

# Diagnosing Neuromuscular Diseases



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The field of neuromuscular diseases (NMD) has evolved at an unprecedented speed over the last two decades. Due to advances in molecular genetics, the number of identifiably different diseases has increased and a higher level of complexity has become apparent. Undoubtedly, the dizzying evolution in genetic knowledge has had a profound impact on this area of medicine. Indeed, the impact of genetics has generated a new classification that is often contrary to classical clinical definitions in many diseases.

The gene table of NMD in its online form (<http://musclegenetable.fr>), prepared by Jean Claude Kaplan and published every year, classifies NMD into 16 groups, lists 884 diseases involving 492 genes and as many proteins, and includes 71 loci that await identification of the corresponding genes.<sup>1</sup>

At the time of writing this article, the 2017 version of this table included 840 genes and 465 diseases and proteins; these numbers give an idea of the growing knowledge in this field. At present, a variety of diagnostic tools can be used in NMD but it is the physician who must wisely select which is the most useful in each case and for each individual patient. To do this, the physician must know exactly what type of information each of the examinations can provide.

## CLINICAL EVALUATION: INTERROGATION AND EXAMINATION

Despite the sophistication of available diagnostic tools, the first approach to managing a neuromuscular patient is clinical; it begins with an appropriate interrogation and is followed by a complete neuromuscular examination. Procurement of a precise family history; accurate starting time of the symptomatology, in turn revealing time of evolution; presence of pain, neuropathic or otherwise; and cramps or sensory symptoms and their distribution are of great value. As most of these diseases are of genetic origin, identification of inheritance pattern (e.g., recessive, dominant, or X-linked) is of key importance.

Observation of the patient can reveal the presence and location of atrophies or muscular hypertrophies, and facial appearance can be very informative and even typical in certain cases. The classical example of this is myotonic dystrophy type I, for which the mere recognition of a facial expression is often enough for diagnosis.

The presence of scoliosis, rigid spine, and contractures in the elbows and ankles point to specific forms of muscular dystrophy (e.g., laminin alpha deficiency, collagen VI syndromes) and is detected only by careful clinical evaluation. Gait is also very important

because it may vary; waddling gait is associated with proximal weakness and foot drop or steppage with distal weakness.

In NMD, the common underlying symptom is muscle weakness. As part of the neuromuscular examination, the manual muscle test (MMT) is the physician's most important tool and performing it correctly requires practice, training, and familiarity with the scales used to assess muscle strength. In fact, MMT is to the neuromuscular neurologist what the stethoscope is to the cardiologist. The MMT allows identification of weakness patterns (e.g., proximal, distal, axial) as well as combinations of individual muscle group involvement, thus constituting the first diagnostic step. However, there are numerous diseases with patterns of involvement that are very similar or indistinguishable from each other, so this part of the examination is necessary but not sufficient. One of the most frequent patterns is that of proximal weakness, usually including axial weakness (e.g., limb girdle muscular dystrophies), which may or may not be accompanied by periscapular atrophies and scapular winging. These patients often exhibit typical waddling gait. Manoeuvres such as standing from sitting on the floor, climbing stairs, and standing up from a chair are very useful in identifying weakness patterns. Distal patterns are classically associated with peripheral neuropathies, which exhibit sensory involvement. However, many primary muscle diseases (e.g., myotonic dystrophy, distal myopathies, inclusion body myositis) present with distal weakness, steppage, and hand and forearm atrophies that result in difficulty performing tasks, such as opening bottles, handling keys, using tools, or fastening buttons. The combination of a distal pattern in the upper limbs with proximal weakness in the lower limbs and vice versa is also possible (e.g., inclusion body myositis). In addition, weakness may even be asymmetrical.

Examination of neck flexor and extensor muscles may uncover axial weakness that should be evaluated alongside abdominal and paravertebral muscles. Axial muscles are affected early in Pompe disease as well as in other myopathies (e.g., myotonic dystrophy, polymyositis, and facioscapulohumeral muscular dystrophy). The neuromuscular examination should also be used to look for muscular hyperactivity

phenomena, such as myotonia, be it spontaneous (making a fist with consequent difficulty in relaxation) or provoked with percussion. Myotonia is the common denominator of various myotonic syndromes (e.g., myotonic muscular dystrophy type I and II). The presence of fasciculations and their distribution is particularly relevant in motor neurone diseases (e.g., amyotrophic lateral sclerosis); however, there are many causes of fasciculations and not all of them should be considered malignant.

A large group of diseases present involvement of the facial muscles (e.g., facioscapulohumeral muscular dystrophy and congenital myopathies) or of the ocular muscles producing eyelid ptosis (e.g., myotonic dystrophy, mitochondrial myopathies, and myasthenia gravis) and/or extraocular muscle paresis (e.g., mitochondrial myopathies). Weakness of the tongue can be observed in several NMD and in some conditions (e.g., Pompe disease) it is of early onset.

Evaluation of the respiratory muscles (diaphragm and accessory muscles) plays a very important role in pattern identification. Respiratory failure may manifest as morning headaches, daytime sleepiness, and sleep disturbances, and these symptoms should be recognised in the interrogation. It is important to stress that these conditions are not only seen in wheelchair-bound patients but can also be observed early in the disease course and even be the first symptom in ambulatory patients (e.g., Pompe disease, myasthenia gravis, and motor neurone disease).

Assessment of tendon reflexes is useful in the evaluation of patients with NMD. Both motor fibres and sensory fibre afferences are involved in these reflexes and they reveal the influence of the central nervous system at the spinal cord level. Reflex hyperactivity can also be seen among NMD (e.g., amyotrophic lateral sclerosis).

Pulmonary function tests (forced vital capacity and maximum inspiratory and expiratory pressures) are part of the neuromuscular patient assessment, as are cardiac function tests. Follow-up of these parameters is of fundamental importance because they may indicate the need for early intervention with noninvasive ventilation or the placement of a pacemaker or defibrillator in some forms of muscular dystrophy (e.g., Emery-Dreifuss muscular dystrophy).

We have seen that evaluation of inheritance mode, age of onset, weakness patterns, presence or absence of sensory disturbances, and existence of respiratory and/or cardiological involvement are key considerations in the diagnostic process of NMD. Thus, the process must begin with a differential diagnosis to distinguish between a primary disease of the muscle, the motor neurons, the neuromuscular junction, or the peripheral nerves.

## ELECTROPHYSIOLOGY

In expert hands, electrophysiology can be decisive in elucidating such differences when the clinical examination is inconclusive. For peripheral nerve disorders, electrophysiology is able to differentiate axonal versus demyelinating disease. It is also capable of accurately diagnosing different types of neuromuscular junction disorders, of establishing lower motor neurone damage, and of recognising primary muscle disease. Electrophysiological studies should be performed with a clinical orientation and correlated with the patient's examination findings.

## LABORATORY TESTS

Determination of creatine kinase levels is the most frequent and useful laboratory blood test in the diagnosis of NMD. These levels can point towards different diagnostic options, varying between normal values (e.g., congenital myopathies, neurogenic disorders) and thousands of units (e.g., muscular dystrophies, polymyositis, and rhabdomyolysis). Other laboratory determinations, such as lactate and pyruvate levels during ischaemic exercise, are useful in the diagnosis of metabolic myopathies.

## MRI AND IMAGING

In recent years, imaging, especially muscular MRI, has become a new diagnostic tool in the field of NMD. MRI can provide information about the structure and level of involvement, the extent of fatty replacement, and fibrosis in different muscles. Muscular MRI does not attempt to replace clinical examination, such as MMT, in any way, but it does provide information that is not clinically detectable, as is the case with early paraspinal muscle involvement in Pompe

disease. Visible alterations seen in MRI may precede clinical weakness. Different patterns of individual muscle involvement visible with MRI have been described in different forms of genetically distinct muscular dystrophies, even though these entities have a significant similarity in clinical phenotypes. MRI is also useful for patient follow-up.

## MUSCLE AND PERIPHERAL NERVE BIOPSY

Despite advances in the use of genetics and molecular biology for the diagnosis of NMD, muscle biopsy continues to play an important and often irreplaceable role in the investigation of a large number of patients. The pathologist must have special knowledge of NMD and access to the patient's clinical information to be able to interpret the findings. Histochemical techniques as well as immunostaining lead to the accurate diagnosis of many NMD as soon as the absence or deficit of certain muscle proteins is detected (e.g., dystrophinopathies and sarcoglycanopathies). In addition, histochemical and morphological studies allow us to distinguish between multiple congenital myopathies, as well as other disorders. Peripheral nerve biopsy has more limited or restricted indications and involves the sural nerve. Nerve conduction studies provide a lot of information on nerve status and in selected cases the information obtained from nerve biopsy is of great value (e.g., vasculitis).

## MOLECULAR GENETICS

The last 25 years have witnessed impressive advances in the field of genetics. Since the gene for Duchenne muscular dystrophy was recognised in 1987, hundreds of genes responsible for numerous NMD have been identified and all types of DNA mutations have been shown to be capable of resulting in a NMD. Mutations include large or small deletions, insertions, duplications, repeat expansions, and, most frequently, point mutations. Such variety of alterations requires a vast number of genetic techniques for their characterisation. These tests have changed the diagnostic algorithms in many diseases; for example, in many instances, muscle biopsies have been replaced by much less invasive blood draws.

Identifying causative mutations of different diseases has become the gold standard in the diagnosis of NMD. Nevertheless, the genetic and clinical heterogeneity in these diseases still represents a gigantic diagnostic challenge for both the clinician and geneticist. With the advent of next-generation sequencing, a large number of genes can now be sequenced in parallel. This technique makes it possible to study patients at low cost through panels of candidate genes grouped according to the phenotypic characteristics of the diseases. Whole-exon sequencing and whole-genome sequencing facilitate the examination of DNA without restriction to the candidate genes and are recommended in cases in which the panels do not permit the identification of the causative mutation.

In spite of all this diagnostic sophistication, the clinician's participation in the diagnostic process is more crucial than ever. Clinical expertise is essential for analysing the phenotype and establishing the differential diagnosis, as well as interpreting the results together with the geneticist. Nevertheless, a high number of patients in clinical practice remain undiagnosed. Rapid progress in the development and improvement of genetic techniques, as well as growing experience accumulating in joint clinical and molecular work, are expanding the diagnostic possibilities. Understanding the genetic basis of NMD has already borne fruit by yielding the first treatments derived from this knowledge. Therefore, the future is promising.

## References

1. Kaplan JC et al. The 2017 version of the gene table of monogenic neuromuscular disorders (nuclear genome). *Neuromuscul Disord.* 2016;26(12):895-929.