Acta neurol. belg., 2005, **105**, 18-22

Review articles

How to approach the patient with muscular symptoms in the general neurological practice ?

Jan L. De Bleecker
Department of Neurology and Reference Centre for Neuromuscular Diseases, Ghent University Hospital, Ghent, Belgium

Abstract

Muscle symptoms and signs are a frequent reason for general neurological consultations. Weakness is the most reliable clinical indicator of myopathy. Fatigue and exercise intolerance and myalgias frequently occur in non-myopathic conditions. Cramps and myoglobinuria are more often due to systemic factors than being a sign of a metabolic or other myopathy. Contractures and myotonia are rare findings but when present are strong leads towards specific myopathic diagnoses. Serum creatine kinase (CK) is the single most useful screening laboratory study. Creatine kinase increase does not only occur in myopathies, and some myopathies cause no CK increase. Rapid recruitment of short duration, low amplitude motor unit potentials is the most typical hallmark of needle electromyography in myopathies. Critical appreciation of the clinical, laboratory and electromyography findings will help general neurologists select the few patients that need referral for muscle biopsy and genetic studies.

Key words : Myopathy ; clinical ; creatine kinase ; electromyography ; general neurology.

Introduction

Myopathies are disorders in which there is a primary functional or structural impairment of skeletal muscle. The myopathies are subdivided into acquired and hereditary disorders (Table 1). In practice, patients mainly seek neurological advice because of muscular symptoms and signs, accidentally discovered creatine kinase (CK) elevation or for genetic counseling. Every neurologist sees several patients a week with exclusive or predominant muscular symptoms or signs. Individuals who will eventually be diagnosed with a myopathy represent a small proportion of this patient cohort. We aim to give an overview of some general aspects of the initial approach and work-up of these people that may lead to an insightful orientation to obtain a final diagnosis. In a logical order we will briefly discuss the value of some clinical symptoms and signs, the meaning of CK elevation as the main biochemical study and some aspects of electromyography (EMG) examination.

Clinical symptoms and signs

Symptoms may either be “negative” or “positive”. Negative symptoms include weakness or fatigue and exercise intolerance. Positive symptoms include commonly myalgias and cramps, and infrequently contractures, myotonia and myoglobinuria (Banwell and Gomez 2004).

Weakness

Weakness is the most common and most reliable symptom reported by patients with an organic muscle disease. The distribution of weakness is variable and may change over time. Many myopathies present with proximal muscle weakness, leading to complaints such as difficulty arising from a chair or low toilet and climbing stairs, a waddling gait or difficulty lifting objects over the head, combing hair or brushing teeth. Distal weakness is less common, but can be the most prominent symptom in some myopathies. Patients presenting with foot

Table 1

Classification of myopathies

Acquired myopathies
Inflammatory myopathies
Endocrine myopathies
Toxic or drug-induced myopathies
Hereditary myopathies
Muscular dystrophies
Congenital myopathies
Metabolic myopathies
Mitochondrial myopathies
Myotonias and channelopathies

Summary of a lecture given at Neurobelgium 2004, a joint meeting of the Belgian neuroscience societies.

drop and lower leg atrophy should not automatically be classified as possible Charcot-Marie-Tooth syndrome. Patients with muscular dystrophy due to dysferlin deficiency often present with distal weakness and gradually progress to more proximal leg weakness in the following few years. Cranial muscle weakness may result in complaints of dysarthria, inability to whistle, dysphagia, coughing during meals, horizontal smile with loss of facial expression and ptosis. Neck flexor or extensor weakness and restrictive respiratory dysfunction should actively be looked for. Note that weakness of trunk muscles leads to scoliosis, lumbar lordosis and protuberant abdomen.

Fatigue and exercise intolerance

This is a less reliable negative symptom since it often reflects the general level of conditioning and health, emotional disturbance or an impaired cardiopulmonary status in elderly subjects. Try to discriminate between physical and mental fatigue. When patients present complaints of diffuse weakness and fatigue, without any objective weakness on segmental muscle strength testing, the possible diagnosis of depression should be considered. Fatiguability should explicitly be asked for and clinically tested, and if present often leads to the diagnosis of myasthenia gravis.

When exercise intolerance and fatigue are truly present, the further work-up has to exclude certain metabolic myopathies or mitochondrial cytopathies. Then ask whether fatigue is elicited by brief or long-term exercise, which orients towards a disorder of glycogenesis or lipid metabolism, respectively.

Myalgias

Myalgias are often unspecific and as a matter of fact occur rather infrequently in most myopathies. Orthopaedic or rheumatologic conditions are far more frequent causes. Constant muscle pain in a proximal distribution often accompanies the inflammatory myopathies dermatomyositis and polymyositis, whereas episodic myalgias after exercise point to metabolic myopathies, but these myopathies will be rare diagnoses among the vast numbers of patients with myalgias as their main complaint. In individuals with waxing and waning, diffuse myalgias, especially in neck and lower back muscles, the possibility of an anxiety disorder should be considered.

Cramps

Cramps are involuntary contractions of muscle that usually last for several seconds to minutes. They are easily seen on EMG as rapidly firing motor unit potentials. Most cramps are benign in nature and occur predominantly in calves. Risk factors are old age, dehydration, use of diuretics, hypothyroid state, and a number of other metabolic disturbances. In neuromuscular patients, they are most common in motor neuron diseases, especially early amyotrophic lateral sclerosis, and in chronic motor or sensori-motor polyneuropathies. They are also part of the cramp-fasciculation syndrome. In myopathies, cramps are only common in metabolic myopathies such as myophosphorylase deficiency (McArdle's disease), and in hypothyroid myopathy. They are very rare in muscular dystrophies or inflammatory myopathies.

Contractures

Joint contractures are uncommon in patients with muscular sympoms, but if present they are of considerable help in orienting the diagnosis. They are part of the initial clinical presentation in most cases of autosomal dominant or recessive and all cases of X-linked recessive Emery-Dreifuss myopathy, and in dystrophies caused by mutations in collagen genes such as Bethlem myopathy. They develop in the course of a number of myopathies, including Duchenne and other muscular dystrophies and early in juvenile dermatomyositis. Unlike cramps, contractures are usually silent on needle EMG.

Myotonia

Myotonia is characterized by impaired relaxation after sustained voluntary contraction. This painless phenomenon commonly involves intrinsic hand muscles and eyelids. It is due to repetitive depolarisation of the muscle fibers which causes tetanic contraction of the fibers. Clinically, myotonia can be seen by tapping the muscle (percussion myotonia) or by voluntary contractions of muscle groups (action myotonia). Typical tests are squeezing the hand of the examiner or forceful closure of the eyes. Some myotonic patients complain of muscle stiffness. Myotonia classically improves with repeated exercise, whereas paramyotonia is typically worsened by exercise. Cold exposure makes both worse. Myotonia is common in sodium or chloride channelopathies and in the myotonic dystrophies. Acquired clinical myotonia is rare, and can be seen after poisoning or in autoimmune hyperexcitability of nerve and muscle membranes.

Myoglobinuria

Myoglobinuria and rhabdomyolysis are used interchangeably to indicate the appearance of excess myoglobin in urine, resulting in a cola-coloured urine. It is an uncommon finding and invariably indicates severe and relatively acute massive muscle fiber damage. The causes are variable, but many cases are idiopathic and occur after

Table 2

Morphological correlation of electrophysiological abnormalities in myopathies

Biopsy finding	EMG finding	Myopathy
Severe atrophy	Reduced CMAP amplitude	Distal myopathies
Muscle fiber necrosis	Fibrillation potentials	Dystrophies Inflammatory myopathies
Muscle fiber vacuolation	Fibrillation potentials	Acid maltase deficiency Chloroquine myopathy
Channel dysfunction with dystrophic or mild unspecific changes	Myotonic discharges Fibrillation potentials	Myotonic dystrophies Myotonia congenita
Increased variation and smallness of fiber diameters	Polyphasic, short duration, small amplitude MUPs	Dystrophies Inflammatory myopathies
Type 2 fiber atrophy	None	Steroid myopathy

unaccustomed strenuous exercise, after drugs or toxin intake and infections, in the wake of prolonged fever or heat stroke, etc. In case of recurrent myoglobinuria, glycogenoses, lipid storage myopathies or central core disease with malignant hyperthermia have to be excluded.

Laboratory approach : creatine kinase

CK determination is the single most useful initial laboratory study in the evaluation of patients with a suspected myopathy. CK is elevated in most patients with structural muscle disease, but may be normal in cases with mild or slowly progressive disease, in end stage myopathy with extreme muscle atrophy, in glucocorticosteroid-treated inflammatory myopathies and rare cases of untreated dermatomyositis, in atypical inflammatory myopathies associated with a collagen vascular disease, in alcohol-related or some endocrine myopathies and in steroid myopathy. Markedly fluctuating CK levels occur in a number of metabolic myopathies, often in direct relation to precedent exercise levels.

Gender and race parameters have to be considered when interpreting the diagnostic significance of CK values. The upper limit of normal has been found to be four times higher in black males compared to non-black females (Harris and Wong 1991). Unexpected increase in transaminase enzyme levels is a common finding in screening biochemistry panels in undiagnosed myopathy patients with diffuse weakness and myalgias consulting internal medicine departments, and should lead to prompt CK measurement to determine whether transaminases are of liver or muscle origin. CK isoenzymes are usually not helpful. CK-MM elevation is typical of myopathies, but CK-MB is also increased in most of these subjects and can not be used as evidence of an associated cardiomyopathy.

CK elevation is not synonymous to the presence of a myopathy. In a general neurological practice, it is rather uncommon to eventually diagnose a myopathy in patients presenting with CK elevation of 2 to 3 times the upper limit of normal in the absence of weakness or myalgias. Many patients with active motor neuron diseases or severe active axonal neuropathies show mild to moderate CK increase. Moreover, muscle trauma (after EMG study, injections, falls), viral infections, generalized seizures or strenuous exercise may all be accompanied by transient but severe CK elevation. Certain drugs may induce symptomatic or asymptomatic rise in CK levels, e.g. statin and non-statin lipid lowering drugs, chloroquine, cyclosporine A, AZT, etc.

Electromyography in myopathy

EMG is mainly used to confirm a suspected myopathy and to exclude other disorders that may mimic myopathy. Sometimes, EMG findings, e.g. myotonia, may provide clues to the etiology of a suspected myopathy. Less commonly, EMG assists in the selection of the biopsy site or in assessment of the treatment response. It is beyond the scope of this text to give a detailed account of the electrodiagnosis of myopathies. Rather, we try to point out some pitfalls and misunderstandings encountered in general neurological practice and to indicate some correlations between common EMG abnormalities and their morphological counterparts (Table 2) (Werneck and Lima 1988). One should try to limit the needle examination to one side of the body in cases with symmetric symptoms and signs, leaving intact muscles for possible subsequent biopsy.

EMG abnormalities may be subtle and may occur in a very patchy distribution. Dermatomyositis typically involves the perifascicular part of the muscle fascicles. Many dystrophies and the inflammatory myopathies may selectively affect some muscles and leave others unchanged (Joy *et al.* 1990). Dermatomyositis and polymyositis often

affect neck flexor or iliopsoas muscles that are often not sampled during routine EMG testing. Some common myopathies, including corticosteroid myopathy, many congenital myopathies and some metabolic and endocrine myopathies are typically associated with normal EMG findings. Some myopathies, including sporadic inclusion body myositis and some congenital myopathies may show mixed myopathic and neuropathic recruitment patterns in some muscles, reflecting grouped muscle fiber atrophy (Joy *et al.* 1990).

Nerve conduction studies

Nerve conduction studies are typically normal, and are mainly used to exclude other neuromuscular diseases. Nerve conduction velocities, distal latencies and F-wave latencies are normal, unless concomitant neuropathy is present, as may be the case in some forms of myofibrillary myopathy. Low compound muscle action potential (CMAP) amplitudes may occur in a number of distal myopathies. It is generally assumed that a more than 50% direct loss of muscle fibers is needed to significantly reduce the CMAP amplitude. Lambert-Eaton myasthenic syndrome should always be suspected when very low amplitude CMAPs are recorded over muscles with normal muscle bulk.

Needle myography

This is the most useful electrophysiological technique to evaluate myopathies. The combined findings in the muscle at rest, i.e. spontaneous activity and abnormal insertion activity, and during voluntary contraction, i.e. early recruitment of small, short duration low amplitude motor unit potentials (MUPs), reflect the underlying pathology affecting the muscle fibers (Table 2) (Uncini *et al.* 1990).

Fibrillation potentials arise when muscle fibers or fragments of muscle fibers are disconnected from their innervating axon terminal. In myopathic conditions, this can occur in segmental muscle fiber necrosis, fiber splitting or vacuolation of the muscle fiber. Some authors have suggested that myopathic fibrillations differ from neurogenic fibrillations by a lower amplitude, slower rate of firing and a positive waveform in some. In practice, these distinctions are not really helpful in the electrophysiological study in individual neuromuscular patients. The distribution of the fibrillations may be patchy, e.g. in dermatomyositis (Wilbourn *et al.* 1979).

Complex repetitive discharges (CRDs) and myotonic discharges represent the two forms of abnormal insertional activity (Auger 1994). CRDs are not specific for a given disease. They indicate instability of the muscle fiber membranes and occur in long-standing neurogenic and myopathic disorders, and very rarely even in some normal muscles. In myopathies they are frequently recorded in vacuolar myopathies, e.g. acid maltase deficiency, and in the inflammatory myopathies (Barohn *et al.* 1983, Jamal *et al*. 1986). Myotonic discharges are repetitively occurring single fiber action potentials that are waxing and waning in amplitude and firing rate, producing the characteristic “dive bomber” sound. They occur at insertion of the needle or are elicited by mechanical stimulation. They are quite specific for the myotonic dystrophies and disorders of sodium or chloride channel dysfunction, but are not different between these disorders.

On voluntary recruitment, the MUPs are of short duration and low amplitude, with increased polyphasia, and are recruited rapidly. The short duration of the individual MUP is the most sensitive needle myography parameter indicating a myopathy, but is often overlooked and difficult to study due to the increased recruitment of MUPs at minor force production (McComas *et al.* 1971).

Conclusion

Critical evaluation of the patient presenting with muscle symptoms and signs based on the abovementioned principles will allow the general neurologist to select those patients that may benefit from referral to tertiary centres with expertise in muscle histology and genetics.

REFERENCES

Auger R. G. Diseases associated with excess motor unit activity. *Muscle Nerv*e, 1994, **17** : 1250-1263.

Banwell B. L., Gomez M. R. The clinical examination. In : *Myology. Basic and clinical*. Engel A. G., Franzini-Armstrong C. (eds.). New York, McGraw-Hill, 2004, 599-617.

Barohn R. J., McVey A. L., DiMauro S. Adult acid maltase deficiency. *Muscle Nerve*, 1983, **16** : 672-676.

Harris E. K., Wong E. T., Shaw S. T. Statistical criteria for separate reference intervals : race and gender groups in creatine kinase. *Clin. Chem.*, 1991, **37** : 1580-1582.

Jamal G. A., Weir A. L., Hansen S., Ballantyne J. P. Myotonic dystrophy : A reassessment by conventional and more recently introduced neurophysiological techniques. *Brain*, 1986, **109** : 1279-1296.

Joy J. L., Oh S. J., Baysal A. I. Electrophysiological spectrum of inclusion body myositis. *Muscle Nerve*, 1990, **13 :** 949-951.

McComas A. J., Sica R. F. P., Currie S. An electrophysiological study of Duchenne dystrophy. *J. Neurol. Neurosurg. Psychiatry*, 1971, **34** : 461-468.

Uncini A., Lange D. J., Lovelace R. E., Solomon M., Hays A. P. Long-duration polyphasic motor unit potentials in myopathies : a quantitative study with pathological correlation. *Muscle Nerve*, 1990, **13** : 263-267.

WERNECK L. C., LIMA J. G. Muscle biopsy correlated with electromyography. Study of 100 cases. *Arch. Neuropsiquiatr.*, 1988, **46** : 156-165.

WILBOURN A. J., STREIB E. W., MITSUMOTO H. Spontaneous electrical muscle fiber activity in polymyositis and dermatomyositis. *Muscle Nerve*, 1979, **2** : 14-18.

Prof. Dr. Jan L. DE BLEECKER,
Department of Neurology,
Ghent University Hospital,
De Pintelaan 185,
B-9000 Ghent, (Belgium).
E-mail : jan.debleecker@Ugent.be.