EVALUATING MUSCLE SYMPTOMS

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The correct interpretation of neuromuscular symptoms is critical, with terms such as fatigue or weakness rarely being used with their medical sense. The *Oxford English Dictionary* defines "weak" as "wanting in moral strength for endurance or resistance; lacking fortitude or courage, strength of purpose or will; unsteadfast, wavering". This breadth of meaning and rather negative connotation further complicates matters!

HISTORY

I always start by asking people to explain why they are there here—"what is the problem?". Encourage them to expand their account and discourage them from using "medical" words. Sometimes this needs to be done repeatedly and patients may look askance but I think it is the best way to give them free rein to actually describe the symptoms rather than use the medical words in an attempt to help. They may also use words or labels from prior medical consultations and this should also be discouraged. What is it they cannot do, why can they not do it, what is it that limits them? Once you have a basic account this can be reiterated and confirmed. It also helpful to dictate the letter with the patient listening—it helps to be sure you have heard and understood what they have tried to tell you.

It is critical to date onset of symptoms—"how far back in time do you think this problem could go?". The age at which symptoms became troublesome is the usual initial response but further enquiry may reveal a much longer story. Questions should be asked (of parents if possible) about birth and the neonatal period. The age at walking should be noted; did they walk or behave differently from their siblings? Parents are good witnesses of differences between children and often suspect a neuromuscular disorder before any professional can find an abnormality. This happens most often where there is a second child with a muscle disorder such as Duchenne muscular dystrophy. Were they always last in races or did they find excuses to avoid sporting activities? What was their nickname? Might it reflect a gait or posture abnormality? Is there a story of delayed recovery or unexplained fever after anaesthesia? Men with dystrophies and congenital myopathies may be aware of their habitus and may confess to never sunbathing or swimming because of embarrassment.

It may be possible to identify fatiguability in metabolic and neuromuscular transmission disorders by asking about such activities as decorating, carrying luggage or climbing stairs. In longstanding disorders it is important to be aware that patients may interpret their fatigue as normal—it is their life experience and comparisons to friends and family may help.

In later onset disorders partners may note a change in gait or abilities before patients and the evolution should be confirmed with them. They may also be able to describe a change in body habitus not apparent to the patient. Old family photographs may help and may also identify other affected family members with, for example, ocular myopathies, the inherited neuropathies or myotonic dystrophy.

It is often forgotten that the heart and gut also contain muscle. Rhythm disorders and cardiomyopathies are an important feature of many diseases and potentially relevant symptoms should be noted. Poor gut motility and detrusor weakness is seen in myotonic dystrophy and the dystrophinopathies, and again should be sought.

Respiratory muscle involvement is an important feature of many disorders and it is essential that symptoms referrable to intercostal or diaphragmatic weakness and fatiguability are recognised. Involvement of these muscles occurs preferentially in acid maltase deficiency, some storage and structural myopathies (desminopathy, centronuclear myopathy), and some varieties of limb girdle muscular dystrophy (LGMD type 2 I). Symptoms of postural and exercise induced breathlessness may be obvious. However, if limb muscle weakness is severe, exercise capabilities are restricted, and symptoms may be masked until respiratory failure, perhaps associated with infection, precipitates an emergency. This is counterintuitive in that those without complaints about breathlessness may be those at great risk of an avoidable respiratory decompensation. Formal functional tests of lung volumes and inspiratory pressures can be used to document and measure such involvement. They

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Taking a neuromuscular history: key points

- Discourage use of "medical" words—they are rarely used accurately
- Is there a history to suggest neonatal or developmental problems?
- Confirm early history with partners/family
- Remember possible value of old personal and family photographs
- Grade severity of weakness with lost functions, not the "MRC" scale
- Fatiguability is often mild and not mentioned by patient with congenital neuromuscular transmission disorders
- Muscle pain is localised to exercising muscle in metabolic myopathies
- Remember cramp is a presentation of spasticity and extrapyramidal disorders
- Ask for symptoms reflecting respiratory muscle weakness

should be performed serially and measurement begun early in the course of disease. In myotonic dystrophy additional central disorders of respiratory control can lead to sleep disordered breathing, and formal sleep studies are necessary to identify treatable components. There is increasing interest in and evidence of benefit from both invasive and non-invasive methods of respiratory support and it is my view that the possibility of support should be raised in all patients with such involvement.

SPECIFIC MUSCLE SYMPTOMS

Muscle as a tissue gives rise to a limited range of symptoms.

Weakness

The nature of and the stage at which symptoms develop depends on lifestyle as much as on the pattern and severity of weakness. A bricklayer or athlete will note different symptoms sooner than a sedentary individual. It is important to define the pattern of weakness and look for symmetry. Useful pointers to proximal lower limb weakness include difficulties with getting out of a bath or chair and in descending (quadriceps weakness) or ascending stairs (hip extensors). Upper girdle weakness will affect combing hair and removing heavy objects from high shelving. Distal upper limb weakness will cause problems with opening spherical door handles and in using a key in a tight lock. (Patients with "grade 4" weakness may be functionally locked out of their homes). Button and zip manipulation require good distal power. It is helpful to get the patient to describe lost skills or abilities; these can give an index of the rate of evolution and in treatable disorders such a polymyositis regaining a lost function is a good indicator of response to treatment.

Pain

Pain arising as a direct consequence of definable metabolic muscle disease is usually precisely localised by the patient to muscle. They know it is muscle pain and not joint or non-specific deep pain. In glycolytic defects such as McArdles disease it is clearly related to exercise—severe pain with contracture develops often within one minute of ischaemic exercise and affects the exercising muscle(s) only—screwdrivers or carrying a heavy bag—and is relieved in minutes after exercise. My experience is that this history stands from others with exercise induced muscle pain. Patients graphically describe the hard painful muscle of a contracture. Disorders of lipid metabolism are associated with metabolic crises, severe pain with focal tenderness and swelling 6–24 hours after prolonged exercise often with myoglobinuria (it looks like a crusted port—not a red wine), and weakness. This history again stands out because of the severity of the symptoms. More generalised discomfort and joint pain occur with advancing weakness in muscular dystrophy as a consequence of changing posture and loading on joints. Complaints of generalised discomfort and aching—often worsened by exercise—are difficult to interpret; time should be spent to ensure the terms are being understood, but the decision to investigate further is in practise often determined by the presence or absence of other features suggestive of neuromuscular or neurological disease. Do not forget that mild spasticity and the early stages of Parkinson's disease may both present as muscle aching and stiffness, but these problems should become apparent by watching the patient walking. Ischaemia (claudication) can lead to focal exercise induced muscle pain, but the usual distal lower limb distribution as well as other aspects of the examination will suggest the diagnosis.

Paroxysmal symptoms: attacks of weakness and cramp

The weakness associated with the periodic paralyses is usually so striking and, in the context of a known pedigree, the diagnosis is obvious. Many are diagnosed before adult life but occasional individuals present as adults. Listening to the story and defining precipitants allows the diagnosis to be made. In severe or longstanding cases a predominantly proximal weakness may develop. The inherited (non-dystrophic) myotonias most often give rise to complaints of stiffness rather than pain or cramp, though these may occur. Stiffness worst in the cold and on exertion is typical of paramyotonia congenita, whereas in myotonia congenita striking "warm up" will be described. Muscle cramps are universal and normal and most often felt in the calf muscles. They are associated with high frequency, irregular bursts of electromyelographic (EMG) activity and most likely originate in distal motor axons. Fasciculations in the context of motor neurone disease are usually asymptomatic but there are prominent fasciculations in Isaac's syndrome. Paroxysmal dystonias and less frequently dyskinesias may present with neuromuscular-like symptomatology, but again listening to the full story and allowing the patient to describe fully what actually happens will usually allow the diagnosis to emerge.

Fatigue

Fatigue can be a nightmare; it is rarely used in the medical sense of an excessive failure of strength on repeated contraction. Patients with myasthenia usually, if allowed, describe this well. Asking (sympathetically) whether they could escape in an emergency such as fire may help to define problems here; in myasthenia or other disorders associated with a failure of strength patients have no doubt they would not or would have major difficulties. Patients with severe fatigue often look grateful that a question has been asked which indicates that the frightening nature of their symptoms has been appreciated. Those with discomfort/aching but not true fatigue look surprised at the question, but usually acknowledge they could. Such true fatigue is seen in both congenital and acquired disorders of neuromuscular transmission, but as indicated above may not be mentioned by those with a congenital disorder as they have no experience of "normal" fatiguability as a reference point. Fatigue may be regarded as normal and comparisons with partners or sibs revealing. It can

Family, drug, and past medical history: key points

- Always draw the pedigree
- Confirm "neurological" diagnoses if at all possible
- Remember to take "informed" pedigree—ask for cataracts in case of ?myotonic dystrophy
- Examine relatives in variable or mild disorders—for example, hereditary motor and sensory neuropathies

be helpful to enquire directly how many flights of stairs they can climb and what is it that stops them. Fatigue is also a major feature of many with mitochondrial disorders where it is often associated with malaise, headache or nausea and sometimes vomiting, reflecting an exercise induced lactic acidosis. The word is also often used to describe the exercise limitation occurring in disorders associated with cardiomyopathies or respiratory muscle weakness (which may exist without clinically obvious limb muscle involvement) such as myotonic dystrophy or acid maltase deficiency.

A full general medical history and drug history are also clearly essential as in any diagnostic exercise. The metabolic and endocrine myopathies I have seen have all been "difficult" diagnoses with none of the characteristic general clinical features of, for example, hypo- or hyperthyroidism being present. This I am almost certain reflects selection bias, but it is always important to check thyroid function (overactivity being a cause of a proximal myopathy and a periodic paralysis in the Japanese; hypothyroidism leading to myotonia cramp and weakness), and to consider Cushings syndrome, osteomalacia, and an alcoholic myopathy.

PEDIGREE

A pedigree should be drawn, including entries for early and neonatal deaths and miscarriages. Causes of death should be ascertained and if suggestive of a neuromuscular disorder should be confirmed by examining records (for example, adrenoleucodystrophy masquerading as "familial MS"). Maiden names should be documented to facilitate the recognition of large pedigrees. It is often helpful to examine other family members, especially in some of the milder neuromuscular disorders such as the hereditary motor and sensory neuropathies where gene carriers may have abnormal signs yet consider themselves to be unaffected. In interpreting this data it is also important to be aware of the need to ask informed questions. For example, if myotonic dystrophy is suspected then cataract surgery, sudden death, and diabetes are relevant and in mitochondrial disorders one would ask about deafness, seizures, and diabetes and "muscle" problems. In difficult cases it is often rewarding to retake the history perhaps with another older family member; problems may be remembered and "family skeletons" may have been revealed in the interim. When analysing the pedigree in cases of suspected neuromuscular disease it is critical to keep in mind mitochondrial, X linked as well as more conventional dominant and recessive modes of inheritance.

EXAMINATION

Always watch the patient walking, if possible along a corridor and not just across the consultation room. Waddling, mild spasticity or an extrapyramidal disorder may well become obvious when less than apparent with examination on the couch. An early scissoring gait with abnormal posturing of the foot is only apparent with a "stride up" and a movement disorder may become clear when patients turn, with hesitancy and festination only then being revealed. Clearly weakness, wasting, and contractures as well as any involuntary movements must be noted, but in particular ask the patient to rise either from lying supine on the floor (if clean) or from a full squat or chair. The Gower's manoeuvre shown by boys with Duchenne is well known, but a similar pattern of turning face down, using the hands to support or using furniture to rise, is used by anyone with weakness affecting hip extensors and axial muscles.

Attempt to define precisely the distribution of any weakness or wasting. Neck flexion and extension should be tested and is useful in the identification of axial involvement. The periscapular muscles (not a part of most "routine" neurological examinations) must be examined and time should be spent watching the shoulders move from behind, and the power of the rhomboids, supraspinatus, serratus anterior, and internal and external rotation at the shoulders properly assessed. Differing patterns of involvement in adjacent muscles supplied by the same root and peripheral nerve is highly suggestive of a dystrophy.

Pseudohypertrophy, most often seen in the calf, is not pathognomonic of Duchenne muscular dystrophy and is also seen with root irritation or in inflammatory peripheral nerve disease as well as other dystrophies.

Wasting is often hard to be certain about; asymmetry of the forearms is normal. The first dorsal interosseus is, I consider, the least difficult small hand muscle to examine. The anterior axillary fold is more prominent and collapses toward the chest wall with pectoralis major wasting. Anterior tibial wasting will produce guttering lateral to the tibial ridge—not normally present with the leg lying on the bed.

Beware mild ophthalmoparesis and bilateral facial weakness. Both are easily missed and should be specifically sought during the examination. I make myself pause after examining eye movements to look at the face carefully. The horizontal smile of a myopathic face is far more likely to be noted if the examiner asks the question. The eyelids should be buried if orbicularis oculi is normal.

Functional lower limb testing is much more help than on the couch. Can they rise from a full squat, stand on either toe and heel? Is the dorsiflexion on performing this manoeuvre symmetrical? Testing on the bed will miss minor weakness such is the normal difference between patient's lower and examiner's upper limb strength.

Look for contractures at neck, ankles, knees, and elbows. They are an important diagnostic feature and would suggest Emery-Dreifuss dystrophy or Bethlem myopathy.

Look for asymmetry—a feature of, for example, inclusion body myositis, facio-scapulo-humeral muscular dystrophy as well as neurogenic weakness.

Myotonia may be most obvious in the face in non-dystrophic myotonias, and not just best examined for by hand grip. The absence of clinical myotonia does not exclude a myotonic disorder.

The grading of muscle strength by the Medical Research Council scale is of limited value, one person's grade 4 strength rarely being the same as the next. The rate of evolution and pattern of weakness, not the severity, is helpful in diagnosis. Quantitative myometry is expensive and requires considerable training to avoid error and for these reasons timed tasks or the monitoring of agreed tasks may better represent changes in muscle strength. This can be helpful in the monitoring of response in polymyositis.

Examination: key points

- Watch the patient walk 10 metres or more
- Assess lower limb power with functional tasks—rising from a squat, standing on toes, heals, etc, rather than examination on the couch
- Examine the shoulders from behind
- Look for patterns and selectivity of any weakness
- Beware of mild ptosis and facial weakness
- Look specifically for contractures particularly at heels and elbows

COMMON PATTERNS OF DISEASE

Some patterns of weakness suggest specific diagnoses.

- Prominent weakness of neck flexion and extension with inability to hold up the head is suggestive of motor neurone disease, polymyositis, and myasthenia gravis. It is also recognised as a rarer late onset idiopathic myopathy reported to be steroid responsive by some authors. It is a late feature in inherited muscle disease.
- Differential involvement of adjacent muscles with identical innervation is highly suggestive of a dystrophy.
- Facial weakness is seen in myotonic dystrophy, facioscapulohumeral muscular dystrophy, mitochondrial disorders, and may be prominent in congenital myopathies.
- Ophthalmoparesis is more often caused by acquired than inherited disorders and the diagnosis, if isolated, can be difficult. Dysthyroid eye disease, orbital myositis, and myasthenia gravis are the most important diagnoses. Chronic progressive external ophthalmoplegia is almost invariably associated with a mitochondrial disease. Rarer causes include the congenital myopathies, neuromuscular transmission disorders (both pre- and postsynaptic), and oculopharyngeal muscular dystrophy.
- Distal weakness is seen in myotonic dystrophy, and the rare dominant and recessive distal myopathies. Weakness of finger flexion, often asymmetrical, is also seen in inclusion body myositis, the most common acquired late adult onset myopathy.
- Prominent contractures, especially if they involve the spine, suggest one form of Emery-Dreifuss muscular dystrophy (important to recognise because of life threatening cardiac associations). They are also prominent in some congenital myopathies (for example, Bethlem myopathy) and are seen in some of the limb girdle dystrophies.
- Diffuse proximal weakness is common in both acquired and inherited metabolic myopathies. Selective involvement suggests a muscular dystrophy.

INVESTIGATIONS

Creatine kinase (CK) is a sarcoplasmic enzyme released from muscle following damage. The quoted reference ranges are based on a skewed non-normal distribution in the population and many normal individuals may have values of 2–300 IU. Furthermore unaccustomed exercise in normals may produce values up toward 1000 IU over the next 1–2 days, and it may be worth repeating CK measurements if an "unanticipated" result is obtained before further invasive evaluation. Values in the hundreds are seen in active denervation, but concentrations persistently over 1000 IU clearly suggest a primary myopathy. It is important to recognise that normal values may be seen in many of the muscular dystrophies, mitochondrial disorders, and structural myopathies. A CK measurement is not a "muscle disease screening test".

Electro-diagnostic studies must be discussed with the neurophysiologist. The detection of inherited neuromuscular transmission disorders or other channelopathies can be extremely difficult and depends on the right questions being asked—"?myopathy" is never enough. It is also important to remember that neurogenic changes may be a feature of "muscle" diseases including the mitochondrial disorders, inclusion body myositis, and acid maltase deficiency, and in some cases of congenital myasthenic syndromes.

Genetic studies are now available for many disorders. There is no indication for EMG in possible myotonic dystrophy—this is now a diagnosis defined by the detection of the trinucleotide repeat expansion. The mutation associated with FSH (facioscapulohumeral) dystrophy is now available as a clinical service and up to 80% of cases of dystrophinopathy can be detected. For an up to date list of defined mutations (some of which are available as a clinical service) see Reilly and Hanna.[1]

Muscle biopsy also must be discussed between clinicians neurophysioloists and pathologists. The developments in immunohistochemistry and the delineation of the genetics of the muscular dystrophies means that processing will be tailored to the clinical question. The decision to perform needle or open biopsy is difficult; both are painful. A needle biopsy is usually easier and quicker to organise, but will carry an increased risk of sampling error—potentially important in inflammatory myopathies or in mitochondrial diseases. The choice of muscle is also critical—vastus lateralis and biceps are most often chosen, but other muscles may be more appropriate and choosing an affected but not severely weak muscle is the usual advice. Remember that a period of immobility following a painful biopsy, perhaps complicated by haematoma formation, can lead to a deterioration in function that is never regained in patients with severe weakness.

Exercise testing can be used in the assessment of glycolytic disorders. Ischaemic forearm exercise in disorders of glycolysis is accompanied by pain, contracture, and no rise in effluent venous lactate. This standard test is dependent on cooperation and should be performed by an experienced individual or false positives will be obtained. Aerobic exercise has been advocated in the past in the assessment of mitochondrial disorders but carries a risk of precipitating a severe lactic acidosis and, in my view, should not be used in routine clinical practice. A recent paper describes its use in glycolytic defects, but again motivation and intensity of exercise is critical.

SUMMARY

The interpretation of neuromuscular symptoms is critically dependent on listening to the patient, taking time to be sure you have heard what they are trying to tell you. Particular attention must be paid to taking a full and accurate pedigree, being precise about the evolution and nature of the symptoms, and in carefully examining skeletal muscle. Further diagnostic evaluation must involve close collaboration between clinicians, pathologists, and neurophysiologists.

KEY REFERENCES

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USEFUL WEBSITES

www.mdusa.org, US site—valuable for patient information and contains research updates

www.mdsguk.org, UK site—contains care card for myotonic dystrophy

www.enmc.org/nmd/diagnostic.html—contains the diagnostic criteria for a range of the more common neuromuscular disorders

www.neuro.wustl.edu/neuromuscular/—an excellent teaching and resource site