Limb-girdle muscle weakness

A concise approach to a patient with proximal myopathy or limb-girdle muscle weakness is important. Owing to the large differential diagnosis it is essential to have a systematic approach and to be thorough in one's assessment. The term proximal myopathy means predominant limb-girdle pattern weakness of the upper and lower limbs. The initial assessment is important as one must ensure that there are no other muscles involved such as cardiac, respiratory or pharyngeal.

Proximal myopathy is frequently featured in postgraduate examinations with causes of the condition seen in multiple choice questions of the MRCP part 1 and 2, and its detection being paramount in both the history and examination stations of the PACES examination.

This article gives a systematic guide to the diagnosis and management of proximal myopathy or limb-girdle muscle weakness.

Aetiology and pathogenesis

The symptoms and signs of proximal myopathy are usually evidenced by weakness of the limb-girdle muscles, seen as weakness of shoulder abduction and hip flexion on clinical examination, but relative involvement of other muscle groups should also be assessed for.

It is not fully explained why myopathies have a predilection for proximal muscles, but Edwards et al (1984) hypothesized that proximal muscles have a much greater role in antigravity posture and in so doing are involved in eccentric contractions to a much greater extent than distal muscles. Eccentric contractions lead to damaged sarcomeres and myofibrillar proteins and so proximal muscles are, in theory, more predisposed to being affected in myopathic disorders.

The pathogenesis varies depending on the cause of the proximal myopathy. In the thyrotoxic patient it is believed that excessive amounts of thyroid hormone lead to increased mitochondrial respiration, accelerated protein degradation and lipid oxidation, and enhanced beta-adrenergic sensitivity. This in turn causes a disturbance in the function of the muscle fibres (Mehta and Iqbal, 2010).

Hypothyroidism-associated myopathy is caused by a shift in the distribution of muscle fibre types from fast-twitch fibres to slow-twitch fibres, leading to slowed muscle contraction and relaxation. A reduction in muscle mitochondrial oxidative capacity and beta-adrenergic receptors, as well as the induction of an insulin-resistant state, may cause these changes. A study by Sinclair and colleagues (2005) suggests that a decrease in muscle carnitine in patients with either hypothyroidism or hyperthyroidism may contribute to thyroid myopathy.

In polymyositis, the abnormal muscle function is caused by myofibre inflammation as a result of T-cell mediated cytotoxicity possibly triggered by viruses. Autoimmune inflammatory myopathies are characterized by a combination of muscle oedema and necrosis (acute myopathy) and fatty infiltration (chronic myopathy) associated with different proportions of perivascular and intramuscular lymphocytic infiltrates and complement deposition (Nagaraju and Lundberg, 2011).

With steroid therapy or in Cushing's disease, current research shows that ubiquitin ligases are induced through steroid-mediated channels resulting in the suppression of rapamycin, causing an imbalance between anabolism and catabolism of muscle proteins, and subsequent muscle atrophy and myopathy (Kohsaka, 2013).

History taking

History of presenting complaint

First, define weakness. Many patients who complain of weakness are not objectively weak when tested on physical examination. They instead use weakness to describe fatigue associated with conditions such as fibromyalgia, anaemia or depression. In differentiating between fatigue and weakness, it is useful to define whether the patient finds all daily tasks difficult or whether tasks predominantly involving proximal muscles are difficult, such as rising from a chair, climbing steps, brushing hair or shaving.

Once weakness is established, the pattern of muscle weakness is essential in formulating a differential diagnosis and patients with respiratory or pharyngeal involvement should be identified promptly – ask about facial muscle weakness, bulbar symptoms such as dysphagia, nasal regurgitation and dysarthria, and respiratory and cardiac symptoms such as palpitations, dyspnoea, orthopnoea and symptoms of nocturnal hypoventilation. Also ask specifically about muscle and neuromuscular junction-specific symptoms such as myotonia, fatigueability and previous episodes of rhabdomyolysis, e.g. myalgia or dark urine.

Onset and duration

This will help to differentiate between inherited and acquired causes. A history of progressive symptoms over years and since childhood would be more suggestive of Becker's muscular dystrophy, whereas an acute history, over days, would be more suggestive of dermatomyositis or a viral cause.

Progression

In general hereditary myopathies will progress slowly and inflammatory myopathies will be acute. Additionally, myopathies which progress to involve other muscle groups, in particular respiratory muscles, need to be detected early and referred to a specialist centre urgently.

Pain

Associated myalgia would suggest conditions such as osteomalacia, polymyalgia rheumatica or concurrent statin use.

Recent illnesses

Any suggestion of influenza, enteroviral infections or seroconversion illness is

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important to exclude because of their association with mainly self-limiting proximal myopathy.

History

Past medical history: Ask about autoimmune conditions – thyroid disease, rheumatoid arthritis, vitiligo as well as other endocrine diseases.

Drug history: Drug history is key as discontinuation of the offending agent may lead to resolution of symptoms. Drugs used commonly that are associated with proximal myopathy include corticosteroids (especially dexamethasone and triamcinolone) and statins (Pereira and Freire de Carvalho, 2011).

Family history: Ask about patterns of inheritance, important in the limb-girdle syndromes. These can be autosomal dominant, e.g. myotonic dystrophy, autosomal recessive, e.g. glycogen storage disorders such as Pompe disease, or X-linked, e.g. some glycogen storage disorders including Fabry's disease

Social and sexual history: Ask about symptoms or risk factors for HIV/hepatitis B and C because of their association with proximal myopathy either directly from the disease process or through medication used to treat the virus. Smoking is a risk factor for malignancy which may make paraneoplastic causes more likely. Alcohol is a toxin and a cause of proximal myopathy. The level of weakness is associated with the amount of alcohol consumed (Urbano-Marquez et al, 1989; Kuncl, 2009).

Examination

Examining for proximal myopathy should be part of a full neurological examination.

Inspection

Inspection is a pivotal start to the examination process as there are usually clear clues as to both the presence of proximal myopathy and the possible cause.

Look at the proximal muscles for muscle wasting which is suggestive of long-standing disease such as in hereditary myopathies. Remember to look at all muscle groups as the pattern of distribution will be a clue in diagnosis. Look for calf hypertrophy as seen in muscular dystrophies such as Duchenne's and Becker's.

Look at the hands for Gottron's papules and the face for the heliotrope rash of dermatomyositis (*Figure 1*). Look for signs of myotonic dystrophy such as myopathic facies, ptosis, frontal balding and evidence of cardiac pacemaker implantation. Look for facial lipodystrophy of highly active anti-retroviral therapy (HAART) and the acne and hirsutism of Cushing's syndrome. Any evidence of tremor and eye disease will be in keeping with thyrotoxicosis. Inspect the abdomen and back for the classic signs of Cushing's, for example an enlarged fat pad at the top of the back and purple striae. Look for signs of malignancy such as finger clubbing and lymphadenopathy, and inspect for skin manifestations of sarcoid. Look for paroxysmal abdominal movements. Photosensitivity, digital ulcers, periungual telangiectasis, frank arthritis and Raynaud's phenomenon are signs of overlapping autoimmune rheumatological conditions.

Next ask the patient to walk. A waddling, myopathic gait is characteristic because the proximal muscles that stabilize the weight-bearing hip are weak, causing the pelvis to drop and the patient to drop to the weight-bearing side to maintain balance.

Palpation

Muscle tenderness is rare in myopathies but its identification can help to differentiate between causes of proximal myopathy. For example, in polymyositis proximal muscle weakness is the cardinal symptom whereas in polymyalgia rheumatica muscle tenderness is the most prominent finding.

Power

Use the Medical Research Council power grading system to assess power (0–5):

5 Normal
4 Movement against resistance but weaker than normal
3 Movement against gravity
2 Movement when gravity eliminated
1 Flicker of contraction but no movement
0 No muscle contraction visible.

Begin with a functional assessment including lifting arms above the head and standing up from a crouched position or walking up stairs (*Figure 2*). This will give an immediate assessment of proximal muscle power. Next assess the power of shoulder abduction and hip flexion. Importantly, power loss is almost exclusively symmetrical.

Gowers' sign was first described in Duchenne's muscular dystrophy but is not

Figure 1. Dermatomyositis.

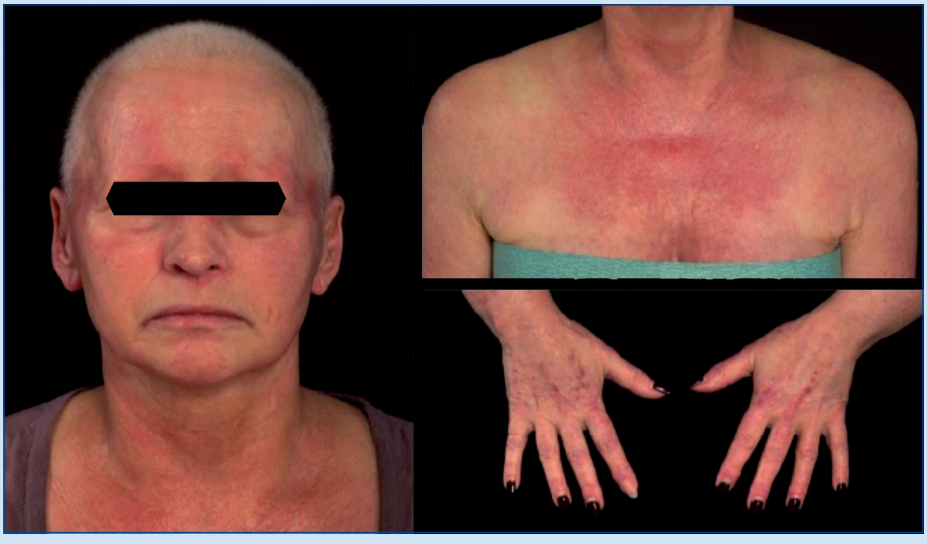

Figure 2. Standing from chair.

exclusive to it. It is a specific assessment of how the patient walks his/her arms up his/her legs to rise to standing from being seated on the floor.

The pattern of weakness outside of the limb-girdle muscles is relevant as a clue to aetiology, so a full examination of all muscle groups is essential. For example in early inclusion body myositis classically the quadriceps, long finger flexors and ankle dorsiflexors are involved (Suresh and Wimalaratna, 2013).

Reflexes and tone

Both are reduced in longstanding myopathies but can be maintained in the acute setting.

Bedside investigations

Routine observations are helpful when the patient is admitted: monitoring temperature and oxygen saturations can help detect an aspiration pneumonia in those where the proximal myopathy affects swallowing. An electrocardiogram is useful in detecting cardiomyopathies and urine sampling to look for rhabdomyolysis.

Bedside spirometry is useful in identifying respiratory muscle involvement early on in the diagnosis and is a good tool for monitoring respiratory function. One would expect to see a restrictive lung function pattern (forced expiratory volume in 1second:forced vital capacity >0.8). Dermatomyositis is also associated with the development of pulmonary fibrosis. In the presence of a restrictive lung function pattern, the diagnosis should be supported with formal pulmonary function tests (reduced gas transfer and total lung capacity) and a high resolution computed tomography scan of the chest. A change in forced vital capacity by more than 50% requires urgent intensive care unit involvement. Arterial blood gas may also be helpful: normal oxygen and carbon monoxide levels in the presence of raised pH and bicarbonate suggest nocturnal hypoventilation. A progressive increase in carbon monoxide levels is an indication for non-invasive ventilation and an intensive care unit referral (Hutchinson and Whyte, 2008).

Causes of proximal myopathy

Once the clinical examination confirms a proximal myopathy, with no other muscle involvement, the underlying cause needs to be identified. As previously stressed, taking a good history and obtaining clues from examination are invaluable in detecting the underlying cause of a true case of proximal myopathy.

An approach to the differential diagnoses is to divide the possible aetiologies into toxic, endocrine, hereditary or congenital, inflammatory, malignant or infective myopathies (*Table 1*). It is worth noting that iatrogenic causes do exist; in fact, therapeutic doses of both corticosteroids and statins are commonly associated with proximal myopathy. Such drug-induced myopathies are often diagnosed shortly after starting or adjusting the dose of the responsible agent.

Special care should be taken to identify treatable conditions. Fabry's and Pompe disease can be treated with enzyme replacement therapy and autoimmune myasthenia gravis can be treated with acetylcholinesterase inhibitors and immunosuppression.

Not often seen by rheumatologists but by neurologists and intensivists and a rare cause of myopathy, is intensive care unit myopathy of which there are three types: acute necrotizing myopathy of intensive care, diffuse non-necrotizing cachetic myopathy and myopathy with loss of myosin filaments also known as critical illness myopathy. These patients are often diagnosed when they fail respiratory weaning off the ventilator (Howard et al, 2008).

Investigation of proximal myopathy

Such a vast array of causes translates to similarly large investigative options. The choice of investigations should be case specific, and requested with features of history, risk factors and clinical signs in mind.

Baseline blood tests

These should include full blood count, erythrocyte sedimentation rate, electrolytes, calcium, magnesium, serum creatinine, thyroid function tests and (25)OH vitamin D levels.

Creatine kinase is a non-specific marker of myopathy which is often markedly raised, especially in those with inflammatory, toxic or infectious causes. However, there is not a correlation between the degree of creatine kinase elevation and muscle weakness. Although disease flares are usually twinned with significant elevations, caution is advised when interpreting levels in those with advanced disease and severe muscle atrophy, where this may not be seen. Aldolase, alanine transaminase, aspartate transaminase and lactate dehydrogenase are released from damaged muscle and elevated levels are often found in autoimmune, infective and toxic myopathies. Troponin I levels are increased in cardiomyopathies.

Other laboratory tests

Myositis-specific autoantibody

Anti-Jo-1 is present in 30% of cases of polymyositis and dermatomyositis, anti Mi-2 are found in as many as 20% of patients with dermatomyositis, and autoantibodies recognizing HMG-CoA reductase are seen in statin-triggered immune-mediated necrotizing myopathy (Thompson et al, 2003; Mammen, 2010).

Non-specific autoantibodies

Antinuclear antibody, antibodies to ribonucleoprotein, anti PM-Scl and Scl-70 are found in association with other chronic autoimmune conditions (Rendt, 2001).

Where simple tests identify no toxic, metabolic or endocrine cause and/or there is a reasonable level of clinical suspicion, further evaluation in the form of neurophysiological studies, imaging or biopsies may be considered.

Neurophysiological techniques

Electromyogram helps with categorization of inflammatory *vs* non-inflammatory causes of myopathy and is useful in guiding appropriate biopsy site by identifying the most affected muscle. A myopathic electromyogram shows a decrease in the amplitude and duration of action potentials.

Nerve conduction studies tend to be unremarkable in myopathy but are used in conjunction with electromyogram to eliminate neuropathies.

Imaging

Magnetic resonance imaging is a non-invasive mode of assessing for the presence of oedema, fatty infiltration or necrosis, but is not routinely used. However, it can help guide appropriate biopsy site and differentiate between acute inflammatory and chronic degenerative muscle changes (Tomasova Studynkova et al, 2007).

Table 1. Differential diagnoses of limb-girdle weakness in descending frequency

Cause	Example	Clinical features	Investigations	Management
Toxins	Statins, alcohol, corticosteroids	Dose- and agent-related properties exist for toxin-induced myopathies (Pereira and Freire de Carvalho, 2011). Features of chronic liver disease may exist in alcohol misuse	Mean corpuscular volume may be elevated in prolonged alcohol abuse. Liver function tests in alcohol misuse: AST:ALT >2, γGT elevated	Altering/withdrawing drug often causes rapid resolution of symptoms. Periodic creatine kinase testing for patients on statins is best practice
Hereditary or congenital	Myotonic dystrophy	Family history of muscle disease	Creatine kinase often increased >40 fold, genetic testing	Referral to specialist centres for genetic counselling and specialized physiotherapy, monitoring and prevention of respiratory insufficiency, enzyme replacement for Fabry's and Pompe disease
	Muscular dystrophy: Duchenne's, Becker's, facioscapulohumeral	Tend to have chronic, slowly progressive courses. Classical physical examination finding of muscular dystrophy = Gower sign		
	Glycogen and lipid storage disorders: Fabry's, Pompe			
Autoimmune	Myasthenia gravis	Complex ophthalmoplegia. Fatiguable ocular, proximal limb and bulbar muscle weakness. Other features of autoimmune disease, e.g. vitiligo, type 1 diabetes	Anti-acetylcholine receptor antibody, anti-MuSK antibody – poorer prognosis	Symptom control with anticholinesterase, i.e. pyridostigmine. Steroids +/- methotrexate or azathioprine to treat relapses. Thymectomy for refractory cases and in the case of thymoma
Infective	HIV, influenza, hepatitis B and C	May be part of seroconversion illness. Treated patients may develop inflammatory myopathy related to immune restoration or drug-induced muscle involvement. Exposure to infectious agent	HIV testing, serological markers for hepatitis B and C viruses	Often self limiting in viral infections. Antiretroviral or antiviral treatment as necessary
Endocrine	Cushing's disease	Features of Cushing's syndrome: central obesity, skin thinning, bruising, hypertension, plethora, striae	Plasma: thyroid function tests, bone profile, (25)OH vitamin D. Confirm raised cortisol levels in Cushing's by overnight dexamethasone suppression test or 24-hour urinary free cortisol	Correct underlying metabolic dysfunction; medically or surgically (Duyff et al, 2000)
	Hyperparathyroidism*			
	Thyroid dysfunction (hyperthyroidism* and hypothyroidism)	Evidence of thyroid dysfunction on examination: e.g. tachycardia, palmar erythema, lid lag in hyperthyroidism. Bradycardia, slow relaxing reflexes and dry, thin hair in hypothyroidism		
	Diabetic amyotrophy	Diabetic amyotrophy presents as painful wasting of the quadriceps		
	Osteomalacia			
Inflammatory	Polymyositis, dermatomyositis	Annual incidence of 2–10 per million, F:M = 2:1 (Rendt, 2001), cutaneous features of dermatomyositis: heliotrope periorbital rash and Gottron's papules	Non-specific autoantibodies, e.g. antinuclear antibody and antibodies to ribonucleoprotein, may be present. Myositis-specific autoantibody Anti-Jo-1 is present in 30% of cases of polymyositis and dermatomyositis. Anti Mi-2 are found in as many as 20% of cases of dermatomyositis (Mammen, 2010)	High dose therapy with corticosteroid (1 mg prednisolone/kg/day) (Cordeiro and Isenberg, 2006). Immunosuppressive agents are reserved for refractory cases
Neuro-degenerative	Inclusion body myositis	Slowly progressive, often asymmetrical weakness in older Caucasian males. Distal>proximal	Serum creatine kinase level is normal or elevated to a mild-to-moderate degree. Muscle biopsy: cytoplasmic vacuoles and intranuclear inclusions	No consistently effective therapies known. Treatment is largely symptomatic
Malignant	Paraneoplastic syndrome, Lambert–Eaton myasthenic syndrome	Lambert–Eaton myasthenic syndrome presents as weakness of the scapular and pelvic girdles with diminished tendon reflexes. Clinical manifestations of underlying malignancy. Most commonly associated with small cell lung cancer	Chest radiograph	Treatment based on two mechanisms: 1) Treatment of underlying malignancy 2) Immunosuppression-based therapy if autoantibodies detected

* Not associated with raised creatine kinase levels. ALT = alanine transaminase; AST = aspartate transaminase; γGT = gamma-glutamyl transpeptidase. Adapted from Rendt (2001)

Biopsy

Muscle biopsy may help to support a diagnosis, but in some cases such as acute rhabdomyolysis it should be avoided. Owing to the nature of skip areas in polymyositis, an open surgical biopsy is preferred to a needle biopsy as it is more likely to obtain an adequate tissue sample for histology. Use of magnetic resonance imaging to guide biopsy may lower the rates of false-negative muscle biopsy, which range from 10–25%, and reduce the rates of misdiagnosis (Mastaglia, 2008).

Genetic testing

Genetic testing in conjunction with clinical presentation, muscle biopsy and muscle immunoanalysis allows a diagnosis of limb-girdle muscular dystrophy in 75% of patients. These tests are not done routinely and are best undertaken through a specialist centre. The genetic testing and characterization of limb-girdle muscular dystrophies has allowed increased awareness and pre-emptive management of cardiac and respiratory complications (Bushby, 2009).

Management of proximal myopathy

Once the clinical mission of identifying the aetiology of a patient's myopathy has been accomplished, management is relatively self-explanatory.

In the case of toxin-induced myopathy, withdrawal of the offending agent often leads to the spontaneous resolution of symptoms (Martin et al, 1985; Sinzinger et al, 1999). A proximal myopathy secondary to endocrine or metabolic disorders has been shown to be reversible upon treatment of the underlying condition (Duyff et al, 2000).

Treatment of inflammatory myopathies relies largely on high-dose oral corticosteroid therapy – prednisolone 0.75–1 mg/kg daily (Cordeiro and Isenberg, 2006). Patients should be informed that steroids are not a short-term treatment and of the likelihood of relapse upon withdrawal of corticosteroids. An increase in symptoms may be the result of a rapid steroid wean – should this occur one needs to increase the steroids to higher dose and gradually start a steroid taper once the symptoms are controlled (Mastaglia, 2008). Often lower doses are needed for maintenance therapy (Suresh and Wimalaratna, 2013). Of note is the relationship between early diagnosis and treatment as well as the response to treatment, both objectively and subjectively. Early diagnosis of inflammatory myopathies leads to a more favourable outcome – those receiving treatment within 6 months of symptom onset obtain most muscle strength in biomechanical testing compared to patients who have later diagnosis and therefore treatment (Fafalak et al, 1994).

Immunosuppressive agents are reserved for patients with rapidly progressive or severe disease involving internal organs, or for those who prove refractory to steroid therapy. Such second-line agents include methotrexate and/or azathioprine, and in the most extreme cases, intravenous immunoglobulin (Cordeiro and Isenberg, 2006). There is increased evidence that mycophenolate mofetil may also be used as a steroid-sparing agent, should azathioprine or methotrexate not provide optimum disease control (Baer, 2006). B-cell depletion therapy and intravenous immunoglobulin have also been successful in selected cases of resistant autoimmune myopathies (Levine, 2005; Marie et al, 2010).

Supportive management of respiratory, bulbar and cardiac dysfunction in both acute and chronic muscle disease is also highly important.

Investigation and follow up of suspected paraneoplastic disorders is important. For example in dermatomyositis and polymyositis initial screening should include a thorough history and examination followed by tumour markers, chest X-ray, age-appropriate cancer screening such as mammography and colonoscopy, and, in those who are at high risk of malignancy, a computed tomography scan of the chest, abdomen or pelvis or whole body fludeoxyglucose (FDG)-positron emission tomography scan. Recommendations are to then screen annually for 2–3 years with the exception of ovarian carcinoma in dermatomyositis where 6-monthly screening for 5 years should be performed. In patients diagnosed with Lambert–Eaton myasthenic syndrome a computed tomography scan of the chest is performed immediately. If initially negative for small cell lung cancer guidelines recommend imaging follow-up every 3–6 months for the first 2 years post diagnosis (Titulaer et al, 2011).

Conclusions

Proximal myopathy or limb-girdle weakness is an important diagnosis as its identification and subsequent treatment can greatly improve the patient's quality of life. Additionally, the diagnosis of a proximal myopathy may herald an underlying condition such as Lambert–Eaton myasthenic syndrome or HIV. Early treatment of these conditions can greatly reduce mortality.

A thorough history is key in the initial assessment, particularly focusing on respiratory and pharyngeal involvement as this can predict impending respiratory failure. Examination focuses on inspection and functional assessment such as standing from a chair. Investigations focus on muscle enzymes and autoantibody testing, electromyogram and if the diagnosis remains in doubt, progression to a muscle biopsy. Treatment is directed depending on the underlying cause including removal of toxins and where necessary initiating corticosteroids. BJHM

Figure 1 *is reproduced from Mahil et al (2012).*

Conflict of interest: none.

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KEY POINTS

- A systematic and thorough approach is key.
- A normal creatine kinase level does not exclude a proximal myopathy.
- A medication and drug history is essential, as these represent easily reversible causes of proximal myopathy.
- Assess respiratory function on history taking and bedside spirometry.
- The mainstay of treatments involve removal of offending agents, treating the underlying cause or treatment with corticosteroids.

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