9 Diagnostic Approach to Proximal Myopathy

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9.1 Introduction

Patients with muscle disorders are a diagnostic challenge to physicians, because of the various ways of presentation. A comprehensive approach should be followed systematically in order to reach the correct diagnosis. Weakness is a common symptom among patients including those with central or peripheral nervous systems diseases and those with muscular and/or neuromuscular diseases. Muscle weakness is not only a regular finding in rheumatologic diseases, but in inflammatory myopathies as well. This chapter focuses on skills needed to approach any patient that presents with weakness, specifically proximal myopathy.

In addition to IIM and CTD, proximal myopathy has a wide range of differential diagnosis including drugs, alcohol, thyroid disease, hereditary myopathies, malignancy, and infections. Clinical assessment should aim to distinguish proximal myopathy from other conditions that present with weakness. Patients with proximal myopathy who need prompt attention, like those with cardiac, respiratory, or pharyngeal muscle involvement, should be identified early and quickly.

In this chapter, the aim is to provide a systematic diagnostic approach to adult patients presenting with proximal myopathy. This is an essential step to establish the correct diagnosis in order to conduct the appropriate management.

9.1.1 Objectives

By the end of this chapter, you will be able to:

1. Identify true muscular weakness by history and physical examination.
2. Construct diagnostic approach to proximal myopathy.
3. Manage a case of inflammatory myopathy.

9.2 Clinical Presentation of Proximal Myopathy

Myopathies are diseases that primarily affect the muscles and are usually characterized clinically by weakness, fatigue, or stiffness. Symmetrical proximal muscle weakness, wasting, normal sensation, and normal stretch reflexes are classical findings in patients with myopathies particularly in IIM and myopathies associated with

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H. Almoallim, M. Cheikh (eds.), *Skills in Rheumatology*, https://doi.org/10.1007/978-981-15-8323-0_9

CTD. Aching muscle cramps can also occur. Clinical presentations sometimes can be complex, hence the need to follow a comprehensive approach to weakness.

9.2.1 History

Weakness is a common complaint with different interpretations by patients. The aim of history taking is to try to define what the patient means by "weakness." The generalized feeling of tiredness and/or fatigability is usually associated with systemic diseases like congestive heart failure, cirrhosis, and anemia. In these patients there is usually a long-standing history of a chronic disease like ischemic heart disease and/or chronic liver disease. The activity in these patients is usually limited by dyspnea, chest pain, joint pain, fever, and/or depressed mood. Long-standing chronic diseases can lead to cachexia with severe muscle atrophy, wasting, and consequent generalized weakness. The sense of generalized tiredness and/or fatigability should be differentiated from the complaints of generalized body aches and pains in patients with fibromyalgia. The generalized body aches and pains have their own approach that is beyond the scope of this chapter.

Once it is established that the weakness is not a consequence of a non-muscular, generalized, systemic disease and there are no generalized body aches and pains, then it is essential to find out whether this weakness is localized to certain areas. Hemiparesis (weakness affecting upper and lower limbs on the same side of the body) should direct the history towards central nervous system diseases like stroke. Paraparesis (weakness of both lower limbs) and/or quadriparesis (weakness of the four body limbs) should limit the differential diagnosis to spinal cord and/or cerebral cortex and/or brain stem diseases. Monoparesis (weakness of one limb) is usually a disease of a peripheral nervous system including disc prolapse causing radiculopathy by compressing on a spinal nerve to peripheral nerve involvement in vasculitis. Figure 9.1 is a schematic that should be fol-

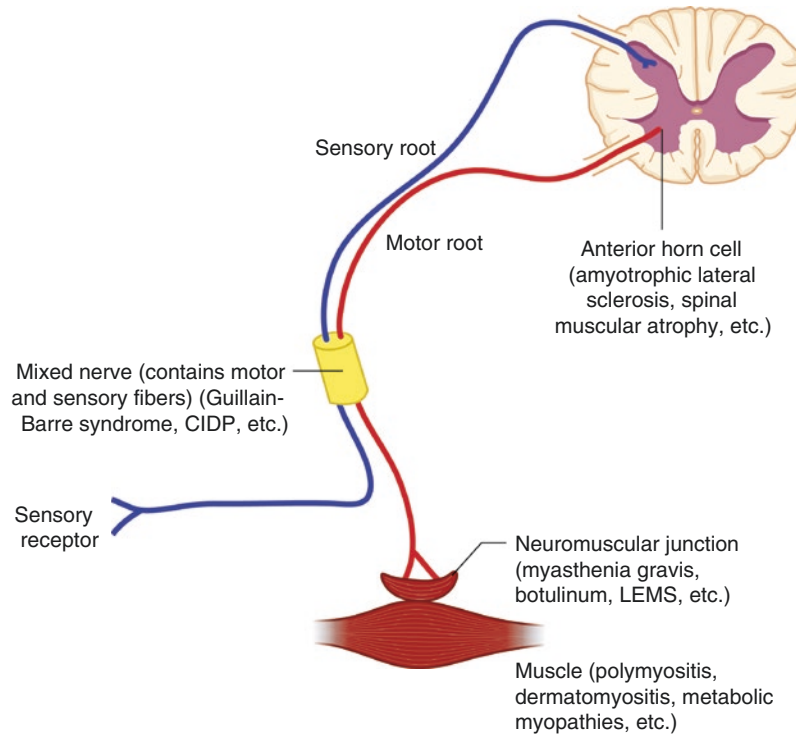

Fig. 9.1 The four anatomic stations underlying lower motor neuron weakness

lowed while obtaining history and examining patients with weakness.

Symmetrical weakness occurs in large number of diseases including inflammatory myositis, inherited muscle dystrophy, endocrine disorders, and neuromuscular junction diseases. In symmetrical and diffuse weakness, it is important to know if the weakness is proximal or distal. There are several clues in the history that point towards proximal myopathy (muscles of the trunk, shoulders, and thighs). The patient will have difficulty combing hair, difficulty climbing up the stairs, difficulty standing from a sitting position, and/or difficulty in getting up from bed. In distal myopathy, the patient will complain about difficulties while performing fine work like handling the objects by hands and driving. These patients may also present with wrist drop or foot drop. It must be noted that there are diseases affecting proximal muscles in an asymmetrical fashion like diabetic amyotrophy as well as diseases with both proximal and distal muscle weakness in symmetrical and/or asymmetrical fashion like in systemic lupus erythematosus (SLE) with myopathy and vasculitis, respectively. Inclusion body myositis, a rare IIM in elderly patients, presents with both proximal and distal myopathies simultaneously. The focus should be simply to identify the localization of the weakness, and then with comprehensive approach to history taking like what is described in Chap. 1, the differential diagnosis should be easier to obtain.

There are special characters for weakness that signify certain alerts to specific diagnoses. Ascending pattern of weakness should direct the attention towards demyelinating diseases like acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome). Descending patterns that start centrally and proceed progressively to distal areas should direct the attention to infections like botulism. The weakness that is worsened by repetitive movement at the end of the day with double vision and drooping eyelids should direct the attention towards neuromuscular disorders like myasthenia gravis.

An extensive review of rheumatologic symptoms should follow; this was outlined thoroughly in Chap. 1. Detailed history of joint pain, skin rashes, fever, recent infections, bleeding tendencies, history suggestive of malignancies, and/or drug history (particularly statins and glucocorticoids) should all be obtained. Endocrine disorders should also be ruled out by reviewing common symptoms like neck swelling, diarrhea/constipation, and heat/cold intolerance. Further details are found below. Detailed family history should be obtained as there are several rare hereditary myopathies that run in families (see below). A family history may also be present in other causes of weakness including dermatomyositis, polymyositis, and potassium-related paralyses. A thorough neurological history is important. Sensory deficits, impaired level of consciousness, speech or visual defect, seizure, and sphincter control should be obtained from patients with weakness. In addition, social history will further help narrow the diagnosis; thus, history of smoking, alcohol, illicit drug use, and exposure to toxins like organic phosphorus should be obtained.

There are life-threatening symptoms associated with IIM like dysphagia and nasal regurgitation resulting from skeletal muscle involvement of the pharynx and upper third of the esophagus and/or chest pain and heart failure from cardiac muscle involvement. These should be identified promptly as they need urgent medical intervention. Breathlessness might suggest respiratory muscle involvement. Respiratory failure can occur in some diseases like Guillain-Barre syndrome, myasthenia gravis, and amyotrophic lateral sclerosis. Table 9.1 summarizes some of the common symptoms of diseases presenting with weakness.

9.2.2 Physical Examination

The physical examination is an objective confirmation of the distribution and the severity of the muscle weakness. The first step is to observe the patient doing certain activities like raising arms, standing up from a chair, or writing. This will determine if the weakness is proximal, distal, or combined. A comprehensive neurological examination should follow with higher function examination and examination of cranial nerves. You may find ptosis, ophthalmoplegia, and/or poor gag reflex in myasthenia gravis patients. The next

Table 9.1 Associated symptoms presented with muscle weakness

Disease	Symptoms
Dermatomyositis	Skin rash, e.g., upper eyelids (*heliotrope rash*), erythema of the knuckles (*Gottron rash*), anterior chest (*v sign*), or back (*shawl sign*) Weight loss, anorexia, bleeding tendency, abnormal vaginal bleeding, chronic cough (malignancy).
Inclusion body myositis	Frequent falls, dysphagia
Myasthenia gravis	Squint, dysphagia Compression symptoms of thymoma (cough, SOB)
Lambert-Eaton syndrome	Autonomic symptoms, e.g., dry mouth, impotence History of lung cancer
Mixed connective tissue disease and overlap syndrome	Other connective tissue disease's symptoms; arthritis, skin rash
Rhabdomyolysis	History of trauma, seizure, dark urine

step is performing detailed motor examination. This starts with inspection of the muscle bulk and determining whether if it is normal, atrophied, or hypertrophied. In addition to observation for any fasciculation that might suggest LMND, tone, power, reflexes, and gait should also be examined. Clear distinctions between signs of upper motor neuron disease (UMND) (hypertonia, hyperreflexia, and upgoing plantar response) and signs of LMND (for lesions from the anterior horn cell until muscles) (hypotonia, normal or low or absent reflexes, and equivocal or downgoing plantar response) should be made. Usually with signs of UMND, patients may present with hemiparesis, paraparesis, and quadriparesis or with variable locations in the central nervous system as in multiple sclerosis. Since weakness is a prominent sign present in both UMND and LMND, it is essential to assess the power and document the degree of weakness, as well as for proper future monitoring of this disease while on

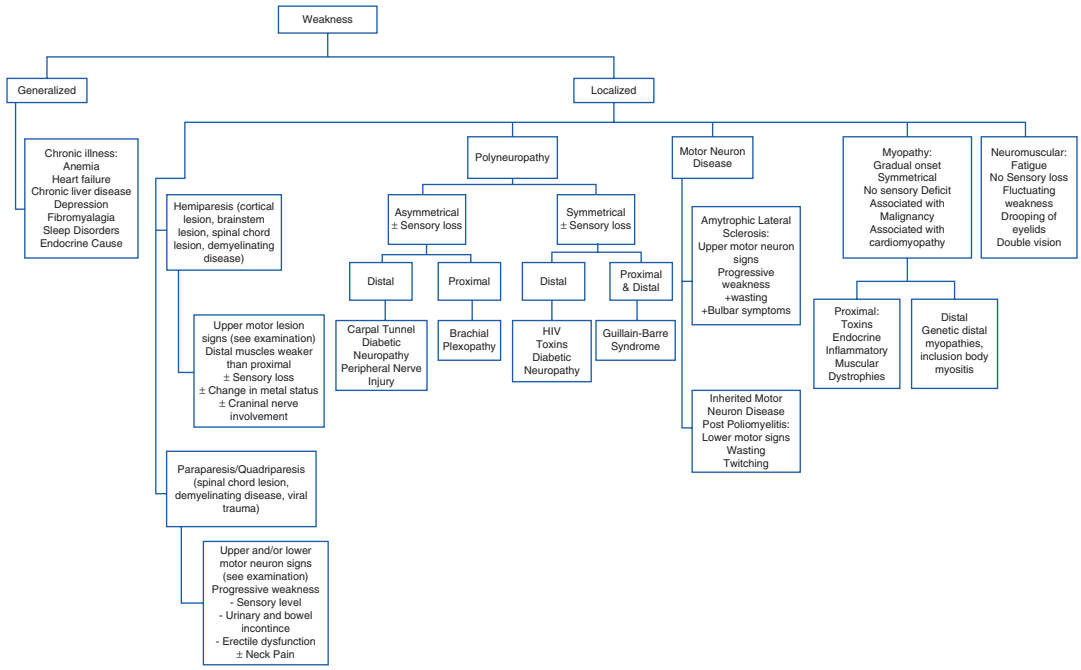

Fig. 9.2 Clinical approach to weakness

treatment. Clinical approach to weakness is illustrated in Fig. 9.2. Grades of power are shown in Table 9.2.

Reflexes are usually intact in proximal myopathy, and any signs of abnormal reflexes suggest neurological cause. The last step in the neurological examination is examining sensory level. For example, in peripheral neuropathy loss of sensation is parallel to the weakness. After comprehensive neurological examination, a search for extra-muscular signs should follow. The examination of the face, hands, lower limbs, chest, and abdomen is important, since any abnormality can help in the differential diagnosis. Few signs of common diseases presenting with myopathy are shown in Table 9.3.

There are certain associations essential to be recognized while performing the physical examination. These associations may easily reveal the diagnosis without spending efforts on unnecessary investigations. Changes in the mental status, for example, with muscle weakness may indicate electrolyte imbalance. Cardiovascular assessment may reveal signs of cardiomyopathy, which is associated with some inflammatory and hereditary myopathies. Pulmonary assessment may reveal crackles of interstitial lung disease associated with some inflammatory myopathies. Lymph node examination is essential as malignancies are associated with a significant number of IID including lymphoma. Small joint examination is essential as well to detect any tenderness and/or swelling suggestive of rheumatoid arthritis (RA) and/or systemic lupus erythematosus (SLE)-associated myopathies. Skin examination is helpful: signs like Gottron's papules in dermatomyositis, erythema nodosum in sarcoidosis, and skin bronzing in adrenal insufficiency (see Dermatology chapter). Also a search for any signs possibly related to underlying malignancy like finger clubbing, fecal occult blood, and hepatosplenomegaly should be made. Table 9.4 lists findings with their most likely definitive diagnosis. The vital signs should be measured to exclude any life-threatening problems. Postural hypotension can be seen in autonomic neuropathy, e.g., in diabetes mellitus and Lambert-Eaton syndrome. Also, body mass index (BMI) should be measured to assess if the patient is underweight suggestive of a malignant disease process.

Table 9.2 Grades of power

5	Normal muscle strength, full resistance
4	Reduced, but still against resistance
3	Further reduced, only against gravity
2	Only moves with gravity
1	Flicker of movement
0	No movement

9.3 Differential Diagnosis of Proximal Myopathy

Several conditions cause proximal myopathy. Myopathies can be classified into idiopathic or acquired. The clinical history and physical exam-

Table 9.3 Common signs with specific myopathies

	Head and neck	Hands	Chest and abdomen
Dermatomyositis	– Upper eyelids (heliotrope ash) – Lymphadenopathy or any mass (malignancy)	– Erythema of the knuckles (Gottron rash) – Clubbing (lung cancer)	– Erythema of anterior chest (v sign), or back (shawl sign) – Axillary lymphadenopathy, breast lump or abdominal mass
Overlap syndrome and MCTD	– Fish mouth, pinched nose (in scleroderma) – Malar rash, discoid lupus (in SLE)	Sclerodactyly, Raynaud's (in scleroderma). Arthritis (in SLE)	Signs of lung fibrosis and serositis
Lambert-Eaton syndrome	– Dry mouth and skin (autonomic neuropathy)	– Clubbing (lung cancer)	– Chest finding if there are complications for lung cancer e.g. pleural effusion, lymphadenopathy
Myasthenia gravis	SVC syndrome (thymoma)	–	–

Table 9.4 Correlation between findings and suggestive diagnoses of weakness

Findings	Suggestive diagnosis
Acute focal weakness decreased muscle power, hyperreflexia, hypertonia, positive Babinski sign, ± sensory deficit, ± loss of bladder/bowel control	Stroke, or spinal cord injury
Diffuse or localized peripheral weakness, muscle atrophy, fasciculations, hypotonia, loss of reflexes	Lower motor neuron disease
Asymmetrical distal weakness, muscle atrophy, hypotonia, loss of reflexes, sensory deficit "Glove and stocking" distribution	Peripheral neuropathy Diabetic neuropathy
Acute onset of combined weakness (ascending), fasciculations, loss of deep tendon reflexes, sensory deficit	Guillain-Barre syndrome
Facial weakness, fatigability, ptosis	Myasthenia gravis
Symmetrical weakness of proximal muscles, muscle wasting, with some types, muscle tenderness, normal reflexes, no sensory level	Proximal myopathies
Symmetrical distal weakness, with myotonic contractions	Myotonic dystrophy
Cardiomyopathy, and proximal muscle weakness	Inflammatory myopathies, hereditary myopathies
Mental status changes with proximal weakness	Myopathy-inducing electrolyte disorder (calcium or magnesium)

ination are essential in identifying the presence of a myopathy and narrowing down the differential diagnosis. In adults a major cause of myopathy is medication like statins [1]. Myopathy due to endocrine causes, for example, thyroid disease, Cushing disease, and adrenal diseases, should be diagnosed promptly because treating the primary condition will result in resolution of the myopathy [2]. Inflammatory diseases typically affect older adults including both proximal and steroid responsive disorders like polymyositis and dermatomyositis and distal and proximal myopathies with less response to steroid like inclusion body myositis. Rheumatologic disorders causing weakness, such as SLE and RA, can occur in young and elderly persons. Figure 9.3 summarizes the differential diagnosis of proximal myopathy. Further details about these disorders will be mentioned briefly in this section.

9.3.1 Toxins- and Drug-Induced Myopathy

Considering toxin and drug exposure in the differential diagnosis of every single patient presenting with proximal myopathy is essential. The timely diagnosis allows for optimum recovery. There are many drugs that cause proximal myopathy, such as lipid-lowering drugs, glucocorticoids, antimalarial drugs, antiretroviral drugs, alcohol, and cocaine [1]. There is an acute presentation in drug-induced myopathy. Statin therapy associated with muscle problems is seen in approximately 10–25% of patients treated in clinical practice. Statin-induced myopathy can present as myalgia and myositis or sometimes is severe enough to cause rhabdomyolysis. The average onset of statin-induced myopathy is weeks to months. The only treatment is discontinuation of statin which results in resolution of muscle symptoms [3]. Glucocorticoids are a common cause of muscle weakness. Long-term use of glucocorticoids results in an insidious onset of proximal myopathy. Muscle enzymes are usually normal. Relief of the weakness occurs with lowering the dose of glucocorticoids [4]. Alcohol-induced myopathy generally follows a history of long-standing alcohol intake and/or consumption of large amount of alcohol. Table 9.5 summarizes pertinent features of the common causes of toxin- and drugs-induced myopathy.

9.3.2 Endocrine Myopathy

Hormones play an essential role in body metabolism. Deficiency or excess in most hormones will affect muscle metabolism. In endocrine-related muscle diseases, the presentation is more likely to be fatigue than true muscle weakness. The

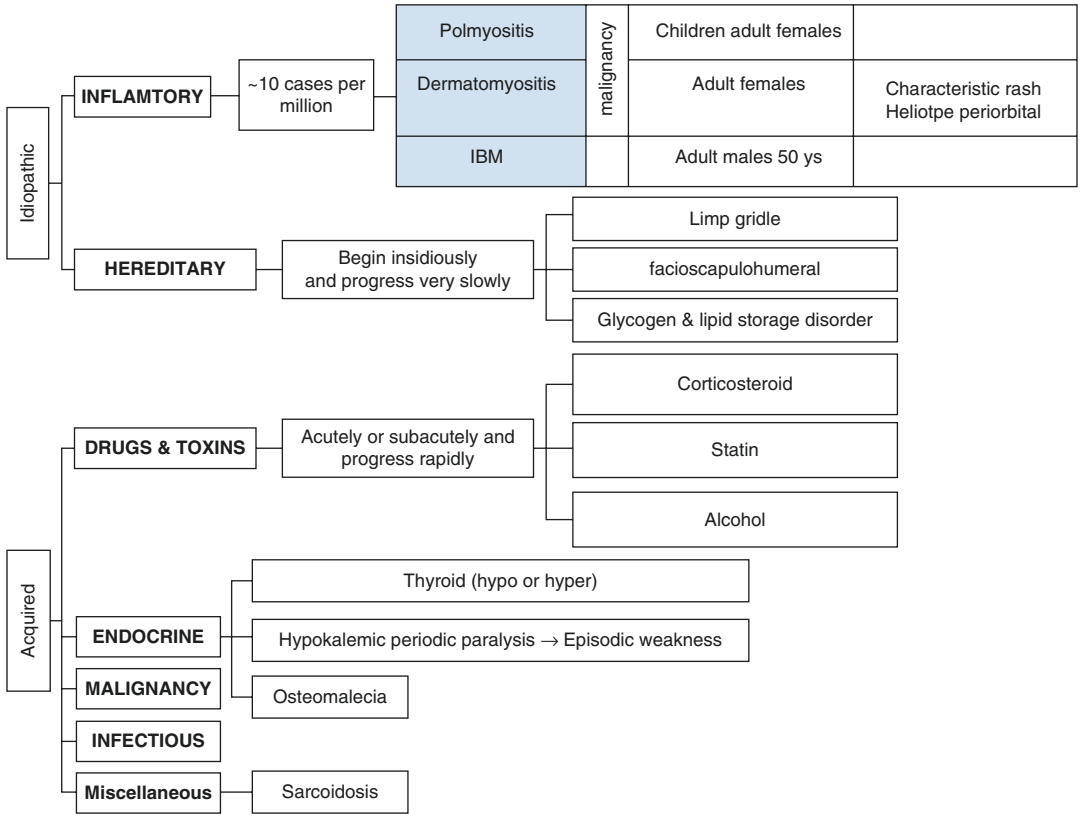

Fig. 9.3 Differential diagnosis of proximal myopathy

Table 9.5 Features of toxin- and drug-induced myopathy

Toxin/drug	Effect on muscle	Characteristics	Management
Alcohol	Large consumption of alcohol will cause direct muscle necrosis	Acute and chronic presentation Calf muscles Tenderness Swelling Generalized muscle cramps	Resolution with cessation of alcohol
Glucocorticoid	Direct catabolic effect Chronic use of prednisone at a daily dose of ≥30 mg/day Risk increases in elderly and malignancy	Proximal lower muscles Progressive Accompanied with atrophy No tenderness	Improved muscle strength within 3–4 weeks after lowering the dose
Statin	Varying degrees of muscle necrosis Severe complications such as rhabdomyolysis and myglobinuria Dose and duration dependent	Myalgia Malaise Muscle tenderness Muscle pain may be related to exercise	Muscle weakness will resolve with decreasing the dose or cessation of the statin

serum CK level is often normal (except in hypothyroidism). Nearly all endocrine myopathies respond to treatment [5].

Abnormalities in thyroid hormone can lead to a wide range of muscle diseases. For example, hypothyroid patients have frequent muscle complaints such as cramps, pain, and weakness. Almost one third of hypothyroid patients present with proximal myopathy. They present mainly with shoulder and hip muscle weakness. Treatment by thyroid replacement usually leads to resolution of symptoms and laboratory abnormalities [6]. Proximal myopathy is a very common presentation in hyperthyroid patients and may be the only symptom of the disease. Bulbar, respiratory, and even esophageal muscles may be affected, causing dysphagia and aspiration. Other neuromuscular disorders may occur in association with hyperthyroidism including hypokalemic periodic paralysis, myasthenia gravis, and a progressive ocular myopathy. Because proximal weakness is a presenting sign of hyperthyroidism and hypothyroidism, checking thyroid-stimulating hormone (TSH) is essential. Adrenal insufficiency causes muscle fatigue rather than true muscle weakness. Conn's syndrome can lead to proximal myopathy which is related to hypokalemia [7]. Pituitary disorders like acromegaly if long-standing can cause myopathy [8]. Neuromuscular complications of diabetes mellitus (DM) are mainly due to neuropathy which can be presented as asymmetrical proximal weakness. Ischemic infarction of the thigh muscles can present with severely uncontrolled diabetes [9] (see Chap. 21 (Diabetes and Rheumatology)). Table 9.6 summarizes pertinent findings of myopathies caused by endocrine disorders.

9.3.3 Dystrophic Myopathies

Dystrophic myopathies are a distinct group of inherited muscle disorders that generally present chronically. They are slowly progressive in nature resulting in muscle atrophy with exception of metabolic myopathies, where symptoms on occasion can be precipitated acutely. Each type of dystrophic myopathy has some characteristic structural abnormalities on muscle immunohistochemistry. Congenital myopathies present predominantly in the perinatal period. Some can present later in childhood, and these children may have a milder course of the disease. Multiple gene defects can give rise to similar clinical and ultrastructural phenotypes; thus, muscle immunohistochemistry should be tested to reach a final diagnosis. Table 9.7 shows the features of dystrophic myopathy [10].

9.3.4 Inflammatory Myopathies

Inflammatory myopathies are a group of complex diseases of unknown etiology. The most common types are dermatomyositis, polymyositis, and inclusion body myositis. Table 9.8 represents the current classification for IIM. The incidence of inflammatory myopathies is 5–10/million cases per year [11]. These diseases are characterized by progressive muscle weakness with extramuscular organ involvement and high serum muscle enzymes. Generally there is a female predominance 2:1, but in inclusion body myositis, the opposite is seen as it is three times more common in males [12]. The main pathophysiology is related to autoimmunity, though recent studies show that the mechanism of muscle damage is multiple and complex [13].

The clinical features of inflammatory myopathy in general are muscle weakness occurring within weeks to months. The distribution of weakness is mainly proximal in dermatomyositis and polymyositis, but as the disease progresses, distal muscles may become affected. On the other hand, distal muscle weakness is the initial presentation of inclusion body myositis. The onset of polymyositis is usually after the second decade of life. Dermatomyositis has two peaks, the first peak at around 10–15 years of age and the second peak between 40 and 70 years. Inclusion body myositis occurs after the age of 50. Table 9.9 summarizes the pathological and clinical features of the most common IID.

Dermatomyositis is known for its cutaneous manifestations. The rashes can precede, follow, or occur simultaneously with the myopathy.

Table 9.6 Pathophysiology and characteristics of endocrine myopathies

Endocrine disease	Pathophysiology	Characteristics
Hypothyroidism	Exact mechanism is unknown T4 is essential for metabolism Decrease in T4 leads to decrease in glycogenolysis which leads to impaired muscle function	Proximal myopathy occurs in one third (shoulder and hip girdle muscles) Muscle cramps, stiffness, pain are common complaints More common in women Muscle hypertrophy is a rare sign (Hoffman's sign) Delayed deep tendon reflexes
Hyperthyroidism	Exact mechanism is unknown Impaired muscle function may be due to increased cellular metabolism and energy utilization, increased catabolism and protein degradation, and inefficient energy utilization	Muscle weakness ± tenderness and atrophy in 60–80% of patients Presentation may be acute or chronic Two-thirds of patients with hyperthyroid myopathy report proximal weakness, mainly hip flexors and quadriceps Cramps are less common Atrophy is usually absent Bulbar symptoms may be present Associated with other neuromuscular diseases: Myasthenia gravis Periodic paralysis Progressive ocular myopathy
Hyperparathyroidism		25% of patients will have insidious onset of proximal myopathy, legs more than arms Atrophy is a common feature Fatigue, muscle pain, and hyperreflexia are common
Adrenal insufficiency		100% of patients present with weakness, but usually there is no objective proximal myopathy
Primary hyperaldosteronism		Weakness is a common complaint Weakness and paralysis are usually due to the hypokalemia
Cushing syndrome (see Glucocorticoid myopathy)		

Gottron's papules and heliotrope rash are pathognomonic features of dermatomyositis [14]. Dermatomyositis and polymyositis are also known to cause manifestations related to the cardiovascular system, respiratory system, and gastrointestinal system.

Patients diagnosed with IID tend to have a higher risk of developing malignancies. Patients with dermatomyositis or polymyositis have an increased risk of developing malignancy. Those with dermatomyositis are three to six times more likely and those with polymyositis are two to four times more likely than the normal population to develop ovarian, gastric, pancreatic, and lung cancer and non-Hodgkin lymphoma. Thus screening for malignancies is highly recommended in this population [15].

9.3.5 Myopathy Due to Infectious Disease

Infectious diseases may cause an acute presentation of weakness with muscle cramps, myoglobinuria, and rhabdomyolysis. Among the infectious causes, viral infections are the most

Table 9.7 Features of dystrophic myopathy

Type of myopathy	Distribution	Characteristic	Mode of inheritance
Duchenne	Proximal	Age of onset 3–5 years Weakness starts in the trunk Spreads to arms and legs Gower's sign Calf hypertrophy Wheelchair by ages 9–10 Cardiomyopathy Scoliosis/respiratory problems Cognitive impairment	X-linked
Becker's	Proximal	Age of onset 3–20 years Less severe than Duchenne	X-linked
Limb-girdle	Proximal	Age of onset 3–20 years Shoulder and hip muscles Low back pain Sparing of the face Cardiac involvement Contractures No cognitive impairment	AR/AD
Facioscapulohumeral muscular dystrophy (FSHD)	Proximal	Age of onset is variable (average 10–20 years) Infant form wheelchair by 9 years Severe facial weakness Inability to close eyes Inability to smile Weakness can involve shoulder and hips Early onset: Hearing loss, seizures, cognitive impairment	AD
Myotonic dystrophy	Distal	Age of onset is variable Most common adult-onset muscular dystrophy Type 1, type 2 Affects facial muscle, arms, legs Multisystem: Cardiac, cataract, sexual organs, cognitive impairment Excessive daytime sleepiness	AD

Table 9.8 Classification of idiopathic inflammatory myopathies

1. Primary idiopathic dermatomyositis
2. Polymyositis or dermatomyositis with malignancy
3. Juvenile dermatomyositis (or polymyositis)
4. Inclusion body myositis
5. Rare forms of idiopathic myositis
   - Granulomatous myositis
   - Eosinophilic myositis
   - Focal myositis
   - Orbital myositis

common. Myalgia is the most common symptoms, but can last up to 2–3 weeks. Usually myopathy due to viral infections is self-limiting, but severe cases may cause myoglobinuria and renal impairment.

Human immunodeficiency virus (HIV) is an important differential when approaching myopathy; the condition is often referred to as HIV polymyositis. HIV polymyositis can be a presenting manifestation of HIV infection or can occur in later stages. Patients with HIV polymyositis may present with asymptomatic elevation of CK levels, or as severe muscle tenderness and muscle weakness. HIV-related myopathy appears to have a better prognosis than idiopathic inflammatory myopathies. See the treatment section for how to manage HIV polymyositis.

Table 9.9 The pathogenetic mechanisms and clinical features of the most common IID

Condition	Pathogenesis	Age/sex	Clinical features	
Dermatomyositis	Humeral mediated process CD4 cells and B lymphocytes attack the vascular endothelium; result in necrosis of capillary and ultimately muscle atrophy	10–15 years 40–70 years F: M—2:1	Symmetrical proximal muscle weakness Pathognomonic: Heliotrope (purple) Periorbital edema; violaceous papules (Gottron's papules) or macules (Gottron's sign)	Both dermatomyositis and polymyositis: • 10% have interstitial lung disease (may lead to respiratory failure and death) • Increase rate of malignancy • Dysphagia, nasal regurgitation, and/or aspiration with increased age • Cardiac involvement in the form of myocarditis, conduction defects, and arrhythmias • Constitutional symptoms
Polymyositis	Cellular mediated process CD8 cytotoxic cells recognize MHC-1 on the muscle fiber, and this is the initiation of the necrotic process	Second decade of life F: M—2:1	Diagnosis by exclusion No skin manifestation Associated with HIV Histopathology is considered the most effective way to establish the diagnosis of PM	
Inclusion body myositis	The mechanism is poorly understood, but histopathology shows inflammatory cells surrounding myofibers and rimmed vacuoles, and some myofibers are attacked by CD8 cytotoxic cells	>50 years 3 times more in men	Insidious onset and progressive asymmetric distal weakness with wrist and index finger flexors weaker than extensors. Associated with early atrophy and poor response to steroid	

9.4 Diagnostic Approach

A thorough history and physical examination is the cornerstone to reach the diagnosis. Investigations should be tailored to screen for reversible causes of a myopathy (Fig. 9.4).

When the cause of muscle weakness is unclear, appropriate testing should be performed, and it is recommended to start with blood tests including electrolytes (potassium, calcium, phosphate, and magnesium), thyroid-stimulating hormone (TSH) level, alkaline phosphatase and 25 (OH) vitamin D level, and HIV [16].

9.4.1 Muscle Enzyme

The measurement of serum levels of muscle enzymes is of critical value for the evaluation and monitoring of muscular disorders. Creatine kinase (CK), lactate dehydrogenase (LD), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and aldolase are the serum muscle enzymes that are measured in clinical practice. In patients with suspected myopathy who do not demonstrate CK elevation, testing for aldolase can be helpful, but it is less sensitive and less specific [17].

Approach to high level of CK is demonstrated thoroughly in Table 9.10. It must be noted that CK elevation is, however, not specific to myopathy and further testing should be performed in a comprehensive approach. Table 9.11 shows the differential diagnosis to high CK level.

While diagnosing myocardial infarction, besides symptoms and abnormal ECG findings, there will be rise in CK-MB, the isoenzyme of CK, electrophoretically distinguished and high in concentration in the cardiac tissue. However, it is neither specific nor sensitive as troponins [18].

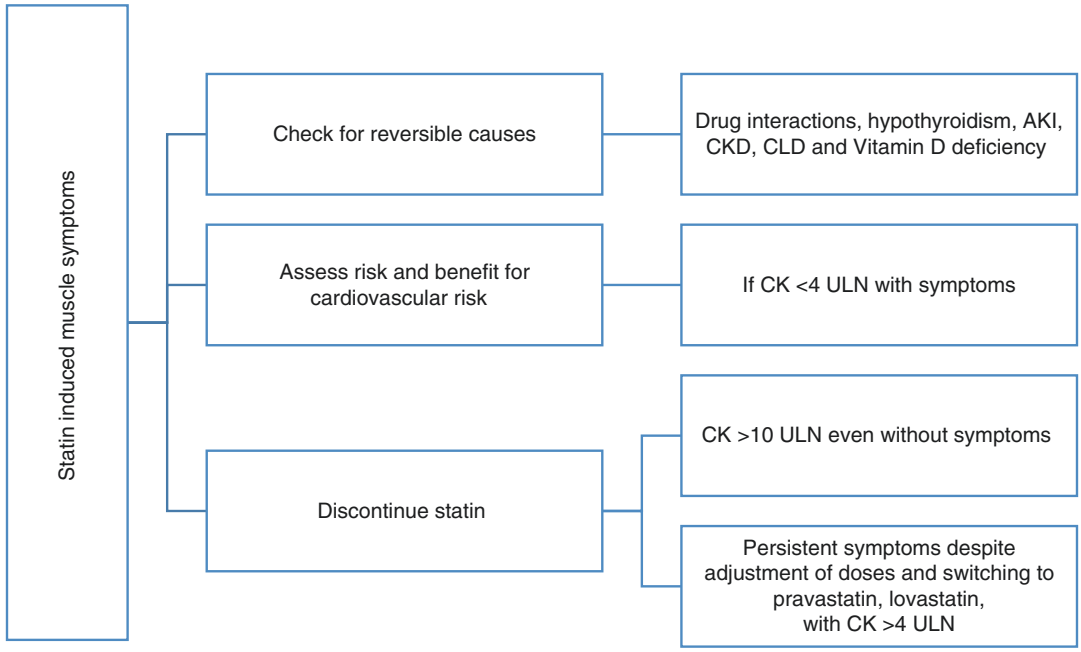

Fig. 9.4 Approach to statin-induced myopathy

CK might be falsely elevated secondary to ethnicity (can be high in Afro-Caribbean men), exercise (can remain elevated for up to 72 h), intramuscular injections, needle electromyography (EMG), medications, hypothyroidism, and motor neuron disease [16].

9.4.2 Rhabdomyolysis

Muscle injury due to vigorous exercise, medication, infection, and metabolic derangements can cause rhabdomyolysis. Severe myalgia, weakness, and red to brown urine due to myoglobinuria are classical initial presenting features. Rise of CK levels is typically seen after 2–12 h of injury and reaches its maximum within 24–72 h. A decline is usually seen within 3–5 days of cessation of muscle injury. Myoglobinuria is present in 50–75% of patients at the time of initial evaluation. Thus it is recommended to perform routine dipstick urine analysis in any patient with extremely elevated CK level and myopathy. There are serious metabolic derangements that complicate this massive muscle destruction in the body. Electrolyte imbalance and acute renal failure are serious examples.

9.4.3 Other Tests

In addition to CK, to diagnose rheumatologic myopathy, erythrocyte sedimentation rate (ESR) C-reactive protein (CRP), antinuclear antibody assay (ANA), rheumatoid factor, anti-double-stranded DNA, antiphospholipid antibodies, and anti-centromere antibodies should be ordered. In case of inflammatory myopathy, check for anti-Jo1 antibody, directed against histidyl-tRNA synthetase. Recognition of anti-Jo1 syndrome is important because such patients can develop extra-muscular features, such as interstitial lung disease, Raynaud's phenomenon, and arthritis [19].

Table 9.10 Approach to high CK level

Episodic Range from normal to rhabdomyolysis	Mild 3–four-fold ULN	High 100 fold ULN
Endocrine Hypothyroidism Hyperthyroidism Cushing's syndrome Acromegaly Electrolyte imbalance	*Drugs* Antimalarial, cholesterol-lowering drugs (statins), cocaine, alcohol, colchicine → 10- to 20-fold	*Rhabdomyolysis* Acute, massive muscle injury due to: Trauma, seizures, electrolyte imbalances, infections The degree of myoglobinuria might Correlate with the risk of acute renal failure CK levels decrease rapidly to normal after managing the cause
Metabolic myopathies Glycogen and lipid storage disease Carnitine palmitoyl transferase (CPT) Muscle phosphorylase deficiency	*Systemic vasculitis* Polyarteritis nodosa Wegener's Behçet's disease Sarcoidosis	
	Connective diseases Rheumatoid arthritis Systemic lupus erythematosus Sjögren's syndrome Scleroderma Specific autoantibodies anti-U1 RNP and anti-PM/Scl	*Infectious myopathies* Viral (EBV, HIV), bacterial, mycobacterium, fungal, parasitic
Periodic paralysis Primary hypokalemic periodic paralysis	*Inclusion body myositis* 80 percent of patients	*Polymyositis & dermatomyositis* Abnormal EMG and muscle biopsy findings correlation between the height of CK elevation at diagnosis and the severity of disease
	Dystrophic myopathies Limb-girdle dystrophies Facioscapulohumeral dystrophy, myotonic dystrophy CK levels peak by age 2 and then progressively fall, often to the normal range, as more and more muscle is replaced by fat and fibrosis	
	Motor neuron disease (amyotrophic lateral sclerosis)	

Table 9.11 Differential diagnosis to high CK level

• Differential diagnosis of CK with weakness – Inflammatory – Metabolic – Endocrine – Drug induced – Infectious (viral)	• Differential diagnosis of CK without weakness – Strenuous exercise – After EMG studies – Trauma – Post-surgery – Intramuscular injections – Metabolic and congenital myopathy – Medications – Race (African Americans)

9.4.4 Electromyography (EMG)

Electromyography (EMG) is a test that is used to record muscle electrical activity and assess the nerves that control the muscles. An abnormal electromyogram can indicate a neuropathy or neuromuscular disease. Characteristic EMG findings of myopathy include short duration and decreased amplitude of action potential unlike neuropathies that are characterized by increased duration and amplitude of action potential.

Although there are no pathognomonic features that distinguish different forms of myopathy, EMG can help distinguish inflammatory from non-inflammatory forms of myopathy. Normal EMG examination, however, would not exclude myopathy [18]. In case of polymyositis, the site of muscle biopsy should be opposite to where the EMG was conducted [16].

9.4.5 Muscle Magnetic Resonance Imaging (MRI)

MRI evaluates deep muscles not readily accessible by EMG and plays a role in the diagnostic process by identifying subclinical signs of muscle involvement. Fat-suppressed and short tau inversion recovery techniques differentiate between active myositis, pictured as edema, and chronic inactive myositis in patients with inflammatory myopathy, presented as fat [20]. A secondary role for muscle MRI is to provide information about the best site for muscle biopsy by showing which muscles are involved in the myopathic process.

9.4.6 Muscle Biopsy

Establishing the diagnosis of IID is essentially based on histopathological grounds. There are currently advanced therapies that can be used effectively in these patients. The justification of using these drugs or even steroids should be based on muscle biopsy. Open surgical biopsy is preferable to closed needle biopsy because of the patchy nature of inflammation in PM and so that adequate tissue could be obtained. However, in some circumstances, the biopsy is performed by expert radiologists. Muscle biopsy is a reliable instrument in the diagnosis of PM in 85% of the patients [18]. It is an outpatient procedure that may cause pain, bleeding, infection, or sensory loss. No special preparation is required other than that patients should discontinue using anticoagulants before the procedure [21].

The best muscles to biopsy are those moderately affected by the disease process but not atrophied. Previous sites of injections, EMG examination, or trauma should be avoided. The most common biopsy sites are the deltoid, quadriceps for proximal myopathy, and gastrocnemius for distal myopathies.

Technology using genetic markers is advancing rapidly. In inflammatory myopathies, immune staining for major histocompatibility classes I and II (MHC-I/II) is upregulated in myofibrils, whereas MHC-I immune staining alone is nonspecific [22].

9.4.7 Screening for Malignancy

Idiopathic inflammatory myopathies PM and DM have positive relation to malignancy; retrospective studies' results justify CT of the chest, abdomen, and pelvis in addition to age-appropriate screening tests such as colonoscopy and mammography for any patient newly diagnosed. This is shown in Southeast Asia where input of otolaryngologists is invaluable due to the higher incidence of nasopharyngeal carcinoma for DM patients. Recent advances in understanding of pathogenesis of idiopathic inflammatory myopathies have led to discovery of biomarkers like type 1 interferon and myeloid cell signatures to distinguish active disease from chronic injury [17].

9.4.8 Genetic Testing

Genetic testing is becoming increasingly useful in confirmation of patient with muscular dystrophies and heritable myopathies. These mutations can be identified through peripheral blood DNA analysis. Molecular testing often eliminates the need for muscle biopsy.

9.5 The Management of Myopathy

9.5.1 Inherited Myopathy

For most patients with congenital myopathy or muscular dystrophy, the treatment is mainly supportive. Physical therapy, occupational therapy,

management of contractures, nutrition, and genetic counseling together play a role in managing congenital myopathies. In patients with Duchenne muscular dystrophy, treatment with prednisone has been shown to improve strength and muscle bulk and slow the rate of natural progression of the disease. Patients should also be monitored over time for complications related to kyphoscoliosis or involvement of cardiac, respiratory, or bulbar muscles. Finally, genetic counseling should be offered to all patients with inherited myopathy and their family members.

9.5.2 Acquired Myopathy

Management of proximal myopathy depends on underlying etiology. Treatable causes should be sought and treated accordingly. Discontinuation of offending drug is likely to improve symptoms in patients with drug-induced myopathy, e.g., statins [5]. Dose reduction should be considered for those patients in whom abrupt discontinuation of drug may not be possible, e.g., steroid myopathy [6]. In HIV-related myositis, treatment with the combination of highly active antiretroviral therapy (HAART) and steroids may be beneficial.

Treatment of IIM is largely empirical because of paucity of well-controlled trials. Current evidence is mostly based on retrospective or open prospective trials involving small numbers of patients. Corticosteroids are the cornerstone in the treatment of PM and DM [19, 20]. In the absence of placebo-controlled trials, the optimal initial dose and duration of therapy are uncertain, but patients are generally started on 0.75–1 mg/kg body weight/day of prednisolone. Intravenous pulse methylprednisolone is initially considered for those with cardiac, respiratory, or pharyngeal muscle involvement to obtain quicker response. Because maximal improvement may not be seen for several weeks, the usual practice is to start tapering the dose of prednisolone only after about 4–12 weeks, guided by clinical improvement. Many patients relapse when corticosteroids are discontinued, and therefore, a maintenance dose of 5–10 mg/day is often required for several years. About a third of patients with PM or DM, and those with IIM, might fail to show any response to prednisolone. Second-line immunosuppressive drugs are tried in patients who do not respond to corticosteroids alone and in those with progressive disease and internal organ involvement. Choice of drug is largely empirical and depends on disease severity, extra- muscular manifestations, and personal experience of treating physician, again because of paucity of well-conducted trials.

Azathioprine [23] or methotrexate is usually preferred. Intravenous immunoglobulin (Ig), the only agent for which there is positive evidence from randomized placebo-controlled trial [21, 24], is especially useful for patients with dysphagia and treatment-resistant DM. Intravenous Ig is, however, expensive and limited in availability. Cyclophosphamide, given as monthly intravenous pulses for 3–6 months, is also an option for patients with respiratory muscle weakness, interstitial lung disease, or cardiac involvement [25]. Plasmapheresis has also been studied, but was not found to be helpful in a double-blind placebo-controlled trial [26]. Rituximab, a CD20 monoclonal antibody that depletes B cells, has been reported to have a favorable effect in small open-label uncontrolled trials [27, 28]. A new double-blind, placebo-phase trial in refractory adult and pediatric myositis using rituximab revealed good results [29]. Tumor necrosis factor inhibitors such as infliximab, adalimumab, and etanercept are ineffective in treating IID and may cause deterioration or trigger the disease [30]. Other biological agents that may be considered as experimental treatments include alemtuzumab, which is reportedly effective in polymyositis [31], and anti-complement C3 (eculizumab), which may be effective for the treatment of dermatomyositis. Overall, the long-term outcome of inflammatory myopathies has substantially improved, with a 10-year survival rate of more than 90% . Table 9.12 shows a step-by-step approach in the management of IID [32].

Input of physiotherapist is also valuable because randomized controlled trials among patients with IIM have demonstrated that exercise therapy, adapted to the patient's condition, is

Table 9.12 Approach to treatment of inflammatory myopathies

Clinical situation	Treatment for IID
New-onset disease	Prednisone (0.75–1 mg / kg) for 4–12 weeks
Weakness is severe + cardiac, respiratory, pharyngeal involvement	Intravenous glucocorticoids (1000 mg/day) for 3–5 days and then switch to oral
If patient responds to glucocorticoids	Start a glucocorticoid-sparing agent • Azathioprine • Methotrexate
If response to glucocorticoids is insufficient	Intravenous immune globulin (2 g/kg in divided doses over 2–5 days)
If response to glucocorticoids and intravenous immunoglobulin is insufficient	Consider initiating treatment with rituximab

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beneficial and safe [33]. Benefits of exercise not only include improved muscle endurance, strength, and functional abilities but also prevent muscle wasting and fibrotic contractures.

Acknowledgments The authors would like to thank Haytham Abbas, MD, for his contributions to this chapter in the previous edition.

References

1. Dalakas MC. Toxic and drug-induced myopathies. J Neurol Neurosurg Psychiatry. 2009;80:832–8.
2. Horak HA, Pourmand R. Neurol Clin. 2000;18(1):203–13.
3. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA. 2003;289:1681.
4. Afifi AK, Bergman RA, Harvey JC. Steroid myopathy. Clinical, histologic and cytologic observations. Johns Hopkins Med J. 1968;123:158.
5. Horak HA, Pourmand R. Endocrine myopathies. Neurol Clin. 2000;18:203–13. https://doi.org/10.1016/S0733-8619(05)70186-9.
6. McKeran RO, Slavin G, Ward P, et al. Hypothyroid myopathy. A clinical and pathological study. J Pathol. 1980;132:35.
7. Cicala MV, Mantero F. Primary aldosteronism: what consensus for the diagnosis. Best Pract Res Clin Endocrinol Metab. 2010;24:915–21. https://doi.org/10.1016/j.beem.2010.10.007.
8. Del Porto LA, Liubinas SV, Kaye AH. Treatment of persistent and recurrent acromegaly. J Clin Neurosci. 2011;18:181–90. https://doi.org/10.1016/j.jocn.2010.10.003.
9. Yildirim Donmez F, Feldman F. Muscle compromise in diabetes. Acta Radiol. 2008;49:673–9. https://doi.org/10.1080/02841850802105269.
10. Emery AE. The muscular dystrophies. Lancet. 2002;359:687.
11. Briani C, Doria A, Sarzi-Puttini P, Dalakas MC. Update on idiopathic inflammatory myopathies. Autoimmunity. 2006;39:161e70.
12. Yazici Y, Kagen LJ. Clinical presentation of the idiopathic inflammatory myopathies. Rheum Dis Clin North Am. 2002;28:823–32.
13. Targoff IN. Immune manifestations of inflammatory muscle disease. Rheum Dis Clin N Am. 1994;20:857–80.
14. Kovacs SO, Kovacs SC. Dermatomyositis. J Am Acad Dermatol. 998(39):899–920.
15. Sigurgeirsson B, Lindelof B, Edna O, Allander E. Risk of cancer in patients with dermatomyositis or polymyositis. N Engl J Med. 1992;326:363–7.
16. Ghaoui R, Clarke N, Hollingworth P, Needham M. Muscle disorders: the latest investigations. Intern Med J. 2013;43(9):970–8.
17. Suresh E, Wimalaratna S. Proximal myopathy: diagnostic approach and initial management. Postgrad Med J. 2013;89(1054):470–7.
18. Weisberg LA, Strub RL, Garcia CA, Strub AC. Diseases of muscle and neuromuscular junction. In: Essentials of clinical neurology: University Park Press; 1983.
19. Inflammatory myopathies. Postgrad Med J. 2006;82:417–24. 59
20. Greenberg SA. Inflammatory myopathies: evaluation and management. Semin Neurol. 2008;28:241–9.
21. Dalakas MC, Illa I, Dambrosia JM, et al. A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis. N Engl J Med. 1993;329:1993–2000.
22. Chawla J. Stepwise approach to myopathy in systemic disease. Front Neurol. 2011;2:49.
23. Bunch TW. Article first published online: 23 Nov 2005. https://doi.org/10.1002/art.1780240107.
24. Wang DX, Shu XM, Tian XL, et al. Intravenous immunoglobulin therapy in adult patients with polymyositis/dermatomyositis: a systematic literature review. Clin Rheumatol. 2012;31:801–6.
25. Al-Janadi M, Smith CD, Karsh J. Cyclophosphamide treatment of interstitial pulmonary fibrosis in polymyositis/dermatomyositis. The Journal of Rheumatology, 1989;16(12):1592—6. http://europepmc.org/abstract/MED/2625692.

26. Miller FW, Leitman SF, Cronin ME, et al. Controlled trial of plasma exchange and leukapheresis in polymyositis and dermatomyositis. N Engl J Med. 1992;326:1380–4.
27. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 2005;52:601–7.
28. Chung L, Genovese MC, Florentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. Arch Dermatol. 2007;143:763–7.
29. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis. Arthritis Rheum. 2013;65(2):314–24. https://doi.org/10.1002/art.37754.
30. Brunasso AMG, Aberer W, Massone C. New onset of dermatomyositis/polymyositis during anti-TNF-α therapies: A systematic literature review. The Scientific World Journal; 2014. https://doi.org/10.1155/2014/179180.
31. Thompson BEN, Corris P, Miller JAL, Cooper RG, Halsey JP, Isaacs JD, Rheumatologist C. Alemtuzumab (Campath-1H) for Treatment of Refractory Polymyositis. The Journal of Rheumatology. 2008;35(10):2080–2. http://www.jrheum.org/content/35/10/2080.abstract.
32. Yin G, Liang Y, Deng R, Wang Y, Xie QB, Zuo C. [Survival analysis and risk factors for survival in idiopathic inflammatory myopathies: a retrospective cohort study]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2013;44(5):818–22. Chinese. PMID: 24325120.
33. Habers GE, Takken T. Safety and exercise training in patients with an idiopathic inflammatory myopathy: a systematic review. Rheumatology (Oxford). 2011;50:2113–24.