Neuromuscular Diseases: Approach to Clinical Diagnosis

Shannon Venance¹ and Rabi Tawil²

¹Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada
²University of Rochester Medical Center, Neuromuscular Disease Unit, Rochester, NY, USA

Effective clinical diagnosis of neuromuscular disorders requires the thoughtful use of the physician's core clinical skills of history taking and examination. Hypotheses are generated based on the clinical presentation and history taking, and tested during the physical examination. Unique to neurosciences is the need for accurate localization within the nervous system, before arriving at the differential diagnosis and identifying the investigations needed to confirm the clinical diagnosis. Only then is confirmation of a clinical diagnosis possible. Once the determination is made that the history and exam are consistent with a disorder of the peripheral nervous system, the clinician has to decide if the presentation is a disorder of peripheral nerve, muscle, neuromuscular junction, or motor neuron. Complicating matters are neuromuscular disorders, such as amyotrophic lateral sclerosis (ALS) in which peripheral and central nervous system (CNS) signs and symptoms coexist. As a general rule, investigations are tailored to reflect the clinical reasoning process and the most likely diagnostic considerations. A diagnosis is important for different reasons in different circumstances and individuals. An accurate diagnosis directs treatment and management, permits a discussion of disease progression, potential complications, and, in certain cases, is required for peace of mind. The approach taken throughout this volume emphasizes a careful history and examination with an insightful approach to the use of newer imaging and molecular diagnostic techniques in arriving at a diagnosis.

History taking: generating hypotheses

The clinical presentations of neuromuscular disorders reflect dysfunction of the lower motor neuron and the peripheral aspects of the sensory and autonomic systems. Similar complaints may be non-neurological or seen with CNS disorders. The art of history taking, allowing the patient to tell his or her story, is a critical aspect in deciding if there is a neurological problem and, in particular, a neuromuscular disorder.

It is helpful to categorize symptoms as positive (e.g. cramping, twitching, stiffness, tingling, pins, needles, burning pain) or negative (e.g. weakness, loss of muscle, numbness, incoordination), recognizing that it is often negative symptoms that have ready correlates on examination. Conversely, examination may be entirely normal in a patient with only positive symptoms. Ask patients to clarify what a symptom means to

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them (e.g. numbness may actually mean weakness or tingling or heaviness), and whether and how this affects their ability to function within their daily activities at work, school, or home. In general, someone with neurological weakness will state what activity they struggle with (e.g. a need for a hand rail on stairs) or a function no longer done (e.g. avoid steak and salads) rather than complain of weakness. Individuals with systemic illness such as cancer, congestive heart failure, or depression will often use the term “weakness” for fatigue or malaise. When appropriate, include a functional inquiry covering the autonomic nervous system.

Classify the onset as acute (hours to days), subacute (weeks to months), or chronic (months to years) and whether the temporal evolution of symptoms is static, progressive, episodic, or fluctuating. A patient presenting with rapidly progressive proximal and distal weakness with four extremity paraesthesiae and areflexia over 5 days is easily recognized as having Guillain–Barré syndrome or acute inflammatory demyelinating polyneuropathy. On the other hand, similar symptoms that relapse and remit over months to years would favor chronic inflammatory demyelinating polyneuropathy.

An organized methodical approach is emphasized in the following chapters to ensure that associated symptoms and any precipitating, aggravating, and alleviating factors are uncovered. The diagnostic possibilities in an adolescent presenting with exertional intolerance, myalgias, episodic myoglobinuria, and a normal examination will differ depending on the type of activity precipitating symptoms, e.g. high-intensity activity, of brief duration, associated with prolonged painful contractures suggests a glycogen storage disorder whereas endurance activities with symptomatic worsening during times of fasting and intercurrent viral illness suggest a disorder of lipid metabolism. A careful inquiry of function, review of systems, and social and occupational history, as well as attention to medication including herbal preparations and supplements, illicit drug use, alcohol, and other potential toxic exposures and hobbies may yield useful clues. A developmental history may be indicated and a three-generation detailed family tree, inquiring about ethnicity and consanguinity, is usually always appropriate if heritable conditions are in the differential diagnosis. It is not helpful simply to ask if anyone else in the family has a nerve or muscle problem.

**Examination: testing your hypotheses**

An initial assessment should consider all elements of the neurological examination to accurately localize within the nervous system and to determine whether the problem is isolated to the peripheral nervous system or also involves the CNS (e.g. ALS, mitochondrial cytopathies, congenital muscular dystrophies). A systemic examination should be part of the routine examination because many hereditary and acquired neuromuscular disorders will have associated systemic manifestations or are, in the case of acquired disorders, the result of a systemic illness. Most critical from a management point of view is the identification of cardiac and respiratory involvement.

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### PRESENCE OF PROMINENT RESPIRATORY INVOLVEMENT

Think of:

- **Acute/Subacute:**
  - Guillain–Barré syndrome
  - myasthenia gravis
- **Chronic:**
  - amyotrophic lateral sclerosis
  - acid maltase deficiency
  - Duchenne dystrophy
  - myotonic dystrophy

### PROMINENT CARDIAC INVOLVEMENT

Think of:

- **Cardiac conduction defects:**
  - myotonic dystrophy
  - Emery–Dreyfuss syndrome
- **Cardiomyopathy:**
  - Duchenne dystrophy
  - limb–girdle muscular dystrophies
  - Pompe’s disease (infantile onset)
  - mitochondrial myopathies
  - amyloidosis
A vigilant motor examination at the first assessment yields useful clues because the patterns of weakness are informative. This should be preceded by careful inspection of the muscle for spontaneous movements such as fasciculations and myokymia, and assessment of muscle bulk. Attention to tone and reflexes can help differentiate neurogenic from myopathic conditions, as well as ruling out the presence of an upper motor neuron component. Direct percussion of the muscles with a reflex hammer can induce rippling, mounding, or myotonia which are important diagnostic clues. A systematic approach that includes all muscle groups about the shoulder, elbow, wrist, hand including the long finger and thumb flexors, hip, knee, and ankle may shorten the differential diagnosis. In inclusion body myositis for example, the quadriceps muscles and finger flexors are preferentially involved early in the disease. And, finally, observing the posture, stance, and gait, including a functional assessment by having the patient lift the arms above the head, walk on heels, toes, hop on either foot, rise from a squat, climb a few stairs, or rise from the floor, often yields important diagnostic information. An individual with a marked lumbar lordosis and Trendelenburg gait has a chronic problem, even if he or she dates symptom onset only back several months.

A brief screening mental status may be indicated. Cognitive impairment is seen as a primary feature of some neuromuscular diseases (Duchenne muscular dystrophy, congenital myotonic dystrophy, mitochondrial cytopathies, frontotemporal dementia in ALS or secondary to the complications of the disease – confusion secondary to chronic respiratory failure and hypercapnia). A relevant cranial nerve examination might include assessment of fundi because pigmentary retinopathy can be a feature of some mitochondrial disorders, pupils (not involved in myasthenia gravis compared with fixed with botulism), eyelids, and extraocular movements. Trigeminal neuropathy may be seen with Sjögren’s syndrome or other neuropathies. Facial weakness is prominent in a number of myopathies but may also be seen in some hereditary neuropathies. Subtle evidence of facial weakness may be an inability to bury the eyelashes. Sensorineural hearing loss may be evident in neuropathies and mitochondrial disorders. A high arched palate may be a clue to a longstanding, inherited disorder, and the quality of the voice, in addition to the elevation of the soft palate, highlights the involvement of nerves IX and X. In addition to tongue movement, the presence or absence of tongue atrophy (hypoglossal nerve involvement, ALS), hypertrophy (Duchenne muscular dystrophy, amyloidosis), and fasciculations should be noted. Neck flexion is often weaker than neck extension in many myopathies and myasthenia gravis, although there are exceptions.

★ TIPS AND TRICKS

**PRESENCE OF PTOSIS AND/OR OPHTHALMOPLEGIA**
Think of:

- **Acute/Subacute:**
  - myasthenia gravis
  - Lambert–Eaton myasthenic syndrome
  - Miller–Fisher variant of Guillain–Barré syndrome
- **Chronic:**
  - myotonic muscular dystrophy
  - mitochondrial disorders
  - oculopharyngeal dystrophy
  - congenital myopathy

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Electrodiagnostic studies (nerve conduction studies, repetitive nerve stimulation, electromyography [EMG], somatosensory-evoked potentials, provocative testing) in skilled hands are generally always helpful in neuromuscular disorders. Electrodiagnostics will help confirm segmental lower motor neuron involvement in motor neuron disease, distinguish between axonal and demyelinating neuropathies, localize particular nerve roots or parts of the plexus, detect increment or decrement in neuromuscular junction disorders, and identify involved muscles in some myopathies to guide biopsy. It is important to note that electrodiagnostic studies are an extension of the history and physical exam, and rarely in and of themselves diagnostic. For example, the individual with the asymptomatic median neuropathy at the wrist on nerve conduction studies does not have carpal tunnel syndrome and the individual with small-amplitude, short-duration motor units with fibrillation potentials and positive sharp waves on EMG may have an inflammatory, toxic, or hereditary myopathy.

In many instances now, DNA analysis is clinically available for a number of disorders, in particular hereditary myopathies. It is appropriate, and less invasive, to confirm a clinical diagnosis with a genetic test in several hereditary myopathies including Duchenne/Becker muscular dystrophy, facioscapulohumeral muscular dystrophy (FSHD), myotonic dystrophy types 1 and 2, and oculopharyngeal muscular dystrophy. It is the responsibility of the ordering physician, however, to understand the sensitivity and specificity of tests ordered.

Muscle biopsy remains a critical investigation for diseases of muscle. However, the timing, site, and subsequent analysis and testing of the muscle, and the utility of a concomitant skin biopsy to generate fibroblast culture for enzymatic assays, are all decided based on the working diagnosis. Increasingly, in the literature, the use of magnetic resonance imaging to guide investigation of muscle disease is emerging; however, the benefits and costs over a careful history and examination in the clinical setting have yet to be determined. Nerve biopsies, on the other hand, are used infrequently in the investigation of neuropathies but remain critical in the diagnosis of vasculitic and amyloid neuropathies. A relatively new technique, punch skin biopsy for assessment...
of epidermal innervation, is helpful in the diagnosis of suspected small-fiber neuropathies that cannot be confirmed by electrodiagnostic testing.

**Diagnosis: putting the story together**

Ultimately, an accurate diagnosis is needed to facilitate management. The needs of individual patients will vary from simple to complex. Having a confirmed diagnosis, however, facilitates discussions with patients and their families. Communication is the cornerstone of effective therapeutic relationships, regardless of whether there are effective treatments for a condition (e.g. Guillain–Barré syndrome, myasthenia gravis) or whether management remains supportive around education, planning and problem-solving (FSHD, hereditary neuropathies, etc.). When possible, interprofessional healthcare teams should be used because they improve quality of life. Lifestyle and behavior adaptation are often required, in addition to medical and surgical approaches.

**References**


