Chapter 1

Introduction: Historical Perspectives

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INTRODUCTION

The role of the clinician in the diagnosis and treatment of a weak child is as important today as it was in the 19th century, when pediatric neuromuscular diseases were first being recognized by such luminaries as Meryon (1852), Duchenne (1861), Werdnig (1891), and Hoffmann (1893), and later by Batten (1903). The clinician needs to react to the concerns of the patient and their parents at the first encounter. A detailed medical history and carefully performed physical examination remain the fundamental tools and starting point for assessing various symptoms and signs. This initial clinical assessment has three possible immediate outcomes: (1) the concerns of the patient and family appear to be unfounded, and the clinician can be reassuring. A follow-up visit is advised to substantiate this outcome and to give the parents peace of mind that all, indeed, is well; (2) the clinician shares the concerns of the patient and family but decides to use time as the first test to determine the natural history of the process; or (3) the clinician recognizes the importance of the clinical symptoms and realizes the need to perform diagnostic procedures as soon as possible.

This clinical approach places great demands on the physician at the first and subsequent encounters. Here, the difference between the 19th-century clinician and the 21st-century clinician is enormous. This difference is a measure of the scholarly advances of the past century, particularly over the past three decades, since the advent of molecular neurogenetics. Examples of such advances include major discoveries in the genetic analysis of the muscular dystrophies, congenital myasthenic syndromes, spinal muscular atrophies, and hereditary neuropathies. These advances in molecular neurogenetics have led to new diagnostic tests, which may confirm the clinical diagnosis accurately and noninvasively. Traditional diagnostic tests such as nerve conduction studies, electromyography (EMG), and open muscle biopsy are less often required in the evaluation of neuromuscular disorders in infancy, childhood, and adolescence. Nevertheless, these traditional tests remain useful in certain situations: to evaluate patients in whom molecular genetic analyses fail to confirm the initial clinical impression, to facilitate the rapid electrophysiologic diagnosis of a neuropathy or spinal muscular atrophy, or to focus more precisely on molecular mechanisms before ordering relatively expensive molecular genetic tests. The dramatic advances in DNA diagnostics have added to the complexity of a challenging clinical field and have left physicians occasionally uncertain about the relative indications for traditional tests such as EMG and muscle biopsy. Clearly, all these diagnostic tests remain useful, and it is up to the modern clinician to make informed decisions, after the initial clinical evaluation, to facilitate an accurate biomolecular diagnosis as quickly and as economically as possible.

TRADITIONAL DIAGNOSTIC TESTS

The technique of muscle biopsy was first introduced by Duchenne in 1868, using a harpoon-like device to sample the affected tissue during life. This crude device was the harbinger of the biopsy needle. Earlier and later investigators used muscle tissues obtained after the patient’s death. These techniques have continued to be refined, and analysis of involved tissue has become increasingly elegant and precise, as demonstrated by advances in electron microscopy, enzyme histochemistry, immunocytochemistry, and single myofiber analysis. Today, a biopsied specimen can be processed for several studies, including light microscopy, electron microscopy, enzyme histochemistry, immunohistochemistry, biochemistry, tissue culture, and molecular studies, and protein expression patterns can be assessed in single 8-micron sections taken from muscle biopsies. Advances in electrophysiology have been equally dramatic. The first application of these physiologic principles to neuromuscular diseases dates to the latter part of the 19th century.
Differentiating a normal immature neuromuscular junction. Additionally, precise microelectrode analysis of a biopsied neuromuscular junction is still necessary for diagnosis of some conditions.

Infant motor unit potentials (MUPs) are typically quite small, mimicking the size of abnormal adult “myopathic” motor units. This maturational distinction sometimes challenges the clinical neurophysiologist who is attempting to differentiate a myopathy in a newborn from a normal response. The rapid acquisition of a full recruitment pattern encompassing very small MUPs may provide the initial clue to the presence of a myopathy. On some occasions, it is equally important for the clinical neurophysiologist to advise the referring physician that even though the MUPs may appear to be normal in a floppy infant, such a finding does not exclude a myopathy.

Similarly, the finding of fibrillation potentials may not define a neuromuscular disorder as either neurogenic or myopathic. Generally, these potentials signify a denervating process, but similar abnormalities are sometimes seen in myopathies. In reality, the fibrillation potential results from the disconnection of all or part of a myofiber from the nerve, so the principle remains intact; that is, fibrillation potentials signify denervation of the myofibers. It is important to emphasize that the MUP is the key to making the neurophysiologic distinction between a primary anterior horn cell process and one that relates to a dysfunction of the muscle fiber. Differentiating a normal immature MUP from a congenital myopathy or early dystrophy is a bigger challenge for the clinical neurophysiologist.

DNA analysis now frequently resolves the confusion in these clinical settings. The benefit of DNA analysis is apparent in the evaluation of Duchenne muscular dystrophy (DMD), where EMG and muscle biopsy were state-of-the-art diagnostic studies three decades ago. Today, the clinical diagnosis of children with suspected DMD or spinal muscular atrophy can be quickly confirmed by specific DNA testing. Similar changes are occurring in a number of the other hereditary neuromuscular disorders, as reviewed elsewhere in this book.

Clinical chemistry methods emerging after World War II provided another important means of distinguishing between neuropathies and myopathies. The serum transaminases and aldolase measures were introduced first, but measurement of serum creatine kinase (CK) activity has proved to be more tissue specific, CK expression being limited to muscle and brain. Elevated values—in excess of 1000 IU—favor a primary myopathic process. Other serum enzyme values usually parallel the serum CK values, but add little to our understanding of the precise disease process. As is true of every diagnostic procedure, the exceptions continue to accumulate. Thus, many “myopathies” often have normal serum enzyme values—witness congenital myopathies, metabolic myopathies, the periodic paralyses, and the various NMTDs. But the
generalization is still helpful diagnostically, and a serum CK value is useful when first evaluating a patient with weakness, hypotonia, fatigue, or pain. A high serum CK value suggests a myopathy and mandates further investigation, but a normal value does not exclude primary pathology of the myofiber (e.g. congenital myopathies).

Other blood and urine tests have become available and provide valuable information as screening procedures. The serum and CSF lactate and pyruvate may be elevated in mitochondrial diseases, and carnitine and its acylated profile may be altered in defects of fatty acid oxidation. Immunologic tests may be informative, such as acetylcholine receptor and anti-MuSK antibodies in myasthenia gravis. As with all tests, abnormal results may be informative, but normal results may be consistent with the initial clinical diagnosis.

MODERN DIAGNOSTIC TESTING

The clinical landscape of modern medicine will continue to change as a result of the breathtaking advances in molecular genetics. These advances can be traced back to several seminal contributions over the past decades since the elucidation of the structure of DNA. Newborn screening was introduced in the 1960s by Robert Guthrie31; and now, with the increasing application of molecular diagnostics, expanded newborn screening has the potential of eliminating the often expensive “diagnostic odyssey” that begins with the onset of clinical symptoms postnatally. Even more exciting is the possibility of treating the genotype, rather than the clinical phenotype, as clearly witnessed by the phenylketonuria (PKU) model. This proactive approach obviates the need to “rescue” the phenotype since the treatment intervention will precede the onset of symptoms. Undoubtedly, there must exist a window of therapeutic opportunity for genetically determined neuromuscular diseases, and this window probably continues to close as the postnatal timeline is extended. For example, we know that the disease process is progressing for a period of time before clinical symptoms become manifest. Children with Duchenne muscular dystrophy have very high serum CK values in infancy, long before they develop symptoms in early childhood. Again, the PKU experience reinforces these basic principles. The longer the patient is symptomatic, the more difficult it will be to react to the symptoms, rescue the clinical phenotype and restore the patient to good health.

In 1969, Tay-Sachs disease was shown to be caused by hexosaminidase deficiency32; and the next year, the concept of preconception testing and counseling emerged. As a long-term result, Tay-Sachs disease has largely been eliminated in the at-risk Ashkenazi Jewish population.33 Now, over 100 recessive diseases, most untreatable and some affecting the neuromuscular system, can be prevented using this same model. Applying next-generation sequencing to preconception screening has the potential of eliminating many recessively transmitted neuromuscular diseases that are discussed throughout the several chapters of this book, analogous to the elimination of smallpox, poliomyelitis, and other infectious diseases by effective vaccine programs.

Next-generation molecular testing also will allow for a more complete interrogation of the human genome in puzzling clinical conditions like myoadenylate deaminase deficiency. This condition is present in 1% to 2% of the population, but most of the carriers are clinically asymptomatic, allowing us to speculate as to whether the condition is truly disease-causing, or whether it is a genetic susceptibility factor that remains silent in the absence of another genetic modifier. In some clinical settings, patients with myoadenylate deaminase deficiency are clearly symptomatic with aches, pain, fatigue, and weakness, and the forearm ischemic exercise test is abnormal with unchanging venous ammonia values. It is possible that these patients have another genetic factor that, when present (or absent), produces a clinical phenotype. The complex molecular mechanisms recently uncovered to explain “reversible cytochrome oxidase deficiency” are another example of multiple molecular factors acting in concert to produce clinical symptomatology.34

When a specific genetic condition currently is being considered, DNA studies are increasingly the first laboratory test performed after the clinical evaluation and measurement of serum CK activity. The DNA studies may be targeted to the sequencing of the suspected gene when the clinical phenotype is essentially diagnostic, or broadened to include whole exome or next generation sequencing when the clinical phenotype is less specific. The traditional diagnostic tests mentioned earlier are increasingly reserved for the evaluation of acquired disorders (e.g. toxic, immune-mediated, and/or inflammatory) or genetic disorders that have failed initial DNA screening. Rarely, however, when DNA analysis in a boy with a DMD phenotype fails to reveal a dystrophin gene mutation and the family history is negative, one proceeds to a muscle biopsy. Immunostaining determines whether dystrophin is present or absent, and Western blot analysis allows the size and abundance of the protein to be determined.

Molecular diagnostics are increasingly valuable in the reclassification of clinical disease groups. One excellent example is limb-girdle muscular dystrophies (LGMDs). This category includes autosomal recessive (LGMD2) and autosomal dominant (LGMD1) forms.35 The autosomal recessive forms usually have an earlier onset, more progression, and higher serum CK activity, with a phenotype that overlaps with the dystrophinopathies. Cognitive involvement, when present, favors a dystrophinopathy, and a serum CK value in excess of 1000 IU/L usually
favors a myopathic process rather than a neuropathic process such as spinal muscular atrophy type III.

DNA testing for LGMD1 and LGMD2 subtypes emerged from several research laboratories over the past decade and is now clinically available.\textsuperscript{36–38} Immunohistochemistry of biopsied skeletal muscle tissue remains useful in demonstrating abnormalities of the $\alpha$-, $\beta$-, $\gamma$-, and $\delta$-sarcoglycans; dystroglycans; dysferlin; and other proteins. The gene localization, mutated protein, and pattern of inheritance of the various LGMDs are discussed in Chapter 34.\textsuperscript{20}

Patients with the autosomal dominant forms of LGMD (type 1) are usually older, with a slower clinical progression and less elevated serum CK values, with the possible exceptions of LGMDs types 1B and 1C.

These few examples emphasize the clinician’s ability to use modern molecular and traditional diagnostics to confirm a clinical diagnosis rapidly and economically. The neurologist has always been an expert in recognizing the clinical phenotypes, but the advances in molecular diagnosis now demand a sophisticated diagnostic approach to the causative genotypes. Although the phenotype-genotype correlation has sometimes remained elusive, probably because the biological rules still remain incompletely understood, the genotypic approach to diagnosis complements the phenotypic approach. While reliable phenotyping of patients will remain the gold standard in the field of neuromuscular medicine, DNA studies will continue to pave the way for a molecular classification of neuromuscular diseases.

**CLINICAL CLASSIFICATION**

The classic phenotypes represent the cornerstone of clinical diagnosis. Adherence to the classic phenotype is mandatory if one needs a clinically pure sample to identify a candidate gene. Misdiagnosis will affect the resulting logarithm of the odds (LOD) score in linkage analysis studies (discussed in Chapter 2). An experienced clinician can diagnose a child with DMD by inspection shortly after he enters the room, but modern neurogenetics has taught us that the phenotypic range of the dystrophinopathies is very broad, ranging from the classic Duchenne and Becker phenotypes to patients with myalgias, cramps, hyperCKemia, and possibly even isolated cognitive deficits.\textsuperscript{39} The expanded clinical spectrum of genetic conditions can challenge even the experienced clinician, and demand an appreciation of phenotypic and genotypic homogeneity and heterogeneity. Several different gene mutations may cause the same phenotype (e.g. emerin and lamin A/C gene mutations causing Emery-Dreifuss muscular dystrophy), and several different phenotypes may result from the same genotype (e.g. LGMD2B, Miyoshi distal myopathy, and distal myopathy with anterior tibial onset caused by dysferlin gene mutations; and autosomal dominant Emery-Dreifuss muscular dystrophy, LGMD1B, cardiomyopathy with conduction system disease, and partial lipodystrophy caused by mutations within the lamin A/C gene). As a result, phenotype-genotype correlations often remain a puzzle. The lack of correlation between gene defect or residual tissue enzyme activity and clinical condition implies that there are other genetic and environmental factors modifying the expression of the primary mutation.

Neuromuscular disorders are conveniently classified according to the anatomic structure of the motor unit. Diseases of the anterior horn cell are referred to as neuronopathies; of the peripheral nerve as neuropathies; of the neuromuscular junction as myasthenic syndromes or, more commonly today, neuromuscular transmission disorders; and of the myofiber as myopathies. Classically, each of these subgroups presents with distinctive clinical features that orient the clinician during the initial patient evaluation.

Neuronopathies and neuropathies represent a continuum of denervating diseases. Neuropathies classically involve the cell body, and neuropathies classically affect their extensions and the investing myelin sheath. The dominant neuronopathies in the pediatric age group are the genetically determined spinal muscular atrophies. Their clinical picture varies to some degree, depending on the age at presentation. Infants with spinal muscular atrophy are typically weak and areflexic. The alert infant lying quietly on the examining table with a wide-eyed expression and tongue fasciculations, and predominantly distal movements of the limbs is easily recognized. The older child with the juvenile presentation has more obvious proximal weakness of the shoulder and pelvic girdle muscles and hyporeflexia, simulating the clinical presentation of a dystrophinopathy.\textsuperscript{40} However, joint contractures are less common in children with juvenile spinal muscular atrophy, and serum CK values tend to be normal or only slightly elevated. These distinctions allow one to quickly arrive at an initial clinical impression of a neuronopathy versus an active, progressive myopathy. Classically, the extensor digitorum brevis muscle is atrophied in juvenile spinal muscular atrophy and hypotrophied in DMD, another subtle finding that quickly leads the experienced clinician to a presumptive diagnosis. Neurogenic disease causes more wasting than myopathic disease does, and the loss of muscle bulk is more distal. However, these generalizations can be misleading in certain clinical entities. As mentioned previously, in the juvenile phenotype of spinal muscular atrophy, there may be more proximal weakness.

In contrast, certain myopathies are associated with predominantly distal weakness, as is seen, for example,
with myotonic muscular dystrophy, desmin myopathy, Miyoshi myopathy, and the myopathy associated with nephropathic cystinosis. Fasciculations of the tongue are prominent in anterior horn cell diseases and may be seen occasionally in neuropathies. Certain metabolic diseases such as Pompe disease also involve the anterior horn cell and may produce fasciculations, but the EMG is distinctive, revealing myotonic discharges that are not seen with infantile spinal muscular atrophy or congenital neuropathies. Combined upper and lower motor neuron signs, the hallmark of amyotrophic lateral sclerosis, are seen infrequently in pediatric patients, but rare examples of juvenile motor neuron disease and neuronal intranuclear hyaline inclusion disease may be encountered, with upper and lower motor neuron signs, bulbar weakness, and fasciculations.\textsuperscript{41,42}

Associated sensory loss implicates the peripheral nerves and argues against motor neuron diseases, NMTDs, and myopathies. Loss of muscle stretch reflexes is also the hallmark of a peripheral neuropathy. Areflexia is the rule when sensory involvement is present. However, muscle stretch reflexes are often reduced or absent in patients with congenital nonprogressive myopathies such as central core disease and nemaline myopathy.

Cramps are the hallmark of denervating diseases and need to be distinguished from muscle contractures. Typically, cramps are associated with intense muscle pain and may cause a palpable mass in the muscle. These symptoms typically occur with the muscle at rest and are brief in duration and sudden in onset. Passive muscle stretching often leads to relief. EMG of a cramping muscle reveals high-frequency motor unit discharges similar to those seen during maximal muscle contraction. Cramps may occur in the absence of definable disease and are generally described as benign, often occurring at night. Otherwise, cramps usually indicate disease of the anterior horn cell, nerve roots, or peripheral nerve elements. Alternatively, cramping may signify the presence of a metabolic derangement altering the neuronal microenvironment, as is seen with renal failure, hypothyroidism, hepatic failure, adrenal insufficiency, or disturbances of electrolyte balance. Cramps and pain, however, are not limited to neurogenic diseases; myalgias and cramps may be seen as the minimal clinical expression of a dystrophinopathy,\textsuperscript{39} and painful cramps may accompany caveolinopathy (LGMD1C) or glycogen storage disease, as discussed in Chapters 30, 34, and 39. Pain and cramping have also been described in mitochondrial diseases and in inflammatory diseases such as dermatomyositis, polymyositis, and Guillain-Barré syndrome. Inflammation of the nerve roots may produce intense pain with the slightest movement, making examination of the child impossible. This discomfort may be so pronounced at times that the child becomes irritable and uncooperative, leading to an initial clinical impression of an acute encephalopathy rather than Guillain-Barré syndrome.\textsuperscript{43}

Contractures differ from cramps clinically and electrically. The contracture is electrically silent and may cause muscle pain and localized swelling of the muscle that persists for hours. Unlike cramps, contractures generally occur with exercise and suggest an underlying metabolic myopathy such as phosphorylase deficiency or other glycolytic enzyme defects. Contractures also may occur in patients with hypothyroidism, rippling muscle syndrome, Brody’s disease, and paramyotonia congenita.

Disorders of the neuromuscular junction characteristically present with intermittent symptoms, including weakness and fatigue. In contrast, disorders of the anterior horn cell, peripheral nerve, and muscle generally present with fixed symptoms that are often progressive over time. Fatigue has been underappreciated as a symptom of denervating diseases, particularly spinal muscular atrophy.\textsuperscript{44} Recent research has highlighted the early targeting of the synaptic region in both conditions, which may underpin their common symptomatology.\textsuperscript{45}

Inflammatory diseases of nerve and muscle may evolve, plateau, and then regress, whereas genetically determined diseases of the motor unit emerge and steadily progress over time. In the pediatric population, disorders of the neuromuscular junction include genetically determined NMTDs, acquired disorders such as infant botulism, and immunologically mediated disorders such as transient neonatal myasthenia gravis, fetal acetylcholine receptor inactivation syndrome,\textsuperscript{40} and immune-mediated juvenile myasthenia gravis. Each of these disorders is distinctive and often recognizable clinically by age at presentation and symptoms. EMG studies of the motor unit, particularly neuromuscular junction testing, as mentioned earlier, may be useful as an initial diagnostic study in these disorders.

Congenital disorders of neurotransmission are described in detail in Chapter 26. These disorders produce varying degrees of weakness and fatigability, often beginning during infancy. Typical symptoms include hypotonia, ptosis, ocular motility disturbances and intermittent apnea. To some extent, these disorders overlap symptomatically with disorders of central neurotransmission, such as aromatic L-amino acid decarboxylase deficiency and tyrosine hydroxylase deficiency (see Chapter 6). Transient neonatal myasthenia gravis and infant botulism are acquired disorders of peripheral neurotransmission. The first follows the transplacental transfer of maternal antibodies in the setting of maternal myasthenia gravis; the second results from the ingestion of \textit{Clostridium botulinum} spores that germinate in the intestinal tract and elaborate the botulinum toxin. Again, the clinical picture is distinctive in each situation. The diagnosis of transient neonatal myasthenia gravis is determined primarily by
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PART I

Since the original description, infant botulism is diagnosed by the clinical symptoms, which include dilated, poorly reactive pupils; constipation; decreased bowel sounds; limpness; apnea, often while feeding at the breast; and weakness, with diminished muscle stretch reflexes. Both conditions improve with time, and no specific treatment may be necessary beyond supportive care.

Acquired, immunologically mediated myasthenia gravis is more frequently encountered in later childhood or adolescence, although we have seen patients as young as 15 months with antibody-positive myasthenia gravis. The intermittent nature of the symptoms is informative, and repetitive motor nerve stimulation is essentially diagnostic, with a characteristic decrement in evoked compound muscle action potential responses. In the morning and at rest, patients are often less symptomatic or asymptomatic. Fatigue associated with repetitive stimulation or with the passage of time during the day is an important clinical characteristic suggesting a defect of neuromuscular transmission.

Intermittent symptoms also raise the diagnostic possibility of a periodic paralysis. The channelopathies are often associated with episodic weakness and myotonia. The myotonias, as a group of diseases, are subdivided into dystrophic and nondystrophic disorders. The dystrophic disorders include myotonic dystrophy and proximal myotonic myopathy. The nondystrophic myotonias and the periodic paralyses, now commonly referred to as channelopathies, result from genetic mutations of various ion channels in muscle. The channelopathies are subdivided according to the ion channel involved in the molecular defect. Sodium channelopathies include the hyperkalemic periodic paralyses and paramyotonia congenita, both transmitted as autosomal dominant conditions. The potassium-aggravated myotonias (myotonia fluctuans, myotonia permanens, and acetazolamide-responsive myotonia) are also transmitted as autosomal dominant conditions and are associated with sodium channel mutations.

Chloride channelopathies include myotonia congenita. This disorder is further subdivided into the autosomal dominant form, known as Thomsen’s disease, and the autosomal recessive form, known as Becker’s disease. Hypokalemic periodic paralysis is the best-known calcium channelopathy. Other channelopathies include Schwartz-Jampel syndrome, rippling muscle disease, Andersen Tawil syndrome, Brody’s disease, and malignant hyperthermia. Andersen Tawil syndrome is associated with periodic paralysis, cardiac arrhythmias, and dysmorphic facial features; Brody’s disease is associated with delayed relaxation and no myotonia; and malignant hyperthermia is an anesthetic-induced delayed relaxation of muscle, one form of which is transmitted as an autosomal dominant trait resulting from a mutation of the ryanodine receptor on chromosome 19.

Evaluation of patients with periodic paralysis is facilitated by an awareness of the phenotype. For example, patients with Andersen Tawil syndrome have characteristic dysmorphic features, including hypertelorism, short stature, low-set ears, and clinodactyly. These dysmorphic features, in the setting of prolonged Q-T interval and life-threatening ventricular arrhythmias, permit an accurate diagnosis in the office. Similarly, patients with Schwartz-Jampel syndrome are phenotypically distinctive, with short stature, bone and joint deformities, chondrodystrophy, hypertrichosis, blepharophimosis, and muscle stiffness. EMG shows nonvariable, continuous high-frequency electrical discharges with delayed muscle relaxation.

Myopathies also are characterized by loss of strength, but the degree of weakness is disproportionate to the degree of muscular atrophy, particularly early in the clinical course. As mentioned previously, the extent of muscular atrophy appears disproportionate in neurogenic diseases. Patients with myopathies appear to be unduly weak, without significant loss of muscle bulk. DMD stands out as a striking example. The muscular-appearing child with DMD appears remarkably weak, struggling to rise from the floor or walk up and down stairs. The large proximal muscles are differentially affected, with relative preservation of the distal muscles. Children with myotonia congenita often appear quite muscular, but struggle to keep up with their peers in sporting activities. Again, there are numerous exceptions to these generalizations, such as the many myopathies that affect distal muscles, including Welander’s and Miyoshi distal myopathies and telethonin deficiency (LGMD2G). Myotonic dystrophy also differentially affects the distal muscles. Gowers’ sign is a manifestation of pelvic girdle muscle weakness, most commonly seen in the setting of DMD (Figure 1.1), but it can also be seen in other neuromuscular disorders, such as juvenile spinal muscular atrophy (type III), CIDP, and mitochondrial diseases.

Gowers’ description of this maneuver occurred in his writings on DMD, and little can be added to the original description. Patients “first put the hands on the ground, then stretch out the legs behind them far apart, with the chief weight of the trunk resting on the hands, by keeping the toes on the ground and pushing backwards, they manage to get the knees extended so that the trunk is supported by the hands and feet, all placed as widely apart as possible. Next the hands are moved alternately along the ground backwards so as to bring a larger portion of the weight of the trunk over the legs. Then, one hand is placed on the knee, and a push with this hand and with the other hand on the ground is sufficient to enable the extensors of the hip to bring the trunk into the upright position.” Gowers thought that this maneuver was pathognomonic for pseudohypertrophic muscular paralysis. Since the original description, however, clinicians have come to understand that this sign is present whenever there is significant weakness of the hip.
and knee extensors, regardless of whether the underlying disease process affects primarily nerve or muscle.

Muscle stretch reflexes tend to be relatively preserved with myopathic diseases and are roughly proportionate to the degree of atrophy. When lost, the proximal reflexes are more affected than the distal reflexes. However, patients with congenital myopathies often have diminished reflexes or areflexia. Clinically, if the patient is notably weak with preserved muscle bulk and loss of muscle stretch reflexes, the condition is most likely a myopathy.

**CLINICAL APPROACH**

The clinical approach to the evaluation of a weak child demands a thorough understanding of the many rules that describe diseases of the motor unit and the several exceptions and overlapping features of the symptoms, as discussed previously. Nothing is more important than a careful history and physical examination. Asking patients or their parents to describe the chronology of the clinical syndrome is of inestimable value. The temporal profile (the onset, duration, and evolution of the symptoms and signs) usually suggests one or more diagnostic possibilities. For example, knowing that patients with DMD typically present with weakness at age 3 years is important. Other conditions presenting in early childhood include Becker’s dystrophy; Emery-Dreifuss dystrophy; facioscapulohumeral dystrophy; limb-girdle dystrophy; myotonic dystrophy; inflammatory myopathies; various metabolic diseases, including lipid storage myopathies; mitochondrial diseases; and various endocrine and metabolic disorders.

**FIGURE 1.1** Duchenne muscular dystrophy and Gowers’ sign. This series of photographs shows the components of a “one-handed” Gowers’ maneuver. The patient uses hand support on the floor, initially bilateral then unilateral (A), and hand support on the thighs, either unilateral (B, C) or bilateral, to attain the standing position (D, E).
The presentation and the pattern of disease over time allow one to categorize the possible clinical conditions. As a rule, the genetically determined neuromopathies and the muscular dystrophies are inexorably progressive from the time of onset. However, in infants and young children, disease progression is often mitigated by normal childhood development. As a result, at certain points in early development, the parents may report that the child has stabilized or actually improved functionally. Similarly, some patients may have seasonal improvement owing to increased outdoor activities, such as swimming. This seasonal effect is particularly evident in patients with juvenile spinal muscular atrophy. Water activity and outdoor play generally have a beneficial effect on all patients with neuromuscular disorders. In contrast, other children have episodic or saltatory patterns to their clinical symptoms, which generally suggest an underlying ion channel disturbance or metabolic disease. In addition, inflammatory diseases of the neuromuscular system may wax or wane symptomatically. Children with dermatomyositis frequently present with this type of history. When the serum CK is markedly elevated, saltatory progression of the illness favors an inflammatory disease of muscle rather than a muscular dystrophy.

Weakness evident during the newborn period raises other possibilities, such as spinal muscular atrophy, congenital muscular dystrophy, myotonic dystrophy, the several congenital myopathies defined by distinctive histochemical abnormalities, and certain metabolic diseases such as acid maltase deficiency, phosphorylase deficiency, and carnitine palmitoyltransferase type II deficiency. These disorders need to be considered, along with the congenital myasthenic syndromes and genetic peripheral neuropathies.

CIDP may mimic many of these disorders. Where an older child has weakness coupled with prominent pain and misery, dermatomyositis is likely, particularly if there are cutaneous abnormalities, including a violaceous discoloration of the upper eyelids and punctate ulcerations of the extensor surfaces of the limbs. Electrical studies of the motor unit, EMG, muscle biopsy, and occasionally nerve biopsy may be valuable in diagnosing these treatable conditions.

Family history may provide valuable insight into the patient’s condition. Most disorders of the motor unit are genetically determined autosomal dominant, autosomal recessive, or X-linked disorders. Others are transmitted as maternal, non-Mendelian traits, pathognomonic for mitochondrial DNA mutations. Nothing may be more informative than examining the mother of a weak newborn infant to determine whether she has evidence of myotonic dystrophy, myasthenia gravis, inflammatory bowel disease, or another immune-mediated condition.51

Similarly, identifying precipitating factors that may trigger the onset of symptoms is informative. A history of pain, weakness, or myoglobinuria provoked by exercise quickly leads to the consideration of a metabolic disease, including the several glycolytic enzyme defects and mitochondrial and lipid storage myopathies. Weakness associated with fever or fasting leads to suspicion of a defect of fatty acid oxidation. Dietary factors, such as the ingestion of a high-carbohydrate meal, lead to the consideration of periodic paralysis. Patients with paramyotonia congenita may report that cold exposure precipitates their symptoms of muscle stiffness.

Involvement of other organs may lead to diagnostic possibilities. Cardiac disease often accompanies DMD, Becker’s muscular dystrophy, myotonic dystrophy, Emery-Dreifuss dystrophy, LGMD1B, LGMD1D, Andersen Tawil syndrome, and various metabolic disorders, including mitochondrial diseases, acid maltase deficiency, and carnitine deficiency. Inflammatory diseases of muscle also may affect cardiac muscle. In contrast, diseases affecting anterior horn cell, peripheral nerve, and neuromuscular junction spare the heart. Multisystemic involvement is common in mitochondrial diseases; strokes or stroke-like episodes, migraine headaches, short stature, pigmentary retinopathy, sensorineural hearing loss, proximal limb weakness, and lactic acidosis are common findings in children with the MELAS (mitochondrial encephalopathy and lactic acidosis with stroke-like episodes) phenotype. Muscle biopsy is distinctive in MELAS, classically showing ragged red fibers (Figure 1.2).

Similarly, respiratory failure leads to the consideration of various diseases that affect the muscle fiber, including the spinal muscular atrophies, muscular dystrophies, metabolic myopathies such as acid maltase deficiency and carnitine deficiency, mitochondrial diseases, congenital myopathies such as nemaline and centronuclear myopathy, and inflammatory myopathies such as polymyositis and dermatomyositis.

Liver involvement may be seen with mitochondrial DNA depletion syndrome, acid maltase deficiency, debrazing enzyme deficiency, and carnitine deficiency. Ocular involvement may be expected with myotonic dystrophy, congenital muscular dystrophies, and mitochondrial diseases. Dysmorphic features may be seen with the congenital myopathies, Andersen Tawil syndrome, and Schwartz-Jampel syndrome. Fixed musculoskeletal contractures are characteristic of certain long-standing myopathies, such as DMD, Emery-Dreifuss dystrophy, and Bethlem myopathy.

Scoliosis is uncommon in ambulatory patients but is characteristic of Friedreich’s ataxia. Spinal curvature may develop and progress alarmingly fast once the child becomes wheelchair-dependent. A multidisciplinary approach to these patients is ideal, and complications can be presented or managed early in the clinical course (see Chapters 52 and 53). Children with neuromuscular disorders benefit from input
from several subspecialties, including general pediatrics, neurology, psychiatry, orthopedics, physical medicine, rehabilitation, cardiology, pulmonary medicine, and genetics. Social services, physical therapy, occupational therapy, and speech therapy are important interventions, assisting in the management of daily living activities. A multidisciplinary clinic is an ideal treatment setting for these patients. Unfortunately, some of these rehabilitative services are economically challenging in today’s health care climate.

Gastrointestinal disturbances may be life-threatening in mitochondrial diseases. Oromotor dysfunction, constipation, diarrhea, malabsorption, and intestinal pseudo-obstruction are well-recognized complications. Less specific complications such as gastroesophageal reflux, with resulting erosive esophagitis, and functional constipation are common to many neuromuscular disorders, particularly when symptoms occur in infancy.

PRESENTING COMPLAINTS

Most children with neuromuscular disorders present with hypotonia, weakness, fatigue, pain, or an elevated serum CK value. Fatigue and pain are symptoms, and the others are signs. The age of the patient influences the presentation. Infants and young children usually present with signs, whereas older children and adolescents may have

**FIGURE 1.2** (A) Muscle biopsy specimen from a child with myopathy and the A3243G mtDNA mutation commonly associated with the MELAS phenotype shows a ragged red myofiber (arrow). The reddish granular material in the subsarcolemmal zone reflects proliferation of mitochondria (modified Gomori trichrome). (B) A similar ragged red fiber exhibits intense histochemical staining of succinate dehydrogenase (complex II of the electron transport chain) (arrow). Complex II is entirely encoded by nuclear DNA. (C) The histochemical reaction for cytochrome-c oxidase (COX, or complex IV) of another fiber is unstained (arrow). Three subunits of complex IV are encoded by mitochondrial DNA and are adversely affected by the point mutation (3243) in MELAS to produce this COX-deficient fiber. (D) The smooth muscle cells of a small blood vessel (arrow) show prominent punctate staining of succinate dehydrogenase. This finding indicates that abnormal blood vessels are part of the pathology of MELAS syndrome. (Histopathology courtesy of Dr. Arthur P. Hays.)
symptoms that dominate the clinical picture. If symptoms are disproportionate or exist in the absence of signs, psychogenic issues must be considered, particularly depression.

The floppy infant is hypotonic and also may be weak. The skill of the examiner is often tested in this setting. Sorting out weakness from hypotonia can be challenging, and occasionally hypotonia and weakness exist without any primary pathology of the peripheral motor unit. Many genetic syndromes are dominated by congenital hypotonia, so-called cerebral or central hypotonia. Examples include Prader-Willi syndrome, Down syndrome, Smith-Lemli-Opitz syndrome, Zellweger syndrome, and Coffin-Siris syndrome, to name just a few. These conditions need to be considered as alternatives to primary neuromuscular disorders such as spinal muscular atrophy, congenital myasthenic syndromes, and congenital muscular dystrophies. Increased muscle stretch reflexes immediately direct attention to the more common central nervous system mechanisms for hypotonia. However, the relationship between tendon reflex activity and limb tone is generally not fixed. Dysmorphic features may help distinguish a newborn with Prader-Willi syndrome from one with Werdnig-Hoffmann syndrome and allow immediate molecular confirmation. Electrophysiologic and morphologic studies of muscle are no longer necessary in most cases.

Determining whether hypotonia is present can be challenging. Several signs aid the clinician, such as the classic scarf sign, in which the hand is drawn across the chest to the opposite ear. Other maneuvers and measures can be used, but tone is qualitative and subjective. Tone itself is nebulous; it is the subliminal muscle contraction that opposes gravity and permits a person to maintain posture. Thus, careful observation of an infant’s posture provides information about resting tone. Obviously, weakness and fatigue contribute to hypotonia, and time of day and relationship to sleep also influence the degree of tone. We have all experienced relative hypotonia at the conclusion of a long and fatiguing day.

Tone is developmentally determined. A 28-week gestation premature infant is normally hypotonic, with minimal resistance to passive manipulation in all limbs. Flexor tone emerges during the remaining period of gestation, and at birth, a full-term infant has strong flexor tone that is evident on passive manipulation of the limbs. Infantile postures and spontaneous limb movements are best observed before intruding on the patient. A full-term infant demonstrates a flexed limb posture at rest and, with advancing postnatal age, shows more spontaneous movements of the limbs and trunk. By 6 months, a normal infant should be strong enough to sit and maintain an appropriate posture. By 12 months, most healthy infants are crawling, pulling to stand, and taking early steps. These “motor milestones” vary from infant to infant, but weakness is easier to detect with advancing age.

One cannot ascertain with certainty the presence of sensory deficits at this young age. As a result, a sensorimotor neuropathy may be difficult to distinguish from a neuronopathy because the sensory loss may be difficult to define. The behavioral response is most valuable. A noxious stimulus elicits a prompt withdrawal of the limbs. If this reflex response is not accompanied by a grimace or cry, one should suspect a sensory disturbance. Deep sensory disturbances affecting proprioception may disturb the early motor milestones. These infants progress normally to the crawling and cruising stages (9–12 months) but then fail to walk independently and continually seek external support to maintain an erect posture. A young girl with a congenital sensory neuropathy is shown in Figure 1.3 as she constantly places her hand on the wall to achieve better balance.

Eliciting tendon reflexes in such young patients also requires experience. Tapping on one’s own fingers held over the appropriate tendon is useful and limits discomfort. Ankle jerks are particularly useful to elicit, as these responses are often absent in infantile-onset neuromuscular disorders. However, tendon reflexes are difficult to elicit in other disorders as well, such as Prader-Willi syndrome—a relatively common cause of neonatal cerebral hypotonia.

Signs and symptoms of neuromuscular disease are more obvious in older infants and children, and symptoms can be elicited more readily after age 2 years, when most children are beginning to speak. Again, the examiner should take advantage of observation before intruding on the child. Observing the child’s behavior and motor activities while taking a history from the parents often provides significant information that leads to a clinical diagnosis. An appreciation of the expected motor milestones during late infancy and early childhood is of paramount importance. For example, one expects most children to be walking around 1 year of age. By age 18 months, children are walking independently, and some are starting to run and climb stairs without assistance. By age 2 years, the child is able to run quite well, kick a ball, and travel up and down stairs without hesitation. Standing on one leg and attempting to jump off a step is often accomplished by age 3 years, and hopping on one foot is attempted by age 4 years. By age 5 years, the child is able to hop well on either leg.

Many important observations regarding movement in the supine, sitting, and standing positions can be made while the child is fully clothed. The stance and gait can be observed, and one can determine whether the child is rising up onto his or her toes or walking on flat feet. Engaging a young child in play with a ball or other object of interest can allow additional observations, such as the child arising from the floor, reaching over the head, or
pulling an object from the examiner’s hand. One can also note eye movements, the position of the upper eyelids, and the facial expression under these conditions, particularly if the child can be encouraged to smile or laugh, or if the child becomes distressed and demonstrates facial grimacing. In fact, most of the important observations regarding the neuromuscular system can be made under these circumstances, and little may be added by the formal examination.

Muscle testing can be accomplished in increasing detail with advancing age, although the functional measures of strength are often the most informative at any age. Determining the child’s strength is central to the neuromuscular evaluation. We never analyze all of the 434 muscles in the human body. Rather, we select certain muscle groups to evaluate routinely, knowing that most diseases of the neuromuscular system are relatively symmetrical and involve limb and axial muscle groups to a greater or lesser degree. Clearly, there are exceptions to this statement. Some diseases are distinguished by the fact that they are quite asymmetrical, such as facioscapulohumeral muscular dystrophy, in which one might find prominent involvement of one side of the body or the congenital absence of a pectoral muscle. Nevertheless, a quick survey of major muscles is often informative and sufficient. Testing of the neck flexors is particularly useful, because these muscle groups are preferentially affected in many myopathies. Weakness of muscle groups in the shoulder and pelvic girdles is a useful finding, as is weakness in the biceps, triceps, iliopsoas,

**FIGURE 1.3** Congenital hypomyelination neuropathy and sensory ataxia. (A–C) Clinical features in this child include poor balance and pes planus and valgus deformities of the feet. She has areflexia and slowed nerve conduction velocities. (D) A transverse section of the nerve biopsy shows no discernible myelinated fibers by routine histology (trichrome). (E) A transverse thin section (1 μm thick) of epoxy resin-embedded tissue has greater resolution than the paraffin section (6 μm thick) and demonstrates a barely visible thin, dark myelin sheath around each large, pale axon (toluidine blue). (F) A teased myelinated nerve fiber (arrow) shows a very thin myelin sheath as a double-contoured structure resembling a railroad track. Myelin sheaths of other fibers are too thin to identify clearly (osmium tetroxide). (Panels D, E, and F, courtesy of Dr. Arthur P. Hays.)
quadriceps, hamstrings, and distal muscles of the hands and feet. Strength in these muscles can be surveyed rather quickly. More formal assessment of all accessible muscle groups is done using the grading system originally developed by the Medical Research Council in 1943.\(^2\) This system has withstood the test of time and is still valuable in recording degree of weakness at presentation and over time.

Physicians have a tendency to be unnecessarily precise regarding clinical observations. The Medical Research Council system has five grades: 0 for no movement of the muscle, 1 for a flicker or trace of movement, 2 for active movement with gravity eliminated, 3 for active movement against gravity, 4 for active movement against gravity and some applied resistance, and 5 for normal power. Strictly speaking, only the 0 grade is unequivocal. Even a grade of 5 can be debated, because each examiner has his or her own idea of normal power. However, to further subdivide these categories by adding a plus or minus sign accomplishes little.

Disrobing the child after initial observations have been made frequently provides important clues. Children are innately modest, and a compassionate clinician takes the time to reassure the patient while performing a careful physical examination. Appreciating the presence of dysmorphic features may be essentially diagnostic, for the reasons mentioned earlier. Patterns of weakness and wasting, and the presence of fasciculations or other spontaneous movements of muscle are important. Eye movements, eyelid posture, facial expression, wasting of the temporalis muscle, failure to close the eyes completely, inability to purse the lips or whistle during expiration, nasality of voice, wasting of the sternocleidomastoid and trapezius muscles, wasting of the tongue, presence of a deep crease running from the axilla obliquely toward the neck, a step-like appearance where the base of the neck and the clavicles meet, winging of the scapulae at rest or when the patient attempts to raise the arms in front of the body, atrophy of the intrinsic muscles of the hand or a semiflexed posture of the weakened fingers with some extension at the metacarpal phalangeal joints, exaggerated lumbar lordosis or curvature of the spine, protuberance of the abdomen, wasting of the quadriceps or the anterior compartment muscles of the legs, tapering of the legs distally, tightness of the heel cords, abnormalities of the foot such as pes cavus and pes planus deformities, and presence of foot-drop are informative and often quickly bring one or more diagnostic possibilities to mind.

The physical examination should end with a search for other diagnostic clues. Retinopathy, deafness, cardiac dysfunction, respiratory insufficiency with paradoxical breathing pattern, visceral enlargement, or cutaneous abnormalities should be noted. A careful evaluation of the sensory system is important, searching for evidence of superficial or deep sensory loss. Limb tone and tendon reflex activity should be assessed, but again, one need not determine a precise grade. The patient has hypotonia, hypertonia, or normal tone; the tendon reflexes are absent, diminished, normal, or hyperactive, with or without clonus. The presence of Babinski’s signs clearly indicates an upper motor neuron disease. A small number of patients with DMD have initial extension of the great toe after stimulation of the plantar surface of the foot. Whether this represents evidence of upper motor neuron disease, or differential weakness within the foot that limits the response of the great toe to one of extension, can be debated. Assessing the response to plantar stimulation in an infant can be challenging and is not critical in the overall assessment. Applying the stimulus laterally on the foot (Chaddock’s reflex) avoids some of the other competing reflexes seen in this area during infancy.

The clinician needs to consider all the diagnostic clues provided by the medical history and clinical examination and then decide whether additional testing is necessary. Often blood studies, including a serum CK measurement, are sufficient. Occasionally, electrophysiologic studies of the motor unit are indicated, particularly if the clinical evaluation points toward a neuronopathy, neuropathy, or neuromuscular transmission disorder. These studies can be performed quickly and relatively noninvasively by nerve conduction studies and EMG. DNA testing may quickly confirm the clinical impression of most muscular dystrophies, including the dystrophinopathies; channelopathies, including many of the periodic paralyses and myotonias; and spinal muscular atrophies. Other testing may be valuable in selected instances. For example, brain magnetic resonance imaging scans may be informative in evaluating congenital muscular dystrophies such as Fukuyama muscular dystrophy, merosin-deficient congenital muscular dystrophy, muscle-eye-brain syndrome, and Walker-Warburg syndrome. Magnetic resonance imaging and magnetic resonance spectroscopy may be informative in mitochondrial diseases, in which selective involvement of the basal ganglia is classic, and signal elevations of brain and ventricular lactate may be seen.

Finally, the modern-day clinician may be overwhelmed by the explosion of new information and can be assisted by several valuable websites: Online Mendelian Inheritance of Man (http://www.ncbi.nlm.nih.gov/Omim/searchomim.html), National Library of Medicine: PubMed (http://www.ncbi.nlm.nih.gov/PubMed/), Gene Clinics (http://www.geneclinics.org), Emery-Dreifuss Muscular Dystrophy Mutation Database (http://www.path.cam.ac.uk/emd/), Leiden Muscular Dystrophy (http://www.dmd.nl/), the Neuromuscular Disease Center at Washington University School of Medicine, St. Louis (http://www.neuro.wustl.edu/neuromuscular), and Muscular Dystrophy Association, USA (http://www.mdausa.org).
CONCLUSION

The field of pediatric neuromuscular disorders has continued to expand scientifically since the era of molecular neuromastics began in the mid-1980s. The rapid changes in the field may be overwhelming to busy, practicing clinicians. Older children and their families are increasingly aware of these extraordinary advances through their own access to the Internet, and they challenge us to remain informed and updated. They wait impatiently for us to translate these scientific achievements into clinical research that will lead to more meaningful treatments and ultimately to cures. The chapters that follow represent an effort to capture this dynamic process at one point in time. The frustration of the editors and the authors is similar to that of clinicians and their patients. On the one hand, much is happening, and the knowledge base is expanding at a breathtaking pace. On the other hand, our daily management of patients is closer to that of our professional predecessors who initially described many of the disorders discussed in this text. Advances in molecular genetics have been breathtaking, and these advances will likely transform the clinical approach from reactive (to presenting symptoms) to proactive (to genotypic lesions) in the near future. Patients will be identified before the onset of clinical complaints, and treatment will be anticipatory and preventive, emulating the successes of newborn screening since the 1960s.

We can, currently, cite several treatment successes, such as intravenous immunoglobulin in autoimmune myasthenia gravis, CIDP, Guillain-Barré syndrome, and inflammatory myopathies; advances in intensive care; and the triumph of immunizations. Infantile poliomyelitis is no longer a significant concern in the industrialized world, but it continues to challenge us in other parts of the world, as do other infectious neuromuscular disorders such as Hansen’s disease, tetanus, and rabies. It is our hope that these treatable, preventable illnesses will eventually become a worldwide footnote in the history of pediatric neuromuscular disorders. For the present, however, they are still an important challenge for our generation. We can cite fewer therapeutic successes in genetically determined diseases of the neuromuscular system, but many promising attempts are underway. Molecular therapies currently are being explored in clinical trials for spinal muscular atrophy, DMD and other neuromuscular diseases. Undoubtedly, future editions of this text will need to devote more pages to the molecular classification of neuromuscular diseases and to a description of their specific treatments and cures.

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