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Myalgia in myositis and myopathies

Stefanie Glaubitz, Karsten Schmidt, Jana Zschüntzsch, Jens Schmidt*

Department of Neurology, University Medical Center Göttingen, Germany

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A B S T R A C T

Myalgia is a common symptom of various neuromuscular disorders: myalgia occurs in metabolic muscle diseases, inflammatory muscle diseases, dystrophic myopathies and myotonic muscle disorders. Myalgia leads to a significantly reduced quality of life. Other muscular symptoms that are present along with myalgia often provide the clue towards a diagnosis and include weakness, cramps and myotonia as well as the type of pain. In addition, extramuscular symptoms like an erythema in dermatomyositis can lead to the correct diagnosis. Basic diagnostic workup includes a detailed medical history, full neurologic assessment, laboratory tests, EMG and nerve conduction studies. Muscle imaging, genetic testing and muscle biopsy may be required to make a diagnosis. Whenever possible, treatment should aim to improve or correct the underlying cause for myalgia such as inflammation or hypothyroidism. Symptomatic therapy includes different avenues: Myotonia can be treated with mexiletine. Carbamazepine or phenytoin can be used in myotonic syndromes, particularly with muscle cramps. Pregabalin, gabapentin, or amitriptyline can be tried in conditions with myalgic pain. This review summarizes the symptoms, diagnostic strategies, and therapeutic approach in neuromuscular disorders that present with myalgia.

* Corresponding author. Department of Neurology, Neuromuscular Center Göttingen, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany.
E-mail address: j.schmidt@gmx.org (J. Schmidt).

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Introduction

Myalgia is a very common and unspecific symptom. Nearly every person will suffer from muscular pain once in a lifetime. Myalgia often occurs as an aching experience after exercise or after mild traumatic injuries. This kind of myalgia seems to be uncomplicated and harmless.

However, what are the hints for a serious and pathological myalgia?

The following review summarizes the most common diseases, which are associated with myalgia. The text provides an overview of the different causes of myalgia and the disease-specific symptoms that may help towards making a diagnosis. The underlying diagnosis and the required diagnostic workup as well as the therapy of myalgia are presented.

Myalgia and disease-specific symptoms

In the literature, muscle pain is defined as a "poorly localizable pain with a tearing, cramping and pressing quality which differs much from cutaneous and visceral pain." In comparison to cutaneous pain, the muscular one is more difficult to tolerate.

Regarding myalgia, it is very important to know the characteristic of the pain. Is the pain diffuse or focal? Does the myalgia occur after exercise or at physical rest? What improves or worsens the myalgia? Typical symptoms associated with myalgia include weakness of the aching muscles, concomitant occurrence of an increase in muscular tone, hypertrophy, atrophy or fasciculations (Table 1).

Myalgia in myositis

Regarding myositis, it is necessary to differentiate between pathogen-associated myositis and idiopathic inflammatory myopathies. In general, pathogen-associated myositis is more common than idiopathic inflammatory myopathies. Typical triggers for a myositis are viral infections, especially an infection with coxsackievirus. The so-called Bornholm disease leads to breathing-dependent myalgia of the breast muscles: It occurs in childhood and has a benign prognosis with a milder course and a complete regression [19]. Myositis is mostly induced by the bacteria streptococci. The patients show severe myalgia and a serious medical condition. *Borrelia* can also cause myositis. Parasitic infection, especially trichinose, causes myalgia. This disease is caused by roundworms of the Trichinella type. The patients simultaneously report high grade fever, diarrhoea and periorbital oedema [11].

Dermatomyositis, polymyositis, and inclusion body myositis are summarized under idiopathic inflammatory myopathies and affect the lives of around 250,000 people worldwide. All these diseases lead to muscle weakness, muscle damage and loss of muscle functionality.

Polymyositis and dermatomyositis are characterized by a proximal weakness of the upper and lower limbs, particularly affecting the hip flexors and the deltoids. Because of the affection of the hip flexors, patients show impairments in climbing stairs or rising from a chair. The weakness is progressive over months and becomes mostly evident in adulthood. In addition to the weakness mentioned above, patients with dermatomyositis present with skin manifestations including Gottron's papules and a heliotrope rash. In both diseases, extramuscular symptoms are frequently seen: Cardiac involvement, an interstitial lung disease as well as Raynaud's syndrome are reported in idiopathic inflammatory myopathies. Severe muscle pain often occurs: Half of the patients with polymyositis suffer from myalgia. The rate of myalgia is higher in dermatomyositis [41]. Regarding dermatomyositis, there are cases with a rapid progressive muscular weakness, severe myalgia and exercise intolerance in the affected muscles. Inclusion body myositis (IBM) affects above 45 years of age and leads to a slowly progressive weakness of the upper and lower limbs. In particular, the finger flexors and the knee extensors are involved. The patients often develop dysphagia. Myalgia is less common in inclusion body myositis compared to other forms of myositis [40].

Myalgia in metabolic muscle disease

In the cases of exercise-dependent myalgia, a possible metabolic muscle disease should be considered. It is important to determine the exact time of occurrence of the muscular pain in order to pinpoint the right diagnosis.

Table 1
Key symptoms and most important diagnostic tests in skeletal muscle disorders.

Disease	Symptom: diagnostic clue	Most important diagnostic test
Myositis		
Dermatomyositis	Proximal weakness, skin manifestation with heliotrophe rash, Gottron's papules	Antibodies, muscle biopsy (perifascicular fibre atrophy, $CD4^+$ T cells in perimysium)
Polymyositis	Proximal weakness, no skin manifestation	Antibodies, muscle biopsy ($CD8^+$ T cells in endomysium)
Necrotizing myopathy	Proximal weakness, no skin manifestation	Antibodies, muscle biopsy (necrotic fibers, no primary inflammation)
Inclusion body myositis	Slowly progressive weakness; predominant affection of finger flexors and knee extensors	Muscle biopsy (rimmed vacuoles, endomysial infiltration, protein accumulation)
Metabolic muscle diseases		
McArdle Disease	Second wind phenomenon	Ischaemic lactate test (no increase in lactate), Laboratory test (enzyme activity)
Carnitine palmitoyl transferase deficiency	Muscle cramps several hours after exercise, myoglobulinuria, worsening after fasting	Laboratory test (Carnithine-profile)
Myoadenylate deaminase deficiency	Post-exercise myalgia	Ischaemic lactate test (no increase in ammonia), Laboratory test (enzyme activity)
Muscular dystrophies		
Duchenne muscular dystrophy	Weakness in childhood with Gowers' sign and Trendelenburg's sign, scoliosis	Genetic-test (dystrophin)
Becker muscular dystrophy	Weakness in adolescence, cardiac involvement, pseudohypertrophy	Genetic-test (dystrophin)
Facioscapulohumeral muscular dystrophy	Myotonic facies, scapular winging	Genetic test (D4Z4-gene)
Myotonia		
Myotonia	Myotonia worsened during cold, improved after warming up, percussion and fist-closure myotonia	EMG (repetitive muscle fibre action potentials)
Myotonic dystrophy type 1	Myotonia, distal weakness, hypogonadism, diabetes, cataract, arrythmia	Genetic test (DMPK gene)
Myotonic dystrophy type 2	Mild or no paresis, muscle pain, cataract, arrythmia	Genetic test (CNBP gene)
Others		
Endocrinologic myopathy	Struma, fatigue	Hypothyroidism: TSH elevated, T3/T4 reduced
Statin-induced myopathy	Occurs after the initiation of statins	Autoantibody (SRP, HMGCR)
Polymyalgia rheumatica	Stiffness and myalgia in neck and shoulder, coincidence with temporal arteritis	ESR increased
Fibromyalgia	Tender points, fatigue	Exclusion of other causes

The exact temporal sequence of substrate utilization in muscle is helpful for understanding the underlying diagnosis. During contraction, the muscle uses rapid energy sources with the consumption of ATP at first. After a few seconds, the muscle utilizes creatine phosphate and, later, glucose. ATP and creatine phosphate are located in the muscle. After around 1 min, the muscle starts to use the stored glycogen. During extensive training, the muscle starts to metabolize lipids and proteins.

Exercise-dependent myalgia, which improves directly after the workload, points towards a lack of phosphorylase. After a short rest, the patients are able to resume exercise without any difficulties. This is called “second wind phenomenon”, which is typical for McArdle disease [7].

In case of a carnitine palmitoyl transferase deficiency, patients typically describe muscle cramps several hours after physical exercise, which is due to the impaired lipid metabolism. Nearly all patients

describe bursts of myalgia (94%), muscular weakness (76%) and myoglobinuria (86%). They notice a worsening after fasting, stress and after lack of sleep as well [23].

The most frequent metabolic myopathy is the myoadenylate deaminase deficiency with an estimated prevalence of 1–2% of the general population. However, only a minority of the patients develops symptoms. Typical symptoms are muscular fatigue, cramps and post-exercise myalgia. The proximal muscles are affected more frequently than the distal muscles without the development of atrophies [47].

Myalgia in dystrophic myopathy

Most of the patients with Duchenne Muscular Dystrophy and Becker muscular Dystrophy have myalgia at the beginning of the disease. Exacerbating factors are lying in bed and sleeping. Myalgia in degenerative myopathies occurs especially in the calves. However, more than half of the patients have pain in more than one location. Myalgia impairs the quality of life [42].

Patients with facio-scapulo-humeral muscular dystrophy (FSHD) display a phenotype of weakness of facial muscles, the shoulder girdle and a scapular winging [20]. In some cases, myalgia can be the prominent symptom [9]. Despite the weakness of limb muscles, the pain is often located in the lower back and lower limbs.

Myalgia in myotonic myopathy

Myotonia is defined as a delayed relaxation of skeletal muscles after contraction. Several hereditary diseases cause myotonia, including congenital myotonia, paramyotonia congenita and the myotonic muscular dystrophies. Apart from myotonic symptoms, patients often complain of myalgia. Exercise often causes cramps, which improve after warming up and typically worsen during cold.

Myotonic dystrophy presents with muscle weakness in distal muscles (myotonic dystrophy type 1, DM1) or predominantly proximal muscle (type 2, DM2). Patients with myotonic dystrophy typically develop a cataract, hypogonadism and cardiac arrhythmias. Myalgia is very prominent in myotonic dystrophy, particularly in DM2, which often leads to an erroneous diagnosis of fibromyalgia [48].

Myalgia caused by medication or in endocrinological diseases

Certain drugs can cause myalgia. Especially the use of statins has been associated with myalgia in up to 5 –10% [13].

Risk factors associated with statin toxicity are female gender, age >80 years, hypothyroidism, polypharmacy, alcohol abuse and multisystem disease [37]. Hypothyroidism can cause myalgia and muscle cramps. Other symptoms include fatigue and muscle weakness, particularly in untreated or severe hypothyroidism [43].

Myalgia in polymyalgia rheumatica and fibromyalgia

An important differential diagnosis in patients complaining of general myalgia is polymyalgia rheumatica. It appears mostly in elderly women and has a high coincidence with giant cell arteritis. Patients with bilateral myalgia in neck and shoulder muscles possibly associated with fever and weight-loss should be tested for polymyalgia rheumatica [5].

The most common cause of generalized muscle pain is fibromyalgia. Its cause is yet unknown, but the symptoms are well defined. Fibromyalgia is characterized by pain, sleep disturbance and fatigue. In fibromyalgia, there are up to 18 defined tender points, which are very painful during palpation. This chronic pain syndrome affects women more often than men. Muscle weakness or atrophy is not present [3]. The latest revision of the fibromyalgia diagnostic criteria was in 2016. In this revision, physician and questionnaire criteria were combined and other clinically important illnesses are no longer considered as an exclusion criterion [50].

Myalgia in diseases of the central nervous system

Damage of the central nervous systems often leads to an increase in the muscular tonus. A spasticity after stroke or other brain damage may cause myalgia. Furthermore, a rigor in Parkinson's disease can lead to muscle pain as well, particularly in neck and shoulder muscles.

Diagnostics in myalgia

Diagnosis in suspected muscle disease can be challenging due to the variety of symptoms and clinical presentations. Different entities of muscle diseases can present with similar symptoms and vice versa [29].

The basic workup for suspected muscle disease includes a careful medical history and physical examination, laboratory tests, EMG and nerve conduction studies. For further testing, depending on the results of the aforementioned tests, imaging studies, genetic testing and muscle biopsy may be required. The diagnostic workup for myalgia should be carried out in a standardized fashion in order to prevent overlook of important information and to avoid invasive examinations if not necessary. In the following part, we will discuss the different diagnostic tools.

History and physical examination

Medical history and clinical examination are key to adequately navigate through subsequent diagnostics. If myalgia is the leading symptom, a standardized pain questionnaire should be used. This should include localization, quality, frequency, time course and triggers of the pain. Myalgia caused by phosphorylase deficiency begins with exercise and could be diminished with continuing exercise, known as “second wind”. In fatty acid oxidation disorders, pain and muscle cramps typically occur hours after prolonged exercise of low intensity or periods of fasting.

Other muscular symptoms such as weakness and atrophy should be examined. The temporal relationship with triggers such as physical exercise, certain foods or temperature changes can indicate metabolic myopathy. In this context, episodes of pigmenturia should be evaluated. Muscle cramps and fasciculation should be specifically asked for. A detailed history of medication and exposure to environmental toxic agents is indispensable. Statins are common inducers of muscle symptoms. Up to 29% of patients treated with statins experience a range of muscle-related side effects from very mild to severe [45]. Because myalgia can also occur in hereditary and metabolic myopathy, questioning about family history and for consanguinity is advisable.

During clinical examination, a possible paresis should be graded according to the MRC scale (0–5). Accordingly, a syndrome diagnosis can often be made based on the distribution of the paresis, e.g. limb girdle syndrome, oculopharyngeal syndrome, fazio-scapulo-humero-peroneal syndrome or distal myopathic syndrome. Mild paresis can be seen in functional examinations such as knee flexion, heel and toe motion. Attention should be paid to scapular winging, facial muscle weakness, hyperlordosis and ptosis. Some patients may also experience hypertrophy (e.g. myotonia) and pseudohypertrophy (e.g. Becker muscular dystrophy). Myotonic phenomena is assessed by testing percussion and prolonged forced closure of the fist. Palpation of muscles and questioning for pain on pressure is conducted as well as checking for tenderpoints in fibromyalgia.

Laboratory tests

The blood test for creatine kinase (CK) provides an initial general overview of the extent of muscle fibre damage. Generally, a CK increase should be confirmed at least once. Because CK can also increase as a result of physical exertion, it is recommended to avoid excessive exercise in advance. Neuropathies can also lead to increased CK values, whereas a 10-fold increase in CK strongly indicates a primary myogenic cause. Highly elevated CK-values should prompt suspicion of myositis: levels >1000 U/l had a specificity 94% in a cohort of 64 patients which underwent a muscle biopsy in a rheumatology department. In most cases, a non-differentiated inflammatory myositis was diagnosed [10]. High levels of a CK of >10,000 U/l can be found in toxic rhabdomyolysis or in glycogen storage diseases. Macro-CK

is caused by atypical isoenzymes that can lead to false-positive test results; this should be tested especially in asymptomatic cases. Other serum muscle enzymes include aspartate amino-transferase (AST), alanine amino-transferase (ALT), lactate dehydrogenase (LDH) and aldolase. TSH, cortisone, sodium, potassium, calcium and phosphate should be evaluated to detect endocrine myopathy. In addition, endocrine studies on diabetes mellitus, hypogonadism and hypothyroidism should be performed to investigate multisystem involvement.

In recent years, many myositis-specific antibodies have been identified, and these antibodies should be tested in suspected cases of myositis. These antibodies are also relevant for the further management of patients, as organ manifestation, tumour manifestation and treatment response are associated with specific autoantibodies.

If a metabolic myopathy is suspected, the respective enzyme activity can be analysed by specialized laboratories from blood samples. For some conditions, tests from dry blood spot tests are available, e.g. in Pompe's disease. In suspected fatty acid oxidation disorders, a serum carnitine/acylcarnitine profile can be performed.

Exercise testing

By using the forearm ischaemic lactate test, glycogenosis on the one hand and myoadenylate deficiency on the other hand can be functionally examined. McArdle disease patients show typically a failure in exercise-associated lactate production, whereas in myoadenylate deficiency, ammonia fails to be upregulated. In order to detect a defect in the mitochondrial respiratory chain, an ergometer test is performed, which typically shows a pathologically elevated lactate value.

Neurophysiology

In every patient with suspected myopathy, an EMG examination should be performed, e.g. to distinguish a neuropathy from myopathy. Attention should be paid to possible myotonic discharges, which would suggest a myotonia or a myotonic myopathy. Depending on the suspected diagnosis, several muscles of different extremities should be examined, particularly sampling proximal and distal muscles. In myositis, abnormal spontaneous activity in the form of fibrillations is often seen, and the amount can be used as an indicator of ongoing disease activity [6]. It is essential to avoid muscle biopsy from a muscle that has undergone recent needle electromyography, as the EMG examination leads to muscle fibre destruction with a cellular repair reaction, which could lead to a misinterpretation as myopathy. Nerve conduction studies (NCS) should be performed to exclude or identify a neuropathy; which is clinically relevant because neuropathies can cause myalgia and may present with a pure motor defect – without sensory impairment – and even a proximal predominance. It is recommended to test at least one motor and sensory nerve in the upper and lower limbs. Particularly in the case of exercise-dependent weakness, repetitive nerve stimulation should be performed to detect a neuromuscular transmission disorder.

Imaging

In recent years, imaging techniques have been used in routine diagnostics for myopathies. MRI is particularly important for initial diagnostics and for the follow-up assessment of myopathies and myositis.

Magnetic resonance imaging (MRI)

The fat-suppressed short tau inversion recovery (STIR) sequence can be used to visualize myoedemia even in clinically asymptomatic muscles [49]. Myodemia is a typical finding in myositis [26] and relates to acute muscle fibre damage. However, muscle oedema is non-specific and can also be caused by intensive muscle exertion, infection, muscle injury, and radiation therapy [27]. In the case of chronic muscle diseases, T1-weighted imaging is best to show fatty replacement, fibrosis, atrophy and calcifications. In addition, a contrast agent can be administered, which provides further information on myositis. MRI is also helpful in determining a suitable biopsy site. In addition, the distribution pattern

visible on a whole-body muscle MRI can indicate the underlying type of myopathy, e.g. limb girdle muscle dystrophy.

Ultrasound

Muscle atrophy or hypertrophy can be recognized by ultrasound. The echogenicity can be increased by fibrous muscle replacement and decreased by oedema. However, sensitivity and specificity are poor compared to MRI studies, e.g sensitivity for ultrasound in myositis ranges from 2% to 82% [33].

Cardiac and pulmonary diagnostics

Many myopathies are accompanied by cardiac involvement. Therefore, an ECG, a holter-ECG, and an echocardiography should be performed in all cases, unless the heart is spared in these diseases. In the case of myopathies with known cardiomyopathy risk, these tests should be carried out on a regular basis, e.g. once per year. Cardiac MRI can be considered as a sensitive method if there is a well-founded suspicion of cardiac involvement.

The vital capacity should be determined to assess affection of respiratory muscle weakness. If myositis is confirmed and there is a question of lung involvement within the framework of multiorgan involvement, a chest X-ray or even CT of the chest should be performed.

Muscle biopsy

A muscle biopsy in myalgia is only indicated if there is suspicion for an underlying myopathy, particularly myositis, and unless one of the unique hereditary conditions is suspected that can be tested genetically. However, there are some hereditary myopathies that can be diagnosed primarily by molecular genetics due to their typical phenotype. A moderately affected muscle should be selected as the biopsy site, ideally chosen by imaging techniques such as MRI or ultrasound. It is recommended that the sample is further processed in a laboratory experienced for muscular pathology. In a retrospective cohort of 240 myalgia patients, Filosto et al. found that only 2% of myalgia patients with normal CK levels had a myopathy. However, if the CK is 7-fold elevated, metabolic myopathy was likely [16]. Inflammatory cells can be classified immunohistologically, and a variety of muscle proteins can be stained if muscular dystrophy is suspected. Electron microscopic examinations also provide further information, e.g. by detecting mitochondrial deformities. Furthermore, a muscle biopsy enables tissue-specific quantitative enzyme activity testing in cases of suspected glycogenosis or mitochondrial myopathies.

Genetic analysis

In some hereditary myopathies, a diagnosis can be hypothesized based on the characteristic phenotype and a positive family history. The diagnosis can be confirmed directly by molecular genetic testing. This applies e.g. to classical forms of myotonic dystrophy type 1 and 2, as well as FSHD. Primary molecular genetic diagnostics is also reasonable for suspected muscle diseases based on ion channel defects. The new high-throughput molecular genetic method of next generation sequencing has enabled an efficient investigation of many genes in one approach. In certain patients, particularly if the phenotype is less typical, this method is often more economical than repeated single sequencing.

Therapy of myalgia

Myalgia is a common symptom in neuromuscular disorders. In terms of treatment perspective, a causal therapy should always be initiated first, if available, followed by a symptomatic treatment. This goal can only be achieved for a small number of neuromuscular diseases, most of which are acquired. Typical examples are toxic myopathies, triggered e.g. by alcohol or statins, where the causative agent can be avoided. Endocrine myopathies such as in hypothyroidism can be treated by correction of the hormone level. Treatment of fibromyalgia is beyond the scope of this review and has been summarized by other researchers very recently [1,4,28,35]. In some hereditary neuromuscular diseases such as

myotonias, causative treatments are available, which will be discussed below. The main focus of the treatment section is on myositis with the exception of IBM.

The symptomatic treatment of myalgia includes classical pain medication (paracetamol, NSAIDs) and muscle relaxants. Centrally effective muscle relaxants like benzodiazepine and baclofen are mostly used for spasms and muscle tenseness. Because of the side effects like fatigue and the risk of addiction, muscle relaxants should not be used regularly. Antidepressant therapy is also very effective in many patients. In addition, heat or cold treatment can be tried to reduce muscle pain. Physiotherapy is recommended for all patients without acute disease phase or rhabdomyolysis.

Treatment of myositis: DM, PM, NM and OM

The goal of therapy is to improve muscle strength, reduce muscle pain and ameliorate extramuscular manifestations. Normally, muscle strength is regained and CK values decrease upon treatment. Nevertheless, a sole chase for CK values should be avoided because there is not a direct association between treatment response and CK values.

Agents used in the treatment of myositis

1. *Glucocorticosteroids (GS)* usually provide a basis for the treatment, particularly in the beginning. They exert a broad effect on the immune system. Controlled trials have not been performed, but expert consensus exists about the beneficial effect of GS. Prednisolone is usually given orally at a dose of 0.5–1 mg per kg daily. Initially, a high-dose pulse therapy at 250–1000 mg per day for 3–5 days may be performed. Upon clinical improvement, usually after 4–12 weeks, prednisolone is slowly tapered every 1–2 weeks by 5–10 mg down to 20 mg per day [39]. The tapering can be done faster if required due to side effects, but it poses a risk of relapse. A maintenance dose of 2.5–7.5 mg per day is often required. To reduce or prevent side effects, calcium and vitamin D should be administered in order to prevent osteoporosis as side effect.
2. In parallel to GS, a steroid sparing immunosuppression should be started with the exception of a mild myositis or a contraindication to these drugs. The occurrence of an immunosuppressive effect is expected with a delay of several months, e.g. 4–6 months for azathioprine. The following drugs are commonly used although a Cochrane analysis of all existing studies did not demonstrate a significant effect [17]: azathioprine (AZA), mycophenolate mofetil (MMF), and methotrexate (MTX).

Before starting a therapy with AZA, a laboratory test for thiopurine methyl transferase levels (TPMT) can be helpful to identify patients with an impaired metabolism who are at risk to develop dangerous leukopenia. Potential toxic effects on the liver, pancreas and kidney should be monitored in routine laboratory work up. AZA therapy is initiated at 25–50 mg/day. In the absence of relevant side effects, the dose is gradually increased by 25–50 mg per week to a dose of 2–3 mg/kg bodyweight. An absolute lymphocyte count should be between 600 and 1000/μl. After a long-term use of AZA, the risk for malignancies increases, particularly of the skin and adequate sun protection is essential. The concomitant use of allopurinol should be avoided due to the risk of added myelotoxicity.

Mycophenolate mofetil (MMF) is well tolerated. MMF is metabolized to mycophenol acid within the body and inhibits selectively and reversibly the enzyme ionosinmonophosphate dehydrogenase, thus diminishing the proliferation of B and T cells. The effects of MMF are not immediate and comparable to other immunosuppressants. The efficacy of MMF in myositis patients was studied in case series with a limited number of patients [34,38] and a small open-label study in combination with intravenous immunoglobulins [15]. The typical MMF dose ranges between 1000 mg and 3000 mg, usually starting at 500 mg twice daily under weekly routine laboratory controls. The main side effects are myelosuppression, gastrointestinal symptoms (diarrhoea, vomiting, nausea, abdominal pain), oedema, hyperglycaemia and – hypercholesterinaemia. During pregnancy, treatment with MMF is not recommended.

Methotrexate (MTX) is a folate inhibitor that has been widely used in rheumatoid arthritis and other neuromuscular autoimmune disease such as myasthenia gravis. MTX can be administered orally or s.c.

once per week. After a starting dose of 7.5 mg per week for the first 3 weeks, the dose can be gradually increased by 2.5 mg/week up to 20–25 mg per week. One day after MTX intake, a supplementation of 10 mg folic acid is required. Pulmonary toxicity represents a potential side effect. Other side effects include gastrointestinal symptoms and myelosuppression. If a stomatitis occurs, the dosage should be reduced.

As alternative immunosuppressant, *cyclosporine A* (CSA) is available. CSA is a calcineurin inhibitor and exerts its main effects by inhibition of T cell activation and reduction of the activity of genes coding for IL-2 and interferon-gamma. According to the spectrum of side effects (e.g. CNS toxicity, hypertension, nephrotoxicity, anaemia, gum hyperplasia), many potential drug interactions via the P450 pathway and high monitoring effort, CSA is less commonly used. The recommended initial dose is 4–6 mg/kg body weight, divided into two doses per day. The maintenance dose is usually 3–4 mg/kg and adapted according to plasma levels.

In case of contraindications for standard immunosuppressants, severe side effects or insufficient treatment response, *intravenous immunoglobulins* (IVIg) have been shown to be an effective add-on or alternative treatment. IVIg has a plethora of hypothesized mechanisms of action including inhibition of complement deposition, modulation of chemo- and cytokines, interference with Fc receptor binding on target cells, competition with autoantibodies and interference with antigen recognition [14]. The effectiveness of IVIg in IIM has been shown in case series and clinical studies [2]. IVIg are given at a dose of 1–2 g/kg, typically distributed over 2–3 days and repeated every 3–6 weeks. The infusion interval of 3–6 weeks is in line with the half-life of IVIgs of 28–32 days. IVIg are generally well tolerated and most side effects are mild such as headache or fever. Skin reactions including urticaria and severe reactions like thrombosis, aseptic meningitis or haemolysis are rare.

For an escalating treatment or in case of organ involvement, in particular the lung, *cyclophosphamide* (CYC) or B-cell depletion by the monoclonal antibody *rituximab* (RTX) are available. CYC is typically applied as monthly dose of i.v. 0,5- 1 mg/m^2. Regular white blood cell monitoring is obligatory. A urine analysis should be performed frequently. Adverse events include haemorrhagic cystitis, nausea and vomiting, bone marrow suppression. Contraception is recommended for both sexes. The side effects on the kidneys and the urinary tract can be reduced by high liquid intake and pre-treatment with mercaptoethane.

RTX has been demonstrated to be effective in a recent clinical trial in myositis [30], although the primary endpoint was not reached. The rational for RTX is the reduction of B cells, the precursors of antibody-producing plasma cells. The standard dosing consists of two injections of 1000 mg at a 14 d interval, followed by 1 g every 6 months. The treatment is usually well tolerated, but caution should be exercised regarding allergic reactions, opportunistic infections and cardiac and renal complications [22].

Therapy of muscle dystrophies

A specific treatment for distinct muscle dystrophies is in development such as for Duchenne muscular dystrophy addressing the restoration of the dystrophin protein. But years might pass until a sufficient dystrophin replacement can be achieved and other dystrophies might be cured [12]. At present, supportive treatments and physical therapy remain the key elements to prevent contractures and to maintain muscle strength. In some muscular dystrophies, steroids or immunosuppressive drugs have been shown to partially maintain muscle mass and function and to reduce myalgia [8,12].

Therapy of myotonias and myotonic dystrophies

No disease-modifying treatment is available for myotonias and myotonic dystrophies, but a strong recommendation exists for the use of mexiletine as symptomatic treatment for myotonia [25]. For the treatment of adult patients with non-dystrophic myotonia, mexiletine has received licensing by EMA in 2018. The dose ranges between 150 and 200 mg three times per day and is well tolerated, but it should be started under the control of ECG. In addition, topiramate could serve as an alternative, especially for the myotonic dystrophies, in which mexiletine has not been approved. The use of opioids is usually not

recommended because of the non-targeted approach, tolerance and multiple side effects. Patients that complain of muscle cramps can be treated e.g. with pregabalin, gabapentin or carbamazepine.

Therapy of metabolic myopathies

For some of these genetic diseases, causative approaches exist with different levels of success, but cure for none of them has been developed so far. In general, lifestyle adaptation and carefully titrated exercise can be used to reduce exercise-induced symptoms [46].

Treatment goals for *glycogen storage disorders* are to avoid hypoglycaemia, hyperlactatemia, hyperuricaemia, and hyperlipidaemia [44]. Glycogen storage disease type (GSD2; Pompe disease; acid maltase deficiency) results from impaired lysosomal acid-α-glucosidase (GAA) function and accumulation of lysosomal glycogen in skeletal, respiratory and cardiac muscles [24]. For GSD2, an enzyme replacement therapy, using human recombinant acid α-glucosidase, is available and approved in the US and Europe since 2006 [21].

Treatment of glycogen storage disease type 5 (GSD5) is based on measured physical training in order to develop mitochondrial oxidation capacities in muscles. In addition, a controlled glucose intake or carbohydrate-rich diet according to exercising periods is recommended. Diets with high protein intake have yielded variable results [36]. Attention should be paid to other glycogen storage diseases because a high carbohydrate intake can exacerbate symptoms e.g. in glycolytic defects such as phosphofructokinase [46].

Fatty acid oxidation (FAO): In patients with impaired FAO, there is a lack of increase of oxidation during exercise. This includes very long-chain acyl-CoA dehydrogenase (VLCAD) and carnitine palmitoyl dehydrogenase II (CPT II) deficiencies. In smaller studies of CPT II patients, a carbohydrate diet and a high-glucose infusion significantly improved exercise capacity [31].

Treatment for mitochondrial disorders

Several approaches have been studied in mitochondrial disorders: coenzyme Q10, creatine monohydrate or a combination of both showed a significant improvement in biochemical markers but no consistent improvement in clinical parameters. Therefore, the efficacy in mitochondrial disorders is uncertain [32]. Exercise therapy has been demonstrated to be beneficial for mitochondrial diseases [18]. Alternative treatments are in progress from bench to bedside and address cell replacement, supplementation of deoxynucleosides and deoxynucleotides, scavenging of specific toxic compounds, gene therapy or mtDNA stabilisation [18].

The risk for developing a *malignant hypothermia* (MH) differs between inherited myopathies and should be evaluated individually. Every patient at risk should receive an emergency pass including advice for the risk of MH and other complications during anaesthesia.

Summary

Myalgia is a common symptom in neuromuscular diseases. Myalgia occurs for example in myositis, myotonia and hereditary myopathies. Other side symptoms and the type of pain may guide towards the correct diagnosis. Basic diagnostic workup includes a detailed medical history, full neurologic assessment, laboratory tests, nerve conduction studies and EMG. Muscle biopsy, muscle imaging as well as genetic testing may be required to make a diagnosis. The therapeutic goal is to cure and remove the cause of myalgia. Symptomatic treatment with mexiletine or carbamazepine can alleviate myotonia; myositis is treated with immunosuppressants; pregabalin or amitriptyline can be given for conditions with myalgic pain.

Conflicts of interest

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Practice point

- Myalgia during physical rest or exercise can be caused by a neuromuscular disease
- A detailed medical history, neurologic assessment, laboratory tests (CK, AST, ALT, LDH, TSH, cortisone, sodium, potassium), nerve conduction studies and an EMG should be performed to find the correct diagnosis
- Myalgia, muscle weakness, and high CK-levels can lead to the suspicion of myositis
- Myalgia also occurs in myotonia and can be treated with mexiletine, carbamazepine or phenytoin
- Symptomatic treatment and treatment of the disease can improve the quality of life

Research agenda

- More research is needed to find further causal or symptomatic treatment options
- Neuromuscular diseases need more attention and should be sent to a neuromuscular centre for treatment.

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