should be monitored.

Conclusion

The diagnosis of muscle diseases is a complex and difficult endeavor. The muscle biopsies of most cases should be done in neuromuscular laboratories equipped with all the technologies necessary for a precise diagnosis, differentiating genetic from acquired inflammatory or toxic conditions and distinguishing the different genetic disorders.

Clinical Take Home Pearls: Patients with very high levels of CPK and aldolase, normal inflammatory markers like ESR and CRP and minimal muscle weakness should be considered suspicious for having a muscular dystrophy. Similar elevations of these

enzymes in inflammatory muscle disease or toxic myopathies are seen only in patients with extreme degrees of muscle weakness. Also, signs of inflammation on skeletal muscle biopsy are not pathognomonic for inflammatory myopathy.

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CME Questions 6a-d

Please select the correct answer for the following:

- 6a. Extraocular muscles are completely spared in LGMDs.
 - a. True
 - b. False

- 6b. Patients with extremely elevated levels of CPK and aldolase should be considered suspicious for having muscular dystrophy.
 - a. True
 - b. False

- 6c. Genetics do not play a role in the diagnosis of LGMD.
 - a. True
 - b. False

- 6d. Cardiac involvement is common among patients with LGMD.
 - a. True
 - b. False