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EFNS REVIEW/CME ARTICLE

EFNS review on the role of muscle biopsy in the investigation of myalgia

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Background: Myalgia, defined as any pain perceived in muscle, is very common in the general population and a frequent cause for referral to neurologists, rheumatologists and internists in general. It is however only rarely due to primary muscle disease and often referred from ligaments, joints, bones, the peripheral and central nervous system. A muscle biopsy should only be performed if this is likely to be diagnostically useful. At present no 'guidelines' exist.

Methods: An EFNS panel of muscle specialists was set to review relevant studies from PubMed dating as far back as 1/1/1990. Only Class IV studies were available and therefore the recommendations arrived at are 'best practice recommendations' based on information harvested from the literature search and expert opinion.

Results: Muscle cramps should be recognized while drugs, infections, metabolic/endocrinological and rheumatological causes of myalgia should be identified from the history and examination and pertinent laboratory tests. A muscle biopsy is more likely to be diagnostically useful if myalgia is exertional and if one or more of the following apply: i) there is myoglobinuria, (ii) there is a second wind phenomenon, (iii) there is muscle weakness, (iv) there is muscle hypertrophy /atrophy, (v) there is hyperCKemia (>2–3× normal), and (vi) there is a myopathic EMG.

Conclusions: Patients presenting with myalgia can be recommended to have a biopsy based on careful history and examination and on simple laboratory screening.

Objective

To provide guidelines on the role of muscle biopsy in the elucidation of the cause of myalgia. The guidelines cover both adult and pediatric populations.

Myalgia is a common symptom but is only rarely due to underlying primary muscle disease. Rather, the pain is frequently referred from elsewhere, including non-muscular tissues such as ligaments, tendons, joints and bones or the peripheral and even the central nervous system [1–3]. Less commonly, it is due to a primary problem within the muscle itself and its associated connective tissue and blood vessels [1].

Population-based studies estimate the incidence of diffuse persistent muscle pain to be about 10% [4]. Elucidating the cause of myalgia, particularly in the absence of other associated features, can be a difficult task, but an invasive and expensive procedure such as a muscle biopsy, be it with a low morbidity, should be performed only if it is likely to be diagnostically useful [5,6].

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Definitions

Myalgia may be defined as any pain perceived to be in muscle.

Muscle cramps are one cause of myalgia and consist of sudden onset, transient, involuntary, painful and vigorous muscle contraction. Cramps may occur spontaneously at rest or more often during or after exercise, and usually last from seconds to a few minutes. Such 'true' cramps are neurogenic in origin and are associated with high frequency motor unit discharges [7,8].

The word contracture is used in two unrelated senses. Transient, electrically silent contractures, which are painful and clinically resemble cramps, are characteristically present in metabolic myopathies and are evoked by exercise. Persistent contractures, which may be focal or more usually involve the whole muscle, causing shortening of the muscle and thus limitation of passive joint movements, are a common late feature of many myopathies, such as dystrophies. They are an early feature in Emery–Dreifuss syndrome. Such contractures are usually painless.

Search strategy

The Task Force members met on 12 September 2011 and decided on a literature search policy. This included a search for any existing guidelines and articles dealing with the indications for muscle biopsy in patients with myalgia. It was decided that the literature search should go as far back as 1 January 1990 and Medline was chosen as the sole database to be searched. It was felt that clinically important studies were unlikely to be left out with this arbitrary decision and furthermore the Task Force did not expect to identify any class I–III studies in the literature. The lack of robust prior studies may paradoxically make these guidelines particularly useful, pending evidence-based knowledge.

It was decided to identify and succinctly summarize commonly reported, non-neuromuscular causes of myalgia, including rheumatological diseases, commonly used drugs and general medical conditions. The main emphasis of the search, however, was to identify primary myopathies presenting with or associated with myalgia. Special attention was paid to studies in which clinical features (e.g. the relation of myalgia to exercise or weakness) or investigations [e.g. hyperCKemia, electromyography (EMG)] were detailed, in order to be able to identify patients in whom a biopsy could be recommended. The Cochrane Library and the American Academy of Neurology were accessed on 17 March 2011 and again on 3 September 2012 and no relevant guidelines were found. The only available guidelines identified were those of the German Neurological Society on the 'Clinical pathway for the investigation of myalgias' [9].

The Medline database was accessed between 12 February 2012 and 16 July 2012 with the following key terms: myalgia, and one of myopathy, biopsy, weakness, exercise, drugs, dystrophy, EMG and hyperCKemia; muscle and pain, and one of weakness, biopsy, exercise, drugs, dystrophy, EMG, myopathy and hyperCKemia; myalgia and exercise, and one of myopathy, biopsy, weakness, drugs, dystrophy and EMG. More than 27 000 reports were identified but there was much redundancy within individual searches and between searches. Abstracts were reviewed and relevant articles were identified. To evaluate articles, the critical review of EFNS guidelines was followed [10]. A hand search was also performed by members of the Task Force. As predicted, only class IV studies were identified and therefore this review is a best practice guideline based on the review of the literature and the Task Force's expert opinion. A first draft was prepared and circulated on 3 September 2012. The draft was reviewed at a meeting on 10 September 2012 and recirculated to members until final consensus was reached.

Myalgia and exercise

Myalgia can occur at rest, during or after exercise. It can be focal or generalized. The circumstances in which myalgia develops provide helpful clues to the etiology. Myalgia at rest, especially in the absence of weakness, is rarely due to a primary myopathy.

There are three major patterns of myalgia in relation to exercise [11]:

1. Pain experienced during (exertional) or immediately following (post-exertional) exercise. Myalgia associated with primary myopathies is commonly exertional (see below). Myalgia associated with primary metabolic myopathies may be associated with transient contractures.
2. Delayed muscle pain (delayed post-exertional) usually occurs 24–48 h after strenuous or eccentric exercise. Soreness is usually accompanied by loss of strength and elevated levels of serum creatine kinase (sCK) activity. It commonly occurs in unfit individuals undertaking unaccustomed exercise and is not a hallmark of primary muscle disease. It is thought to be due to microtrauma and local inflammation.
3. Muscle cramps *per se* are of heterogeneous origin (Table 1) and may be associated with specific neurogenic disorders (Table 2).

Table 1 Common causes of muscle cramps

Idiopathic
Familial
Pregnancy
Endocrine
Electrolyte disturbances (e.g. dehydration)
Neurogenic disorders
Medications
Metabolic

References 7, 8, 12.

Table 2 Neurogenic diseases associated with muscle cramps

Motor neuron disease
Cramp-fasciculation syndrome
Neuralgic amyotrophy
Radiculopathy
Peripheral neuropathy
Isaac's syndrome
Post-polio syndrome
Kennedy disease
Satoyoshi syndrome
Myokymia–hyperhydrosis syndrome
Stiff person syndrome

References 7, 8, 12–14.

Metabolic and endocrine causes of myalgia

There are several metabolic and endocrine causes of myalgia (often associated with muscle cramps). These types of myalgia are usually not related to exercise. In these cases the medical history together with the pertinent blood analyses usually allow the correct diagnosis to be made (Table 3).

Infectious causes of myalgia

Infections, either systemic or localized, are a frequent and well recognized cause of myalgia. The history and examination of the patient including fever, localized tenderness and raised inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein are often helpful for the diagnosis (Table 4).

Table 3 Metabolic and endocrine causes of myalgia

Hypothyroidism
Osteomalacia
Uraemia
Hemodialysis
Hypoparathyroidism
Liver failure
Magnesium deficiency
Hypoadrenalism
Selenium deficiency
Thiamine deficiency

References 12, 13, 15–17.

Table 4 Infections commonly associated with myalgia

Influenza viruses	Trichinosis
CMV	Toxoplasmosis
HIV	Cysticercosis
Coxsackie B virus	Pyomyositis
Epstein–Barr virus	

References 18–20.

Drugs frequently associated with myalgia

There are numerous drugs that, at therapeutic doses, may cause myalgia either alone or in association with other myopathic symptoms such as weakness, sCK elevation or myoglobinuria [21]. The most commonly implicated drugs are the statins. A temporal relationship between the onset of myalgia and the initiation of the drug often enables the physician to make the correct association. It is particularly important to be aware of drug interactions (e.g. statins and ciclosporin) (Table 5).

Rheumatological causes of myalgia

Fibromyalgia is one of the most prevalent causes of diffuse muscle pain in the general population with a prevalence reaching 1% [3]. The pain occurs both at rest and on exercise and is typically characterized by trigger points and associated with fatigue, poor sleep and sometimes cognitive symptoms. There is no weakness and sCK is normal. Polymyalgia rheumatica usually has an onset in individuals over the age of 60 years and typically presents with early morning stiffness and myalgia, eased by exercise. The ESR is almost invariably elevated. Other rheumatological diseases associated with myalgia, such as rheumatoid arthritis, present with additional distinct clinical features and antibody profiles and in these conditions myalgia is rarely an isolated symptom.

Most rheumatological causes of myalgia in adults can also occur in children except for polymyalgia rheumatica. Benign nocturnal pains of childhood usu-

Table 5 Drugs and substances commonly associated with myalgia

Statins, fibrates	Labetalol
Ciclosporin	L-tryptophan
Zidovudine	Captopril, enalapril
Retinoids	Cytotoxics
Colchine	Suxamethonium
D-penicillamine, gold	Lithium
Interferon-α	Salbutamol
Anti-malarial drugs	Cimetidine
Tumor necrosis factor α inhibitors	Alcohol
	Cocaine

References 21–24.

Table 6 Rheumatological causes of myalgia

Polymyalgia rheumatica[a]
Fibromyalgia
Myofascial pain
Systemic lupus erythematosus
Mixed connective tissue disease
Sjögren syndrome
Inflammatory arthritides (e.g. rheumatoid)
Idiopathic musculoskeletal syndromes
Benign hypermobility syndrome
Benign nocturnal pains of childhood (growing pains)[b]

References 3, 25–30; [a]exclusive to adults; [b]exclusive to children.

ally involve the lower limbs, deep in the thigh, shin and calf or behind the knee. The pains often occur late in the evening or may wake the child from sleep.

Caution is needed to exclude infection or malignancy before labeling pain as 'benign' or 'idiopathic' in children (Table 6).

Metabolic myopathies commonly associated with myalgia

Metabolic myopathies which encompass the disorders of muscle carbohydrate and fat metabolism [and of which myophosphorylase deficiency, carnitine palmitoyl transferase II (CPT II) deficiency and very long chain coenzyme A (CoA) dehydrogenase deficiency are by far the most common] typically present with exercise-induced myalgia (exertional myalgia) and often with transient contractures (electrically silent contractures). Less commonly mitochondrial cytopathies can present with isolated myopathy accompanied by exertional myalgia.

The timing of onset of symptoms in relation to exercise provides a clue as to the nature of the underlying problem and guides further investigation. Aerobic glycolysis is the main source of energy at rest and during sustained moderate exercise. In early exercise, particularly during high-intensity exercise such as weight lifting or sprinting, and before adaptive changes such as increased respiration and blood flow, muscle energy demands are met primarily by anaerobic glycolysis. Thus, in muscle glycogenolytic disorders myalgia develops early during exercise. In most cases the onset of symptoms starts in childhood although their significance is often missed. sCK varies greatly, depending on prior physical activity level, and is typically constantly elevated in patients with complete enzymatic blocks (McArdle disease and phosphofructokinase deficiency). In these two conditions, fixed weakness may develop later in life. Recurrent myoglobinuria is common in all these disorders. A history of a 'second wind' phenomenon is suggestive of McArdle disease.

Table 7 Metabolic myopathies commonly associated with myalgia

Phosphorylase deficiency
Phosphofructokinase deficiency
Phosphoglycerate kinase deficiency
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
Acid maltase deficiency (GSDII)
Phosphorylase *b*-kinase deficiency
Phosphoglucomutase deficiency
Muscle glycogen storage disease O
Primary carnitine deficiency
CPT II deficiency
Very long chain acyl CoA dehydrogenase deficiency
Multiple acyl CoA dehydrogenase deficiency
Mitochondrial trifunctional protein deficiency
Mitochondrial myopathies

References 31–35.

Fatty acids are the major substrate at rest and in prolonged low-intensity exercise such as during a marathon. Myalgia in fatty acid oxidation defects occurs later in exercise than in glycolytic disorders. Recurrent myoglobinuria following prolonged aerobic exercise is common in these disorders, especially if preceded by fasting. Between attacks sCK is usually normal.

Although myoadenylate deaminase deficiency is often considered a cause of metabolic myopathy the Task Force does not consider this to be a well proven disease entity (Table 7).

Myopathies occasionally associated with myalgia

There are numerous primary myopathies in which myalgia is reported with variable frequency. The list in Table 8 is a comprehensive (but probably not exhaustive) list compiled from searching the literature. Most reports are isolated cases or small series. The myopathologist may consult the list to appreciate the spectrum of histopathological abnormalities seen in myopathies associated with myalgia. For the clinician the list serves as a guide in the search for supplementary subtle features in the phenotype of the patient and his/her family history.

With the exceptions of limb-girdle muscular dystrophy 2I (LGMD 2I), LGMD 2L and myotonic dystrophy 2, where exertional myalgia is a well recognized presentation, the rest of the myopathies do not commonly exhibit myalgia. In Becker muscular dystrophy myalgia and cramps are common mainly in young patients. Most of the myopathies are rarely seen outside tertiary neuromuscular centers. In almost all the reports myalgia was exertional and this feature should always be specifically asked for. In addition to exertional myalgia, there was always one or more of the following features: weakness, significant hyperCKemia

(3–5× normal), myotonia, rippling muscle disease, atrophy/hypertrophy or a history of myoglobinuria. None of the reported cases had both a normal examination and a normal sCK. EMG was commonly performed but was not particularly informative.

Thus, from considering these reports, the likelihood of finding a specific primary myopathy is greatly increased if the myalgia occurs predominantly on exertion (exertional myalgia), in the presence of significant hyperCKemia (3–5× normal) or in the presence of other 'core' neuromuscular features (Table 8).

Inflammatory/infiltrative myopathies associated with myalgia

There are several inflammatory myopathies besides the idiopathic inflammatory myopathies (polymyositis, dermatomyositis and inclusion body myositis) that have been reported to be associated with myalgia. Despite popular misconception myalgia is rarely prominent in the idiopathic inflammatory myopathies. It is only exceptionally present in inclusion body myositis but is more common in dermatomyositis, often with an exertional component, which is a vasculopathy.

Myalgia in these inflammatory/infiltrative myopathies may be generalized although focal muscle pain and tenderness is not uncommon. It occurs at rest and can be exacerbated by movement or exercise, but typical exertional myalgia is rare. The general medical history of the patient and associated features are helpful clues to a local inflammatory/infiltrative process and are unlikely to be confused with primary non-inflammatory myopathies. Magnetic resonance imaging may be usefully employed to show local or more generalized hyperintensity in muscle on T2 weighted and short TI inversion recovery (STIR) images, indicating edema, and it may serve to guide location for biopsy [65] (Table 9).

Patients with isolated myalgia

One recent study examined the diagnostic contribution of hyperCKemia, EMG and muscle biopsy in a cohort of 240 patients with isolated myalgia (without weakness) in whom other causes of myalgia such as rheumatological, infectious, metabolic and endocrine

Table 8 Myopathies occasionally associated with myalgia

	References
LGMD 2I[a]	[36,37]
Becker muscular dystrophy[a]	[38]
Dystrophinopathy carriers	[39]
Facioscapulohumeral muscular dystrophy	[40]
Caveolin-3 deficiency[a]	[41]
LGMD 2L[a]	[42]
Sarcoglycanopathies	[43]
Myotonic dystrophy type 2	[44]
Myotonia congenita[a]	[45]
Oculopharyngeal muscular dystrophy	[46]
Acid maltase deficiency[a] (GSDII)	[47]
Miyoshi myopathy/LGMD 2B	[48]
Laminopathy (LMNA)	[49]
Myosin heavy chain 2 myopathy	[50]
Immune mediated rippling muscle disease	[51]
LPIN1 myopathy[a]	[52]
Neuromyopathy with internalized capillaries	[53]
Tubular aggregate myopathy[a]	[54]
Myopathy with hexagonally cross-linked tubular arrays[a]	[55]
Congenital fiber type disproportion and minicore myopathy	[56]
Nemaline myopathy	[57]
Central nuclei myopathy[a]	[58]
Central core myopathy[a]	[58]
Myopathy with lobulated type I fibers[a]	[58]
Hyaline body myopathy	[59]
Cylindrical spiral myopathy	[60]
Desminopathy[a]	[61]
Familial myopathy with conspicuous depletion of mitochondria	[62]
Lambert–Brody disease	[63]
Channelopathies with myositis	[64]

[a]Weakness may be absent.

Table 9 Inflammatory/infiltrative myopathies associated with myalgia

	References
Macrophagic myofasciitis	[66]
Eosinophilia myalgia syndrome	[67]
Churg–Strauss syndrome	[68]
Polyarteritis nodosa	[69]
Whipple's disease	[70]
Sarcoidosis	[71]
Eosinophilic perimyositis	[72]
Panniculitis	[73]
Inclusion body myositis	[74]
Behcet's disease	[75]
Dermatomyositis	[76]
Polymyositis	[77]
Focal myositis	[78]
Non-necrotizing autoimmune myopathy with pipestem type capillaries	[79]
Myopathy with antibodies to the signal recognition particle	[80]
Granulomatous myositis	[81]
Primary Sjögren's syndrome	[82]
Idiopathic systemic capillary leak syndrome (Clarkson's disease)	[83]
Familial Mediterranean fever	[84]
Muscle infarction	[85]
Skeletal muscle metastases	[86]
Multiple myeloma/amyloid	[87,88]

Table 10 Laboratory investigations that may be performed prior to biopsy

Resting lactate (respiratory chain defect)
Non-ischaemic forearm exercise test (glycolytic enzyme defects)
Dry blood spot or acid maltase in leukocytes for GSDII
Fasting acyl carnitine blood spot profile (fatty acid oxidation defects)
Magnetic resonance imaging (local and diffuse inflammatory myopathies)
CPT II in leukocytes and cultured fibroblasts (CPT II deficiency)
Genetic screening for common mutations of suspected myopathy

Table 11 Possible muscle biopsy investigations

Histology and histochemistry
Haematoxylin and eosin, modified Gomori trichrome, Oil red O, periodic acid–Schiff, adenosine triphosphatase, combined succinate dehydrogenase–cytochrome *c* oxidase, NADH dehydrogenase, myophosphorylase, phosphofructokinase, acid phosphatase, Congo red
Immunohistochemistry
Dystrophin, α-, β-, γ- and δ-sarcoglycans, dysferlin, caveolin-3, MHC-1, α-dystroglycan
Western blot (if indicated)
Dystrophin, calpain-3, dysferlin, α-sarcogygan
Mitochondrial enzyme activity
CPT II activity
Glycolytic enzyme activities

disorders, fibromyalgia, radiculopathy, plexopathy, drugs associated with myalgia, alcohol abuse, electrolyte disturbance and hypereosinophilia were ruled out [58]. In 92 patients (38%) myalgia was exercise induced (exertional myalgia), in 111 patients (46%) myalgia was present both at rest and on exercise whilst in 37 patients (16%) myalgia was only present at rest.

One hundred and sixteen patients (48.3%) had a non-specific myopathy on muscle biopsy. A specific 'structural' myopathy was diagnosed in eight patients (6.5%), including tubular aggregate myopathy in three, central core disease in two, centronuclear myopathy in one and myopathy with lobulated type I fibers in two.

A glycolytic enzyme defect was diagnosed in six patients (2.4%) and in a further 47 patients (20%) mitochondrial abnormalities were present in the biopsy, out of which eight (3.3%) also exhibited abnormal mitochondrial enzyme activity indicating a primary mitochondrial myopathy. Thus out of 240 patients with isolated myalgia of 'unknown origin' a specific myopathy was diagnosed in only 22 (12.2%).

Predictive value of various types of myalgia

In the whole group the positive predictive value (likelihood of an abnormal biopsy) of exertional myalgia was 72% but biopsy findings were non-specific in the majority. The negative predictive value for exertional myalgia (likelihood that lack of exertional myalgia predicted a normal biopsy) was only 14%.

The positive predictive values of exertional myalgia, resting myalgia and myalgia present at rest and on exercise for a glycolytic enzyme defect were 6.5%, 0% and 0% respectively.

The negative predictive value of exertional myalgia for a glycolytic enzyme defect (likelihood that there is no glycolytic enzyme defect if there is no exertional myalgia) is 100%. The negative predictive value of exertional myalgia for a mitochondrial myopathy is 76%–95%.

The positive predictive value of any form of myalgia for a primary mitochondrial myopathy was only 2%–4%. Unfortunately, the relationship of myalgia to exercise could not be ascertained in the eight patients with a specific structural myopathy.

Predictive value of hyperCKemia

Serum creatine kinase was elevated in nearly half of the cohort. Only in the six patients with glycolytic enzyme defects was the sCK 7–10 times the upper limit of normal and thus the positive predictive value of these levels of hyperCKemia is extremely high.

Overall, the positive predictive value of an elevated sCK (likelihood of an abnormal biopsy) was 86% whilst the negative predictive value of a normal CK (likelihood that a normal CK will predict a normal biopsy) was only 28%.

Predictive value of electromyography

Nerve conduction studies and EMG were performed in 190 patients. The positive predictive value of an abnormal EMG (likelihood for an abnormal biopsy) was 82%. The negative predictive value of a normal EMG (likelihood of a normal EMG to predict a normal biopsy) was only 19%. The above predictive values apply to patients with isolated myalgia in whom other causes (see above) have been excluded.

Thus, it appears that exertional myalgia has good negative predictive value (76%–100%) for glycolytic enzyme defects and mitochondrial myopathies. Exertional myalgia, hyperCKemia and an abnormal EMG each have a high positive predictive value for an abnormal biopsy in patients with isolated myalgia of unknown origin but in the vast majority the result will be a non-specific myopathy. Only significant hyperCKemia (7–10× normal) in isolated exertional myalgia is highly predictive for a glycolytic enzyme defect.

Recommendations

The recommendations are based on class IV studies and expert opinion. The guidelines outline the sequential steps in deciding whether a patient with myalgia should be offered a muscle biopsy.

1 Establish from the history the onset, location, nature of the myalgia (muscle ache or cramp), its relation to exercise and the effect of rest/posture.
2 Enquire about drug or substance history (Table 5), recent infections/fever (Table 4) and features in the history that may suggest a rheumatological condition (Table 6) or a metabolic/endocrinological etiology for the myalgia (Table 3).
3 Perform a general and neurological examination to document any true weakness, muscle or tendon tenderness, spasticity, contractures or joint inflammation.
4 Request resting sCK, ESR and/or C-reactive protein and any other blood tests pertinent to step 2 above.
5 If the myalgia is due to muscle cramps (Tables 1 and 2):
   a) Perform a nerve conduction study and an electromyogram to rule out neurogenic disease (Table 2).
   b) Consider biopsy if the cramps are exertional cramps (and thus may in fact be electrically silent contractures) (Table 7) and limit exercise and/or if sCK is raised ($>$ 3–5$\times$ normal).
6 If the myalgia occurs at rest with/without exacerbation by movement or exercise consider biopsy if there is suspicion of local/generalized inflammatory muscle involvement (Table 9) based on history, blood tests and magnetic resonance imaging.
7 If there is exertional myalgia, biopsy if one or more of the following occur:
   a) if there is a history of myoglobinuria,
   b) if there is a second wind phenomenon,
   c) if there is muscle weakness,
   d) if there is muscle hypertrophy/atrophy,
   e) if there is significant hyperCKemia ($>$3–5$\times$ normal),
   f) if there is a myopathic EMG.
8 Prior to biopsy, supplementary investigations (Table 10) may be carried out subject to availability.
9 The extent of the diagnostic work-up to be performed on the muscle biopsy will vary but must include histology, histochemistry, immunohistochemistry and any relevant biochemical enzyme measurements (Table 11).

Disclosure of conflict of interest

The authors declare no financial or other conflict of interests.

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