Approach to Motor Unit Diseases and the Floppy Infant Syndrome

Mustafa A. M. Salih and Peter B. Kang

38.1 Definition/Classification

The anatomy of the motor unit, also known as the lower motor neuron system or peripheral nervous system, has four major components: (1) a motor neuron in the brainstem or ventral horn of the spinal cord; (2) an axon, which is bundled with other axons to form a peripheral nerve; (3) a neuromuscular junction; and (4) a group of myofibers that are ultimately innervated by the motor neuron. Disorders affecting these motor units may be classified anatomically into these four categories and also classified into inherited versus acquired diseases and into those that present with acute or chronic manifestations.

38.2 Epidemiology

Peripheral nervous system diseases occur worldwide and affect many children. An epidemiologic study from Sweden estimates that neuromuscular disorders (NMDs) occur with a point prevalence of $63.1 \times 10\ (-5)$ children under the age of 16 years [1]. There is, as expected, some variability among countries and regions, especially

M. A. M. Salih (✉)
Division of Pediatric Neurology, Department of Pediatrics, College of Medicine and King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia
e-mail: mustafa@ksu.edu.sa

P. B. Kang
Division of Pediatric Neurology, University of Florida College of Medicine, Gainesville, FL, USA

with founder effects for specific mutations in some countries and high rates of consanguinity in others. Examples include subtypes of congenital muscular dystrophy in Finland and Japan, spinal muscular atrophy and severe childhood autosomal recessive muscular dystrophy (SCARMD, limb-girdle muscular dystrophy [LGMD]) in Middle Eastern and North African populations.

38.3 Diagnostic Approach

Despite the impressive new developments in genetic diagnosis, especially with next-generation sequencing rapidly becoming available for clinical use, a careful history and physical examination remain the cornerstones of diagnosis and should not be neglected in the approach to the diagnostic evaluation of a child with suspected neuromuscular disease [2].

38.4 Symptoms

In infants, NMDs often present with hypotonia and weakness. Later in infancy and in early childhood, delayed motor milestones are common presenting complaints. In school age children and adolescents, symptoms of NMDs may include an abnormal gait, tendency to fall, toe-walking, muscle weakness, muscle cramps and/or muscle stiffness. It is important to ascertain in the history whether the symptoms are improving, worsening, static or episodic. Key skills to ask about include running, climbing stairs and getting up from the floor. Diurnal patterns, fatigability and warm-up phenomena may provide valuable clues. A history of recurrent episodes of muscle weakness may suggest periodic paralysis (in channel disorders), myasthenia gravis, dermatomyositis or polymyositis, rhabdomyolysis or relapsing polyneuropathy. The occurrence of muscle cramps with exertion and their relief by rest may be a manifestation of some of the milder forms of muscular dystrophy (MD) such as Becker MD. They also occur in metabolic disorders of muscle (glycogenosis types V and VII and lipid metabolic disorders due to carnitine palmitoyl transferase deficiency, as well as other syndromes associated with myoglobinuria). Any observed muscle enlargement (hypertrophy) or wasting should also be ascertained. Difficulty with chewing or swallowing and associated respiratory deficit or disturbed sleep (indicating sleep apnea) are also important to identify. Temperature sensitivity, especially when there is a question of myotonia, may be very helpful to know about.

Family history may be very helpful if other family members are affected, if there is consanguinity or if the ancestry is one in which certain inherited diseases are known to cluster. A negative family history does not exclude recessive or X-linked diseases but makes an autosomal dominant disorder less likely, barring de novo mutations.

38.5   Signs

The goal of a physical examination is to obtain as much relevant data as possible. In children, a flexible approach is the key to optimizing the quality and quantity of such data. Infants, school-age children, and adolescents will typically cooperate with a complete examination on a traditional examination table. However, toddlers fall in a category all their own when it comes to cooperating with a physical examination. Those children often do best in a parent's lap or other arrangement in which the feeling of security can be maximized. A great deal of useful information can be obtained merely through careful observation, sometimes assisted by playing with the child or offering a toy. Such maneuvers can help with the assessment of oculomotor movements, grasp, transfer, pincer grasp, and coordination. Eliciting a laugh via tickling or other strategy will permit assessment of facial strength. Lower motor neuron lesions that involve the face will typically cause diffuse facial weakness, while an upper motor neuron lesion will typically cause lower facial weakness only (Fig. 38.1a). The lower face can be assessed by asking the child to pout his lips, blow (or whistle), smile, show his teeth, and buff out his cheeks.
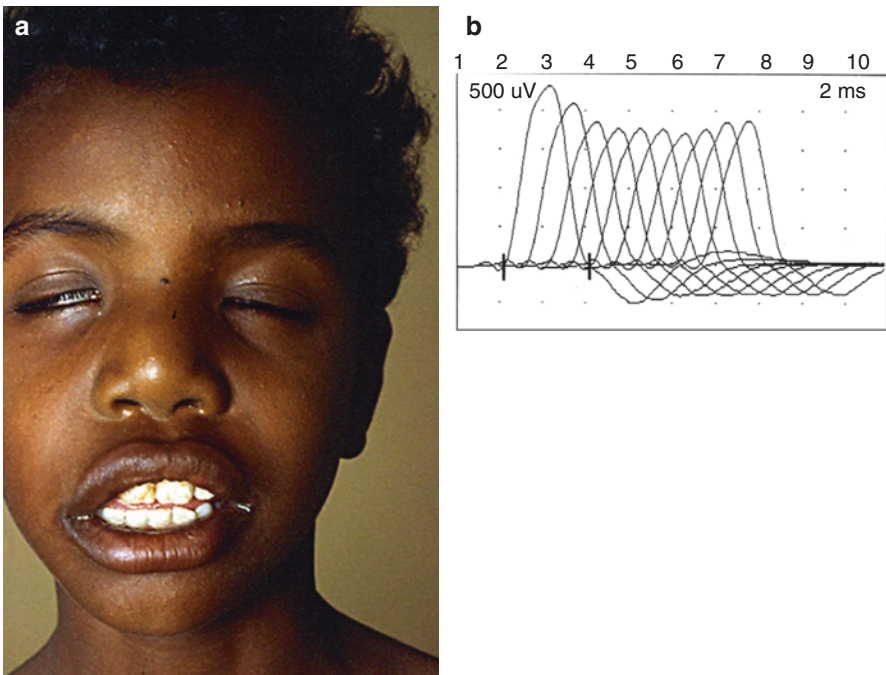

Fig. 38.1 (**a**) Bilateral lower motor neuron facial weakness in a 12-year-old boy with fascioscapulohumeral muscular dystrophy. The patient cannot bury the eyelashes when asked to close his eyes tightly. The mouth is open with trickling saliva. (**b**) Repetitive electrical stimulation of a motor nerve showing myasthenic decremental response. There is a fall-off in the size of muscle action potential of greater than 10% between the first and fifth response (Incorporated from Reference [2] with permission)

Table 38.1 Medical Research Council grading scale for evaluation of muscle power

Grade	Muscle response
0	No contraction
1	Flicker of contraction
2	Active movement, with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal power

Examination of the upper and lower limbs should include determinations of muscle bulk, tone, and power. Any abnormalities should be further ascertained whether they are proximal or distal, symmetric (involving both sides of the body), or asymmetric. The Medical Research Council (MRC) scale for evaluation of muscle power (Table 38.1) is a useful and practical guide for comparing muscle groups (proximal vs. distal) initially and during follow-up examinations [3]. This scale may be used in most developmentally normal children 5 years and older, and cooperative toddlers may sometimes be able to cooperate with at least parts of a full confrontation motor examination.

Deep tendon reflexes are generally absent in neuropathies and in motor neuron diseases (including spinal muscular atrophy). Their presence and vigor in myopathies and muscular dystrophies depend on the severity of the impact on the reflex arc. Reflexes tend to be absent in congenital myopathies, for example. In Duchenne muscular dystrophy (DMD), reflexes are often diminished but detectable early in the course, and then extinguish as the disease progresses.

Joint abnormalities should also be assessed. These can manifest as laxity of ligaments or limitation of joint movement as a result of permanent shortening (contractures). Heel cord contractures are perhaps the most common limitation of joint movement present in neuromuscular diseases, and as such they are non-specific findings, and may sometimes be present in children who have an upper motor neuron disease such as cerebral palsy, or in children who do not have a neurological disease at all. Other contractures may occur at the knees, hips, wrist, elbows, and shoulders. In inherited peripheral neuropathies, pes cavus is the usual joint abnormality, though pes cavus may also be an isolated finding in children without neuropathy [4]. Scoliosis complicates many neuromuscular disorders and is more common in specific subtypes.

Assessment of gait begins as soon as the child comes into the physician's field of vision. Toe-walking accompanies heel cord contractures and is thus a non-specific finding in isolation but in combination with other abnormalities may indicate the presence of a neuromuscular disorder, and upper motor neuron lesion such as cerebral palsy (Video 38.1), or a genetic disease such as hereditary spastic paraplegia that is difficult to localize anatomically. Asking the child to perform heel walking (Video 38.2) and tandem walking tasks will also assist in the assessment. The ability to rise from the floor or from a chair may provide useful information about possible

proximal weakness that is present in muscular dystrophies, spinal muscular atrophy type III (Video 38.3), and other neuromuscular disorders.

Following assessment of a child, it is often possible to determine whether the history and physical signs suggest the presence of a specific neuromuscular or a disorder outside the neuromuscular system.

38.6   Investigations

For much of the twentieth century, physicians relied on three diagnostic tests to confirm the diagnosis of a neuromuscular disorder: serum enzymes, electromyography, and biopsies of the muscle and/or nerve. With the increasing use of genetic diagnostic testing, electromyography and biopsies are ordered more selectively but still play an important role in the diagnostic evaluation of children with suspected neuromuscular disorders. The volume of electromyography studies in particular has, if anything, risen over the past decade in certain centers [5].

38.7   Serum Enzymes

Creatine kinase (CK), normally found in skeletal and cardiac muscle fibers, is abnormally released into the bloodstream when the integrity of muscle fiber membranes is damaged. The CK may be separated into three isoenzymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. Serum CK determination is a very useful screening test for a suspected neuromuscular disease, especially muscular dystrophy. In DMD the level is grossly elevated 50–200 times the reference range [6]. Other lysosomal enzymes present in muscle such as aldolase and aspartate aminotransferase (AST), as well as the liver-specific alanine aminotransferase (ALT), are also elevated. The associated presence of high CK should rule out considering a liver biopsy [6]. Serum CK levels are generally lower in Becker muscular dystrophy (BMD), reaching a maximum at 10–15 years of age [7]. Elevated CK (2–150 times normal) is seen in most patients with congenital muscular dystrophy CMD due to laminin-a2 (merosin) mutations or abnormal glycosylation of a-dystroglycan [8, 9]. Normal or mildly elevated levels (≤5 times normal) are seen in patients with other forms of CMD.

In severe childhood autosomal recessive muscular dystrophy (SCARMD, limb-girdle muscular dystrophy [LGMD] types C, D, E, and F) and in dysferlinopathy (LGMD2B), CK levels are elevated by 10–150 times normal [6, 10]. Other forms of dystrophy such as Emery-Dreifuss MD may have a more modest elevation; and in congenital myopathies with structural muscle abnormalities, it is likely to be normal or only slightly elevated. CK levels are usually normal or mildly elevated in neurogenic syndromes such as spinal muscular atrophy. Carriers of Duchenne muscular dystrophy may have normal or mildly elevated CK levels.

38.8   Electrophysiological Investigations

38.8.1   Nerve Conduction Studies

Nerve conduction studies are often very useful in the diagnostic evaluation of suspected neuromuscular disorders, especially neuropathies. Motor and sensory nerve conduction latencies and amplitudes can be measured by surface electrodes, and the velocity can be calculated from the latencies if distances are measured. The conduction velocity is dependent on the diameter and the degree of myelination of the axon. In full-term neonates, nerve conduction velocities are about half of the typical adult values and reach adult levels by 3–5 years of age. In peripheral neuropathies, the pathology may be primarily in the axon (axonal neuropathy) or in the supporting Schwan cell, leading to uniform or segmental demyelination (demyelinating neuropathy). The nerve conduction velocity (NCV) is markedly decreased in demyelinating neuropathies. In axonal neuropathy, the NCV may be normal or slightly decreased, whereas the compound muscle action potential (CMAP) will be significantly low. Determining the physiology of an inherited polyneuropathy helps to guide genetic testing for the various forms of Charcot-Marie-Tooth disease (CMT, also known as hereditary motor and sensory neuropathy).

In cases of dominantly inherited demyelinating CMT, it is helpful to assess the NCV in both parents and siblings to seek subclinical or preclinical cases. Post-infective polyneuritis (Guillain-Barré syndrome and diphtheritic polyneuropathy) may manifest as a demyelinating neuropathy. Measurement of the sensory conduction velocity and sensory action potential are useful diagnostic tools in certain disorders. For example, Friedreich ataxia is associated with a sensory neuronopathy [11]. Nerve conduction findings in hereditary sensory and autonomic neuropathies are variable depending on the subtype [12]; in some cases, nerve conduction studies will be normal in this disorder.

Repetitive stimulation of a motor nerve is a special study performed when a disorder of the neuromuscular junction is suspected, such as congenital myasthenic syndromes and myasthenia gravis [13]. Fatiguability of the muscle can be demonstrated by a decrement in the amplitude of the compound motor action potential (CMAP) by the fourth stimulation on a low frequency (less than 10 Hz, typically 2–3 Hz) stimulation protocol (Fig. 38.1b).

38.8.2   Electromyography (EMG)

Needle electromyography is typically paired with nerve conduction studies and measures electrical potentials in muscle fibers at rest and during voluntary contractions. Abnormalities may help diagnose either neurogenic or myopathic disease, depending on the specific finding. In the right hands, this technique may be as useful in children as it is in adults. However, given the fear of needles common among children, especially toddlers, it is important for this study to be performed by an electromyographer who is experienced with conducting the test on children. It is

also important to prioritize the muscles most important to sample and to examine those first, in case the child's level of cooperation deteriorates suddenly. Electromyography remains an important diagnostic test modality, despite the rapid advances in genetic testing technologies. It continues to be useful in the diagnosis of traumatic nerve injuries, including brachial plexopathies and mononeuropathies. As noted above, it is very useful in determining what type of polyneuropathy may be present; and it can narrow the differential diagnosis dramatically when myotonia is observed. Electromyography is the diagnostic modality of choice for muscle diseases manifesting with myotonia, including myotonia congenita, paramyotonia congenita, myotonic dystrophy, and some glycogen storage diseases. Myotonia consists of runs of fluctuating fibrillation potentials and/or positive sharp waves. A typical sound of the "dive bomber" or "departing motor cycle" sound will be heard on acoustic amplification (Video 38.4). It is usually present in the dominantly inherited congenital myotonic dystrophy, but appears later in childhood, and may not be detected in neonates with congenital myotonic dystrophy. Thus, mildly affected mothers of babies with congenital myotonic dystrophy may paradoxically have more dramatic myotonia than their affected children.

38.8.3 Muscle Biopsy

Muscle biopsy continues to be a useful diagnostic modality, though it is not used as often as in the past, in large part due to the advances in genetic diagnosis over the past several decades. Muscle biopsy is particularly useful in cases where there is a high degree of suspicion for a muscle disease, but less invasive evaluations such as genetic testing do not yield a definitive diagnosis. An experienced pathologist will often be able to distinguish between neurogenic and myopathic features on muscle histology. In some cases, analysis of muscle specimens can also pinpoint the specific protein that is deficient, though histological studies cannot identify specific mutations.

   An open biopsy has traditionally yielded better specimens for a full set of histological analyses. A needle biopsy has sometimes yielded suboptimal specimens. However, open biopsy typically requires general anesthesia in young children (though it is often performed under local anesthesia in adults), and in experienced hands, the quality of needle biopsies may be quite high. The vastus lateralis (quadriceps femoris) is the muscle which is usually sampled, unless the pattern of weakness suggests that sampling a different muscle would generate a higher yield. Histochemical studies of frozen sections are the mainstay of muscle biopsy analysis. Immunohistochemical studies may be quite helpful, especially in cases of suspected muscular dystrophy, as assessment of various proteins associated with muscular dystrophy may pinpoint specific protein deficiencies and suggest subtype-specific diagnoses. A portion of the biopsy specimen should be fixed in glutaraldehyde for potential electron microscopy, which may be very useful in the diagnostic evaluation for several congenital myopathies and mitochondrial myopathy.

38.8.4   Sural Nerve Biopsy

The sural nerve is the most commonly biopsied nerve for the evaluation of potential neuropathy, as it is a pure sensory nerve. However, the disadvantage of sampling the sural nerve is that pure motor abnormalities may not be detected. Electron microscopy of a nerve specimen can help differentiate between axonal and demyelinating neuropathies, as well as allow assessing the population types of fibers in cases of hereditary sensory and autonomic neuropathies. Teased fiber preparations are more sensitive for segmental demyelination but are labor-intensive and thus not routinely performed. The presence of inflammatory infiltrates may help diagnose cases of inflammatory/autoimmune neuropathies.

38.8.5   Imaging of the Motor Unit

Imaging protocols for skeletal muscle have matured immensely in recent years. Ultrasound has been used for several decades in this setting. Advantages of ultrasound evaluation include the portability of the equipment, ease of use, lack of pain, and low cost. Patterns of echogenicity may help distinguish between neurogenic and myopathic diseases and in some cases even suggest specific myopathies. Muscle magnetic resonance imaging (MRI) has also been developed over several decades but is a slightly newer technology in the setting of muscle disease [14]. The main advantage of muscle MRI is the high resolution and thus the ability to determine detailed patterns of individual muscle involvement [15]. Disadvantages include the high cost and need for the patient to lay still for an extended period of time, which may be difficult for younger children. Ultrasound and MRI technologies are used less frequently to image nerves, but in recent years, the utility of these modalities for the diagnosis of nerve disorders has become increasingly appreciated. Brain imaging is useful for the diagnosis of selected neuromuscular disorders, especially some congenital muscular dystrophies. Spine imaging may help diagnose inflammatory neuropathies [16].

38.8.6   Respiratory and Cardiac Investigations

Baseline pulmonary function tests should be obtained on children who are diagnosed with inherited neuromuscular diseases. Follow-up studies should be performed when the baseline study is abnormal and/or when the disease entity is associated with a high risk of pulmonary complications. Polysomnography studies, also known as sleep studies, are often helpful in patients who have respiratory issues at night. Such studies should be interpreted by a pediatric pulmonologist. Similarly, baseline electrocardiograms and echocardiograms should be obtained on children who are diagnosed with inherited muscle disease, given the risk of dilated cardiomyopathy and/or arrhythmias with specific diseases. Patients who are determined to

have a high risk of cardiac complications based on the initial studies and/or prior knowledge of the specific disease process should have regular follow-up studies accompanied by consultations with a pediatric cardiologist.

38.9   Floppy Infant Syndrome

Floppy infant syndrome occurs when an infant is found to have generalized persistent hypotonia. One classic sign of generalized hypotonia in infants is the frog leg posture (Fig. 38.2a). Hypotonia becomes more apparent in certain positions. On
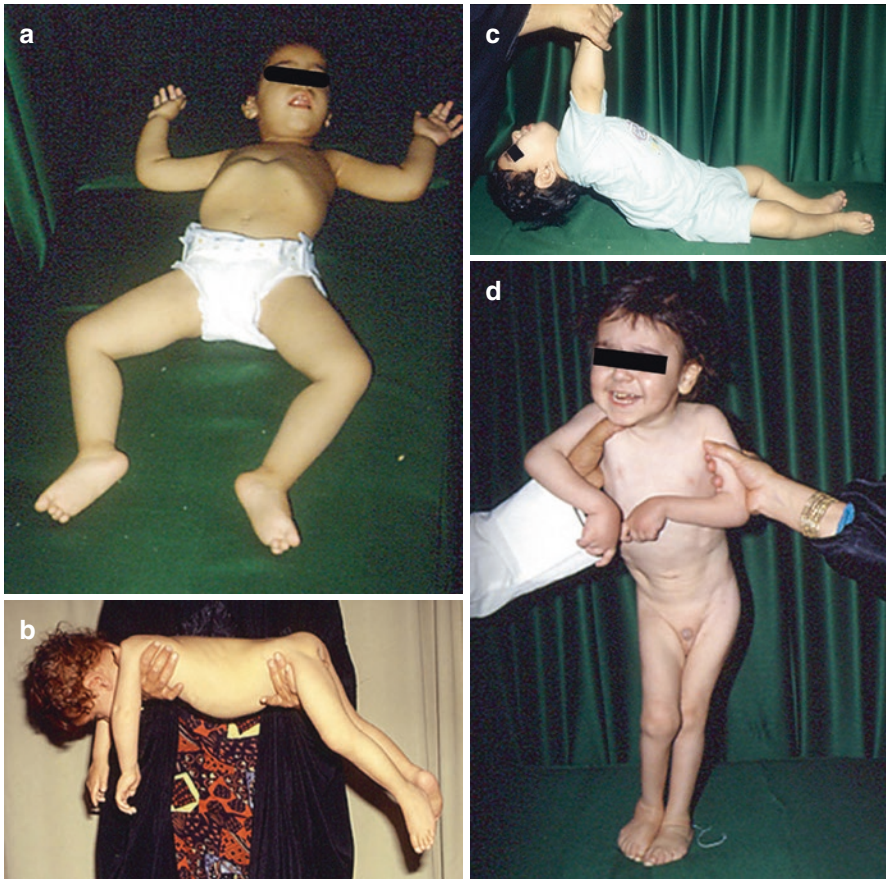

Fig. 38.2 (**a**) A floppy infant with frog-like position when supine. (**b**) On ventral suspension, the limbs are dangling. (**c**) Prominent head lag on pulling to the sitting position. (**d**) Central nervous system (CNS) disorder causing floppy infant syndrome. When assessing the ability to support weight, there is scissoring of legs, flexion of elbows, and clenching of the hands (Incorporated from Reference [2] with permission)

ventral suspension, a floppy infant will have difficulty raising the head to a level position. The limbs will be dangling instead of the usual flexed posture (Fig. 38.2b). The traction maneuver consists of pulling the infant up by his/her hands from a supine position. This maneuver will reveal a head lag if present (Fig. 38.2c). After the neonatal period, these signs will often persist, but delayed motor milestones may also become apparent. The differential diagnosis of hypotonia is broad and may be difficult to filter without the interpretation of specific clues that may point to certain disease categories.

38.10   A Practical Approach to Diagnosis

For infants with hypotonia, it is crucial to determine whether the hypotonia has a central (upper motor neuron) or peripheral nervous system origin. A common misconception is that central hypotonia is synonymous with axial hypotonia and that peripheral hypotonia is synonymous with appendicular hypotonia. Axial and appendicular hypotonia refer to physical examination localization of low tone, whereas central and peripheral hypotonia refer to neuroanatomical localization. In central hypotonia, strength is largely preserved and this becomes apparent when the infant becomes upset. In peripheral hypotonia, weakness is present and may be confirmed by paucity of movement when the infant is upset. Assessing weakness can be achieved even in very young infants by observing the spontaneous movements of the face and limbs, response to stroking the soles, and the ability of sustaining passively elevated arms or legs. Deep tendon reflexes may also hint at the presence of central versus peripheral hypotonia, the former being associated with increased reflexes and the latter with depressed or absent reflexes; however, reflexes may sometimes mislead and thus should be interpreted in the context of other neurological examination findings. As the child grows older, hypotonia is gradually replaced by hypertonia in central nervous system disorders, and neonatal reflexes such as the grasp, Moro, and tonic-neck reflex may persist far beyond the usual age when they extinguish. When these children are held up to assess weight-bearing ability, the legs will be kept crossed (scissoring) and there is plantar flexion of the feet. The elbows are typically flexed, hands are clenched, and the thumb is kept across the palm (fisting position, Fig. 38.2d).

38.10.1   Disorders of the CNS (Cortical, Subcortical, and Cerebellar)

Congenital or acquired disorders of the central nervous system (CNS) account for the majority of the causes of floppy infant syndrome (Table 38.2).

Table 38.2 Disorders of the central nervous system manifesting as floppy infant syndrome

Static encephalopathy
Cerebral dysgenesis/dysplasia: Lissencephaly, holoprosencephaly, Joubert syndrome, pontocerebellar hypoplasia
Perinatal hypoxic/ischemic insult, kernicterus, and intracranial hemorrhage
Congenital infections: TORCH
Genetic syndromes and chromosomal abnormalities: Down syndrome (trisomy 21), trisomy 18, Prader-Willi syndrome, cri-du-chat [5p-] syndrome
Metabolic disorders
Disorders of carbohydrate metabolism: Galactosemia, hereditary fructose intolerance
Disorders of amino acid metabolism: Phenylketonuria, tyrosinosis type 1, sulfite oxidase deficiency, nonketotic hyperglycinemia, argininosuccinic aciduria
Organic acidemias: Maple syrup urine disease (MSUD), methylmalonic academia, glutaric aciduria, propionic acidemia, malonic aciduria, multiple carboxylase deficiencies (defects in utilization of biotin).
Mitochondrial disorders: Respiratory chain and Kreb cycle disorders, Leigh's syndrome, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency.
Lysosomal storage disease: Mucopolysaccharidosis, lipidosis (Gauher type 2, Nieman-pick type A, Tay-Sachs disease), mucolipidosis (sialidosis type II, I-cell disease).
Perioxosomal disorders: Zellweger syndrome, rhizomelic chondrodysplasia punctata.

38.11   Clinical Manifestations

38.11.1   History: Pregnancy, Birth, and Perinatal

A detailed birth history may provide important clues regarding possible causes of central hypotonia. For example, advanced maternal age increases the risk of chromosomal aneuploidies. Other risk factors include maternal fever, infections, or exposure to teratogens; polyhydramnios or oligohydramnios; recurrent abortions or stillbirth; and the presence of any abnormalities on screening ultrasounds.

The duration of pregnancy and the birthweight are also vital statistics. Preterm delivery increases the risk of perinatal hypoxic-ischemic insult. The mode of delivery is important to note, as well as the Apgar scores. When the Apgar score is not available, details regarding whether the baby breathed spontaneously and cried immediately after birth may provide a general idea of the circumstances of birth. Difficulties in sucking and swallowing in the immediate post-partum period are concerning. Whether the baby needed to be admitted to the neonatal intensive care unit (NICU), required mechanical ventilation, or had seizures; and the duration of stay in the NICU and the hospital overall are also salient.

Following the neonatal period, history of delayed motor development and learning disabilities may suggest genetic disorders or structural brain abnormalities. Sustained developmental regression raises concerns for neurodegenerative and metabolic disorders. Seizures may be associated with cerebral dysgenesis, perinatal stroke, hypoxic-ischemic encephalopathy, or chromosomal disorders.

Fig. 38.3 Prader willi
syndrome manifesting with
remarkable floppiness.
Note the characteristic
obesity and small hands

38.11.2 Signs

Altered mental status in a neonate may suggest the possibility of certain diagnoses
such as hypoxic-ischemic encephalopathy, structural brain malformations, or meta-
bolic disorders. Dysmorphic features may suggest the presence of specific genetic
syndromes, whereas skin examination should be performed to identify neurocutane-
ous stigmata. Anthropometry (weight, height, and head circumference) should be
routine. Obesity, small hands and feet, and short stature are features of Prader-Willi
syndrome (Fig. 38.3), whereas microcephaly is common in chromosomal abnor-
malities, brain dysgenesis (e.g., microlissencephaly syndromes), TORCH infec-
tions (except for congenital toxoplasmosis which can present with hydrocephalus),
and other central nervous system disorders.

Ophthalmologic examination may reveal important diagnostic signs. Oculomotor
apraxia is a prominent feature of Joubert syndrome. A cherry red spot raises con-
cerns for an underlying lipidosis, while pigmentary retinopathy is associated with
mitochondrial disease. Ptosis and ophthalmoplegia (or ophthalmoparesis) are found
in neonatal myasthenia gravis, congenital myasthenic syndromes, some congenital
myopathies, and some mitochondrial disorders.

Examination of the chest, cardiovascular system, and abdomen may reveal other
signs of a multi-organ system disease. Neonatal cardiomegaly is a classic finding in
infantile Pompe disease. The presence of hepatosplenomegaly may be associated
with lipidosis (e.g., Niemann-Pick disease types A and C), glycogen storage dis-
ease, and TORCH infections (Fig. 38.4a, d, f).

38.11.3 Spinal Cord Lesions

Spinal cord lesions may arise from damage to the spinal cord during delivery, the
presence of a congenital tumor or dysraphic states (tethered cord and myelomenin-
gocele). Traumatic lesions involve either the lower cervical and upper thoracic cord

Fig. 38.4 (**a**) Floppy infant syndrome due to Niemann-Pick disease. The enlarged liver and spleen are marked. (**b**) Bone marrow showed the characteristic foam cell (arrow). (**c**) Bladder distension associated with hypotonia due to spinal cord injury. (**d**) An infant with Pompe disease (glycogenosis type II). (**e**) Echocardiography showed hypertrophic cardiomyopathy and small left ventricle (LV). (**f**) Cranial computed tomography (CT) scan showing periventricular calcification and brain malformation in congenital cytomegalovirus infection (Fig. 38.3d, e are courtesy of Dr. Elsayed Ali) (Incorporated from Reference [2] with permission)

with breech delivery, or the upper cervical region with cephalic presentation. Mid-forceps extractions with excessive longitudinal traction or rotation may also contribute to injuries.

Children with spinal cord lesions typically present with hypotonia, which may persist or evolve into spasticity, associated with paraplegia or tetraplegia, respiratory insufficiency or paradoxical breathing, bladder distension, impaired bowel control, pyramidal tract signs, and/or a sensory level (Fig. 38.4c). The lower roots of the brachial plexus may be affected, leading to weakness or paralysis of the intrinsic hand muscles. Congenital spinal cord tumors may cause similar clinical syndromes.

Table 38.3 Diseases of the motor unit associated with the floppy infant syndrome

Anterior horn cell
Acquired: Poliomyelitis, West Nile virus, other viral syndromes (e.g., Coxsackie A)
Hereditary: Spinal muscular atrophy (SMA) type 1 (Werdnig–Hoffman disease) and SMA type 2.
Peripheral nerve
Acquired: Guillain-Barré syndrome
Hereditary: Congenital hypomyelinating neuropathy
Neuromuscular junction
Acquired: Transient neonatal myasthenia, botulism
Hereditary: Congenital myasthenic syndrome
Muscle
Congenital myopathies: Myotubular myopathy, nemaline myopathy, congenital fiber–type disproportion, central core disease, multiminicore disease, Salih myopathy
Metabolic myopathies: Glycogenoses types II (Pompe disease) and III.
Mitochondrial myopathies, lipid storage myopathies
Periodic paralysis
Congenital myotonic dystrophy
Neonatal Schwartz-Jampel syndrome
Congenital muscular dystrophies

38.11.4   Diseases of the Motor Unit

Disorders of the motor unit (also known as peripheral nervous system or lower motor neuron disorders) account for 18–47% of the cases of hypotonia in infancy. In these conditions, a significant degree of weakness is associated with the hypotonia. The anatomic localization of these is detailed in Table 38.3.

38.12   Clinical Manifestations

38.12.1   History: Pregnancy, Birth, and Perinatal

Family history, especially the mother's family history, may provide valuable clues regarding the diagnosis. For example, a maternal history of myotonic dystrophy or myasthenia gravis may suggest a potential diagnosis in the infant. Prenatal history is also important. Polyhydramnios is a sign of impaired swallowing, and diminished fetal movements indicate fetal muscle weakness. Such prenatal phenomena may be found in cases of congenital myotonic dystrophy and other congenital neuromuscular disorders. Prenatal screening tests may detect evidence for trisomy 21. Prenatal ultrasound will often detect major brain malformations, including those found in some congenital muscular dystrophies, as well as other abnormalities such as joint contractures that suggest the possibility of arthrogryposis multiplex congenita. At birth, infants with congenital neuromuscular disorders may have impaired respiratory effort, as well as dysphagia.

38.12.2 Signs

Findings on general examination may be very helpful in narrowing the differential diagnosis. For example, glossomegaly and hepatosplenomegaly are found in glycogenosis type II (Pompe disease), as well as cardiac abnormalities.

Patterns of weakness may help to distinguish between various neuromuscular causes of hypotonia. Loss of antigravity movement of the limbs suggests proximal muscle weakness, whereas distal weakness indicates a peripheral nerve disorder. In SMA type 1, respiratory muscles are severely affected and affected infants typically display an abdominal pattern of breathing. Tongue fasciculations also suggest the possibility of SMA, though the absence of this sign does not exclude the diagnosis. Ophthalmoplegia and/or ptosis is found in disorders of the neuromuscular junction (transient neonatal myasthenia, congenital myasthenic syndrome, and botulism), mitochondrial myopathy, some congenital myopathies (e.g., myotubular myopathy), and myotonic dystrophy. Ocular muscles are spared in SMA. Asymmetric ptosis is found in some cases of Salih myopathy [17]. Facial muscle weakness is common in CMD, myotonic dystrophy, certain congenital myopathies (myotubular myopathy and nemaline myopathy), but not in SMA. A pursed-mouth appearance while crying is characteristic of neonatal Schwartz-Jampel syndrome. Asymmetric palsies of cranial nerves VI and/or VII are seen in acquired neuromuscular diseases such as poliomyelitis and diphtheritic polyneuropathy. Facial nerve involvement, when present, is typically symmetric in Guillain-Barré syndrome. Deep tendon reflexes are typically diminished or absent in neuromuscular disorders, but in some cases, they may be preserved, such as in certain disorders of the neuromuscular junction.

Arthrogryposis is common in certain neuromuscular disorders in which weakness develops prenatally. These include congenital myotonic dystrophy, some subtypes of CMD, and a severe form of SMA sometimes referred to as SMA type 0. Ullrich CMD is characterized by a distinct combination of proximal contractures and distal laxity, sometimes accompanied by congenital hip dislocation. Neonatal Schwartz-Jampel syndrome features pectus excavatum, camptodactyly, bowed lower limbs, and talipes.

38.12.3 Systemic Disorders

Some systemic disorders may present with hypotonia, as detailed in Table 38.4.

Table 38.4 Systemic disorders that may manifest as floppy infant syndrome

Endocrine disorders
Hypothyroidism, hyperparathyroidism
Nutritional disorders
Primary: Severe childhood undernutrition (protein-energy malnutrition), rickets
Secondary: Malabsorption syndromes (coeliac disease and cystic fibrosis), AIDS, cardiac disease, renal disease, pulmonary disease (tuberculosis)
Electrolyte disorders: Renal tubular acidosis, marble bone-marble brain disease (type III osteopetrosis)
Connective tissue disorders: Congenital laxity of ligaments, osteogenesis imperfecta, Ehlers-Danlos syndrome, Marfan syndrome, arachnodactyly.

38.13 Investigations

These should be guided by the overall presentation of symptoms and signs. During the neonatal period, especially when encephalopathy or recurrent vomiting is present, the possibility of inborn errors of metabolism should be examined closely. Most inborn errors of metabolism with significant neonatal manifestations are lethal if not treated promptly.

Metabolic screening should typically begin with the measurement of serum concentrations of ammonia, bicarbonate, and pH. Many inborn errors of metabolism cause a metabolic acidosis due to excessive production of ketoacids, lactic acid, and/or other organic anions. Evaluations of blood ammonia with normal serum pH and bicarbonate values are characteristic of urea cycle defects; however, it should be remembered that an upset infant or poor quality of blood sampling may be associated with mild false-positive elevations in ammonia levels. Determination of anion gap $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$ may also be helpful. A high anion gap associated with an elevation in serum ammonia is found in organic acidemias, whereas a normal anion gap and normal serum ammonia are found in aminoacidopathies and galactosemia. Lactic acidosis unrelated to an enzymatic defect may be caused by hypoxemia. When lactic acidosis results from an enzymatic defect in gluconeogenesis or the pyruvate dehydrogenase complex (pre-electron transport chain), plasma lactate and pyruvate levels are increased proportionately (i.e., the ratio is less than 20:1). In mitochondrial diseases due to defects in the electron transport chain, the serum pyruvate concentration may remain normal (<1.0 mmol/L) with an increased lactate:pyruvate ratio of greater than 20:1. Elevation of lactate dehydrogenase (LDH), serum aspartate aminotransferase (AST), also known as glutamate-oxaloacetate transaminase (SGOT), and serum alanine aminotransferase (ALT), also known as glutamate-pyruvate transaminase (SGPT), indicates hepatic involvement in galactosemia, urea cycle defects, aminoacidurias, and organic acidurias. However, it should be remembered that ALT and AST are found in small amounts in skeletal muscle and mild elevations without other signs of liver dysfunction should lead to checking serum creatine kinase level. Other routine blood tests that may be helpful include a complete blood count (for neutropenia and thrombocytopenia seen in organic acidurias), glucose, urea, electrolytes (Na, K, and Cl), creatinine, blood gases, and thyroid function tests. The widespread availability of tandem mass spectrometry (MS/MS) has enabled many countries to establish clinical biochemical neonatal screening programs. In addition to the tandem mass spectrometry, blood spots obtained from newborns on Guthrie cards can also be used to screen for hypothyroidism, biotinidase deficiency, congenital adrenal hyperplasia, and galactosemia using high-throughput fluorometric assays. In suspected cases of nonketotic hyperglycinemia, the diagnosis is confirmed by demonstration of elevated plasma and cerebrospinal (CSF) glycine levels, accompanied by a high glycine CSF/plasma ratio. In organic acidurias, findings on tandem mass spectrometry can be further confirmed by gas chromatography/mass spectrometry analysis of the urine organic acid profile. In countries where a comprehensive neonatal screening program is not available, simple urine screening tests may be used. These include the ferric chloride test (phenylketonuria [PKU], tyrosinosis), the dinitrophenylhydrazine test (PKU, Maple syrup urine disease), the cyanide-nitroprusside test (homocystinuria, cystinuria), Benedict's reagent or Clinitest tablets test (galactosemia), ketones (organic acidurias), and

cetyltrimethyl-ammonium bromide (mucopolysacharidosis). These may provide sufficient evidence for a disorder to justify the initiation of therapy in the appropriate clinical context. Nevertheless, they should never be considered definitive.

Whenever a neuromuscular disorder is suspected, assessment of a serum creatine kinase (CK) should be considered. The serum CK level is usually moderately elevated in congenital muscular dystrophy (CMD) but can range from normal to marked elevation depending on the underlying degree of muscle degeneration. It is also likely to be normal or only slightly elevated in several congenital myopathies with structural abnormality, such as central core disease or nemaline myopathy. In Salih myopathy serum CK is mildly elevated in the first 4 years of life (4 times the upper normal limit) and increases slightly more by 10 years (5.5 times the upper normal limit) [6, 17]. In SMA types 1 and 2 and other neurogenic syndromes serum CK is usually normal but may be mildly elevated, in some cases up to 1000 U/L. As noted above, the serum transaminases ALT and AST may be mildly elevated in muscular dystrophy. Finding an associated elevation of CK will spare the child from unnecessary, hepatic testing, including a liver biopsy.

A routine chest X-ray may sometimes provide helpful diagnostic hints. For example, in congenital myotonic dystrophy diaphragmatic elevation may be present due to hypoplasia of the diaphragm, along with thin ribs that point to the antenatal origin of the condition. The cardiomegaly in the infantile form of Pompe disease (type II glycogenosis) can be apparent on chest X-ray (Fig. 38.5a), as well as the
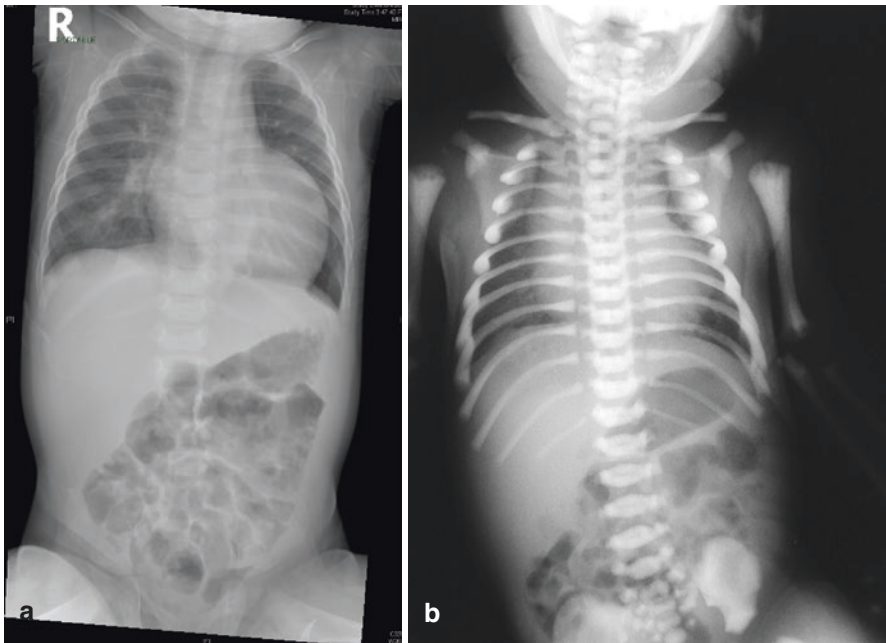

Fig. 38.5 (**a**) X-ray showing significant cardiomegaly and hepatomegaly in a 6-month-old infant with Pompe disease. (**b**) Universally increased bone density in infantile malignant osteopetrosis. The X-ray also reveals cardiomegaly (secondary to severe anemia) and hepatomegaly

radiologic features of rickets and osteopetrosis in the ribs and spine, respectively (Fig. 38.5b). Vertebral anomalies may be seen on chest X-ray in mucopolysaccharidosis, although other types of X-ray studies are more suited to detect such abnormalities.

Electrocardiography (ECG) is very useful in the diagnostic evaluation of possible SMA (Fig. 38.6a), as it may show a characteristic tremor of the baseline, particularly in the limb leads, probably reflecting fasciculations of the underlying skeletal muscle. In the infantile form of type II glycogenosis (Pompe disease), an ECG will often reveal features of hypertrophic cardiomyopathy (Fig. 38.6b), which may be delineated in greater detail on echocardiography (Fig. 38.4d, e).

Bone marrow aspiration and biopsy may show the characteristic cells in type 2 Gaucher disease and Niemann-Pick disease (NPD) types A and C (Fig. 38.4b).
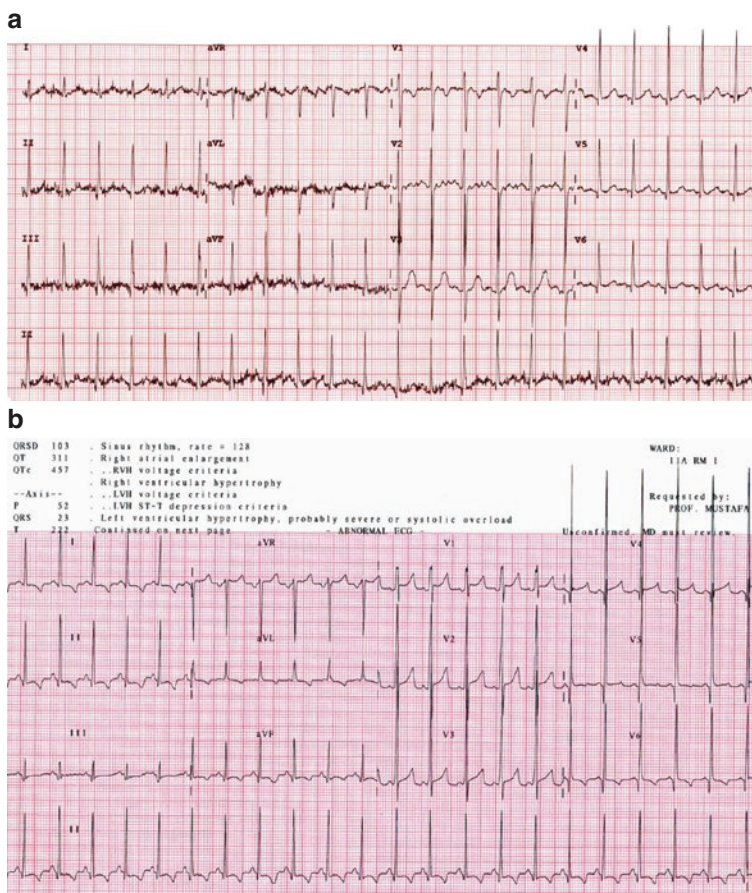
Fig. 38.6 Electrocardiography (ECG) showing (**a**) baseline tremors in SMA type III. These are most prominent in leads I, II and III. (**b**) Biventricular hypertrophy and right atrial enlargement in a 6-month-old infant with Pompe disease

38.14 Neuroimaging

Cranial ultrasound is non-invasive, easy to perform, and less expensive than other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI). Cranial ultrasound may be performed as long as the anterior fontanelle is open. Cystic encephalomalacia, intraventricular hemorrhage, porencephaly, and hydranencepahly may be detected by cranial ultrasound. Cranial computed tomography (CT) is helpful in detecting neonatal intracranial hemorrhage or brain edema secondary to hypoxic-ischemic encephalopathy (HIE), some of the inborn errors of metabolism (e.g., glutaric aciduria type 1), and the presence of lissencephaly. It is also sensitive for identifying intracranial calcifications, as seen in congenital TORCH infections (Fig. 38.4f), isolated sulfite oxidase deficiency (Fig. 38.7a), and marble brain disease with renal tubular acidosis (Fig. 38.7b). Later in infancy, CT may show signs of periventricular leukomalacia, bilateral thalamic
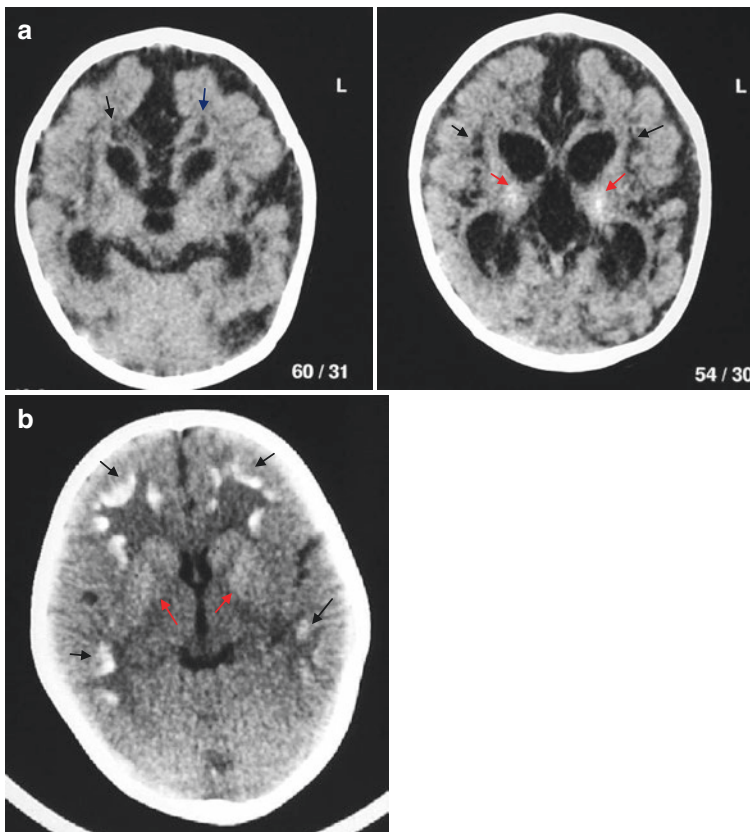

Fig. 38.7 Cranial computed tomography (CT) scans showing (**a**) calcification in both thalami (red arrows) and periventricular leukomalacia in isolated sulfite oxidase deficiency (black arrows). (**b**) Brain calcification in basal ganglia (red arrows) and white matter junction of frontal and temporal lobes on both sides (black arrows) in osteopetrosis with renal tubular acidosis

calcifications that complicate hypoxic-ischemic encephalopathy, and also isolated sulfite oxidase deficiency (Fig. 38.7a). These imaging studies may also show the basal ganglia cavitations that characterize biotin-responsive encephalopathy.

Magnetic resonance imaging (MRI) has a significantly higher resolution for many abnormal findings compared to CT, but costs more and often requires sedation for young children. MRI is the most sensitive modality for characterizing the brain malformations associated with the more severe forms of congenital muscular dystrophy (CMD) such as Walker-Warburg syndrome (Fig. 38.8a). It also delineates the characteristic white matter alterations found in merosin-deficient CMD (Fig. 38.8b), and basal ganglia and brainstem lesions found in Leigh's disease (Fig. 38.8c).
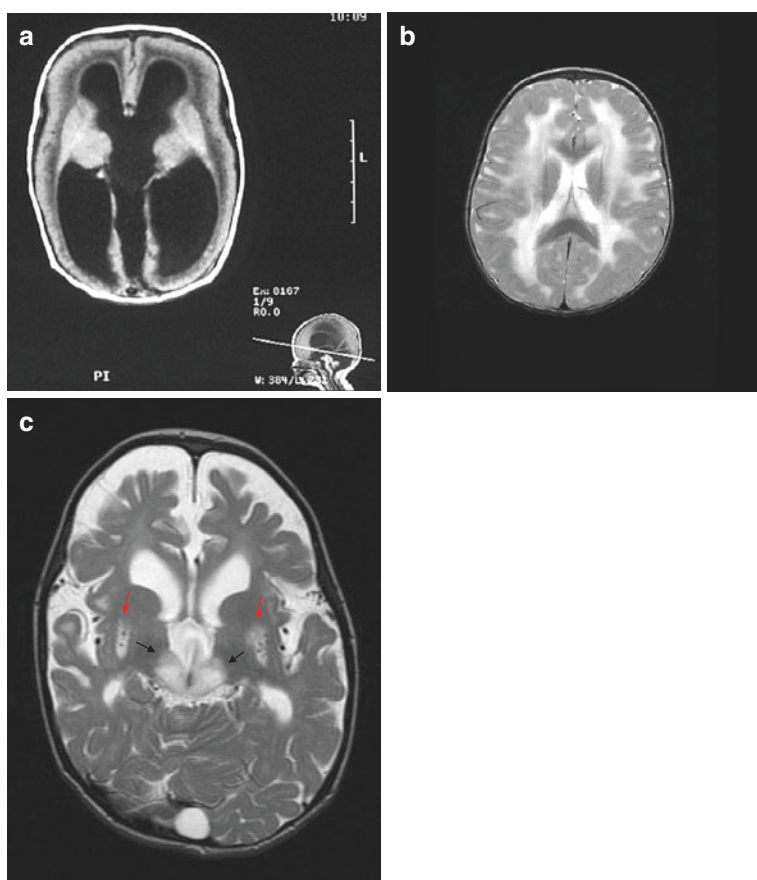

Fig. 38.8 Magnetic resonance imaging (MRI). (**a**) Flair MRI image in a patient with Walker-Warburg syndrome featuring diffuse cobblestone cortex, hydrocephalus and pontocerebellar hypoplasia (shown in the small sagittal image). (**b**) T2-weighted MRI image of merosin-deficient congenital muscular dystrophy, taken at the age of 19 months, showing abnormal periventricular and subcortical white matter signal. (**c**) T2-weighted MRI image of Leigh's disease showing high T2 signal intensity lesions affecting the basal ganglia (red arrows) and brainstem (black arrows). There is also reduced bulk with abnormal high T2 signal intensity of the cerebral white matter

38.15 Neurophysiology

Nerve conduction studies (NCV) and needle electromyography (EMG), often referred to collectively as "EMG," are established and often useful diagnostic test modalities that are especially helpful for the evaluation of possible neuropathies, motor neuron diseases, and myotonic disorders. Specialized electrophysiologic techniques are also useful in the diagnostic evaluation of possible disorders of the neuromuscular junction and some myopathic disorders. EMG has been demonstrated in numerous settings to have immense diagnostic utility in children. However, the approach to testing differs in children compared to adults, and thus children should be examined by physicians and technologists who are experienced with the use of EMG in this age group. The scope and limitations of this testing should be clearly understood by any physician interpreting the data. For example, electrophysiologic myotonia (Video 38.4) is often not present in its classic form in infants with congenital myotonic dystrophy. However, electrophysiologic myotonia can typically be detected in the mother, who is usually affected with or without frank symptomatology. Repetitive nerve stimulation (Fig. 38.1b) and stimulated single fiber EMG are specialized techniques for detecting signs of disorders of the neuromuscular junction. Repetitive nerve stimulation tends to have lower sensitivity but reasonably high specificity, while stimulated single fiber EMG has higher sensitivity but lower specificity. Both techniques require extensive training and the ability to discern artifacts and accurately determine when true abnormal findings are present.

38.16 Muscle Biopsy

Muscle biopsy may provide important diagnostic information in neuromuscular disorders, especially in primary muscle diseases such as congenital myopathies and muscular dystrophies. It is important to remember that muscle biopsy often yields non-specific findings in certain diseases such as congenital myotonic dystrophy and congenital myasthenic syndrome. In congenital myopathies, the specific structural defect is frequently evident on basic histochemical stains; however, in some cases electron microscopy may be helpful, for example, in identifying nemaline rods (Fig. 38.9a). Accumulation of glycogen is seen in various glycogenoses, including Pompe disease, and accumulation of lipid is seen in lipid storage myopathy. Mitochondrial myopathies are characterized by ragged-red fibers (Fig. 38.9b), along with an absence of COX staining (complex IV of the mitochondrial respiratory chain) in the appropriate setting (Fig. 38.9c). Immunohistochemistry may be extremely valuable in determining the absence of specific muscle proteins associated with inherited diseases. Such proteins may include dystrophin (Fig. 38.9d), sarcoglycans (Fig. 38.9e), and merosin, among others. It is important to consider the differential diagnosis with respect to specific muscle disease subtypes, as the precious muscle tissue may be depleted if a large array of immunohistochemical stains are applied indiscriminately.
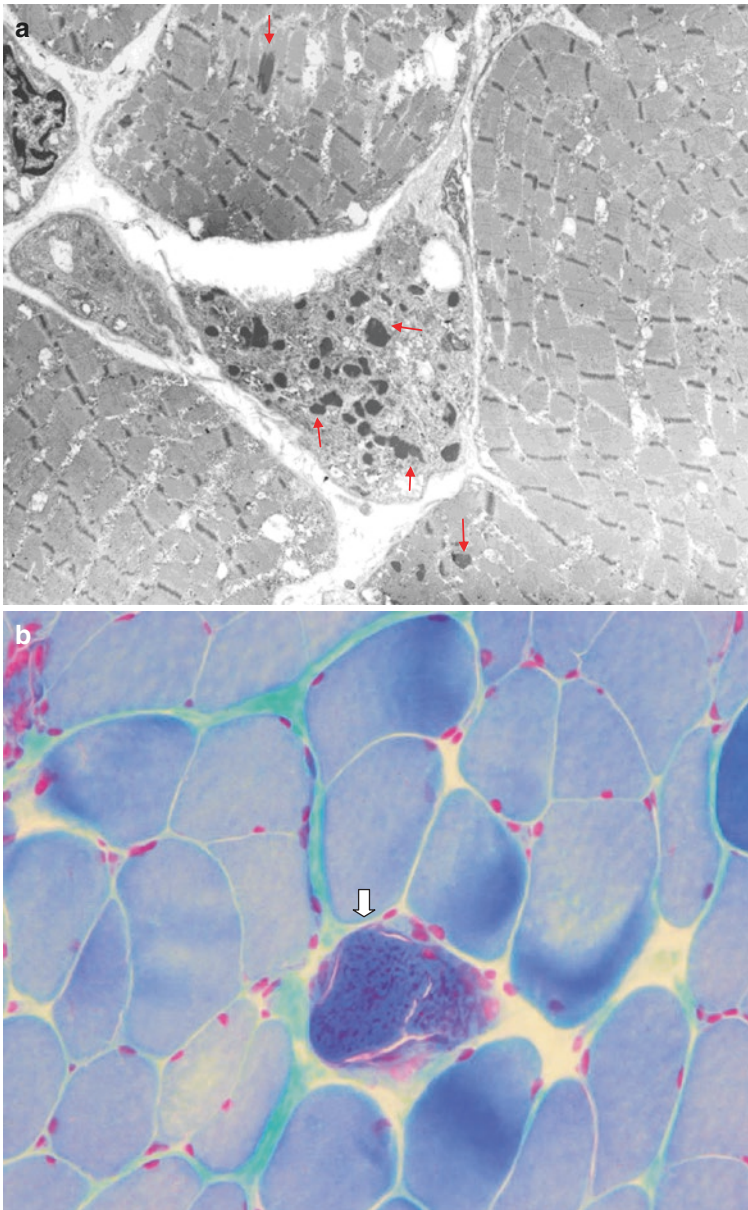
Fig. 38.9 (**a**) Electron microscopic feature of nemaline myopathy showing multiple nemaline rods (red arrows) mainly within atrophic muscle fibrils (magnificationx5000). (**b**) Ragged-red fiber (arrow), which characterizes mitochondrial myopathy, exhibiting a disrupted, red-staining sarcoplasm (Gomori trichrome ×400). (**c**) There is also absence of COX staining (complex IV of the mitochondrial respiratory chain) in the pale-appearing fiber (arrow, COX ×400). (**d**) Dystrophin immunostain (C-terminus) in Duchenne muscular dystrophy showing lack of reactivity of the muscle fibers, whereas (**e**) alpha-sarcoglycan (adhalin) staining (×400) showed clear reactive circumference of the fibers (**b**–**e** are courtesy of Dr. Hisham Alkhalidi)
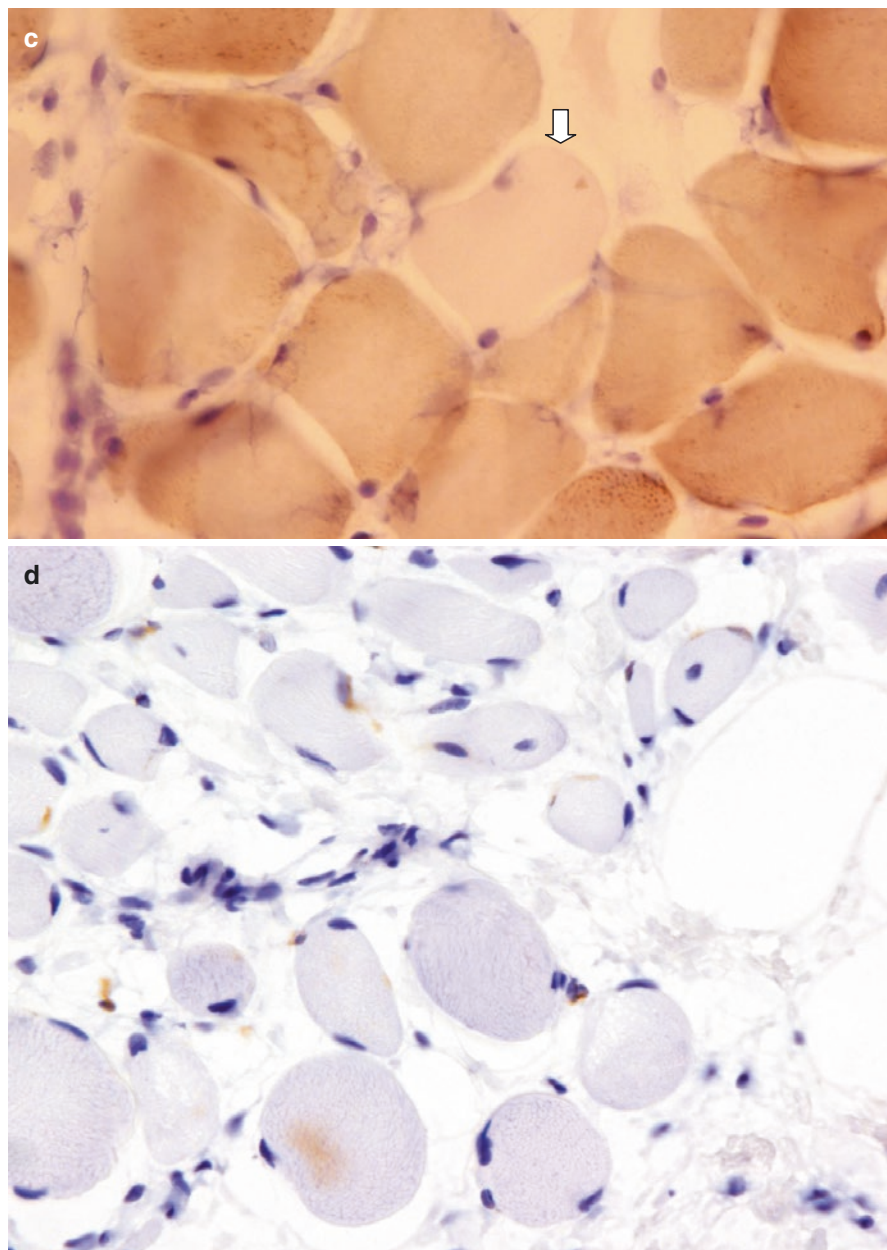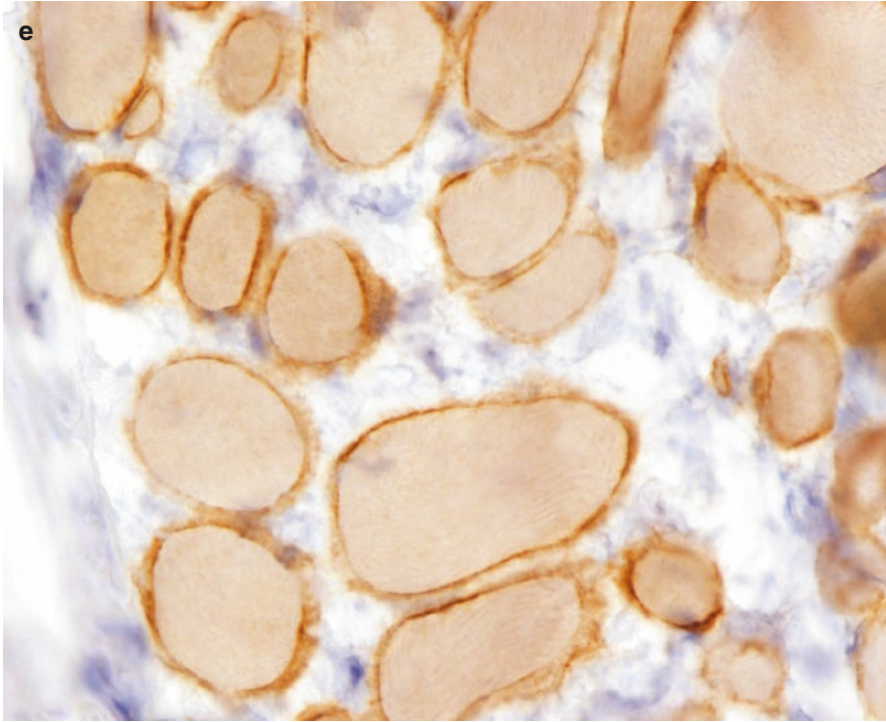
Fig. 38.9   (continued)

Fig. 38.9 (continued)

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