14 Transition of Sleep Care in Patients with Neuromuscular and Neurodegenerative Disorders

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Abbreviations

ACh	Acetylcholine
AChE	Acetylcholinesterase
AChR	Acetylcholine receptor
AD	Autosomal dominant
ADHD	Attention-deficit hyperactivity disorder
AR	Autosomal recessive
BMD	Becker's muscular dystrophy
CDM	Congenital myotonic dystrophy
CLA	Congenital lactic acidosis
CMD	Congenital muscular dystrophy
CMS	Congenital myasthenic syndromes
CNM	Centronuclear myopathies
CP	Cerebral palsy
DM	Myotonic dystrophy
DM1	Diabetes Mellitus type 1
DM2	Diabetes Mellitus type 2
DMD	Duchenne's muscular dystrophy
DS	Downs syndrome
EDS	Excessive daytime sleepiness
GERD	Gastroesophageal reflux disorder
ID	Intellectual disabilities
KSS	Kearns-Sayre syndrome
LS	Leigh syndrome
MD	Muscular dystrophy

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MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
MERRF	Myoclonic epilepsy with ragged red fibers
MIDD	Maternally inherited deafness and diabetes
MNGIE	Mitochondrial neuro-gastrointestinal encephalopathy
mtD	Mitochondrial diseases
mtDNA	Mitochondrial DNA
NARP	Peripheral neuropathy, ataxia, and retinitis pigmentosa
nDNA	Nuclear DNA
NIV	Noninvasive ventilation
NMD	Neuromuscular diseases
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PDC	Pyruvate dehydrogenase complex deficiency
PEO	Progressive external ophthalmoplegia
PLMS	Periodic limb movements of Sleep
PSG	Polysomnograms
REM	Rapid eye movement
SCCMS	Slow-channel congenital myasthenic syndrome
SD	Sleep disorders
SDB	Sleep-disordered breathing
SMA	Spinal muscular atrophy
TNMG	Transient neonatal myasthenia gravis
XLMTM	X-linked myotubular myopathy

Sleep disorders (SD) are commonly associated with neurodegenerative and neuromuscular disorders such as Down syndrome (DS), cerebral palsy (CP), and disorders of the anterior horn cell, neuromuscular junction, and muscles. In this chapter, we will highlight important disease-specific SD in the above-mentioned patients with focus on management and transition of care.

14.1 Neurodegenerative Disease

Several studies have confirmed an increased prevalence of SD in patients with intellectual disabilities (ID) who live at home. Richdale et al. found that SD were more frequent in children with mild-to-profound ID (57.7%) than their non-disabled peers (16%) [1]. Sleep problems include excessive daytime sleepiness (EDS), frequent awakenings, early awakenings, and parasomnias such as teeth-grinding and night terrors [2]. Sleep disturbances are reported more frequently in children and adults with Down syndrome (DS) and cerebral palsy (CP). As these patients also experience neurodegeneration, their brain could be at increased risk to the additional negative effects of obstructive sleep apnea (OSA) such as lower IQ and

behavioral disorders, as OSA appears to have a negative impact on brain function and structure [3].

Down Syndrome (DS)

DS is the most common chromosomal disorder caused by trisomy of chromosome 21 with an incidence of about 6000 births each year [4]. Throughout the years, medical interventions have resulted in increasing their life span from an average of 12 years in the 1940s to an average of 57.8 years for women and 61.1 years for men [5]. Many age-related changes such as reduced DNA repair, increased biological aging, and mortality occur at an earlier age than those without this disorder [5]. In addition to ID, individuals with DS have craniofacial abnormalities such as midface hypoplasia, micrognathia, macroglossia, narrow nasopharynx, small larynx, and hypotonia, leading to floppiness of the upper airways and an increased risk of sleep-disordered breathing (SDB), particularly OSA [6]. OSA is present in 30–55% of children with DS, rising to more than 90% of adults with DS [7, 8]. As discussed earlier, other sleep-related problems occur more frequently in patients with ID including frequent awakenings, difficulty initiating and maintaining sleep, Excessive daytime sleepiness (EDS), and parasomnias.

Screening for sleep disorders and management of comorbidities contributing to OSA should be done throughout childhood and into adulthood. Polysomnograms (PSG) remain the gold standard for diagnosis of OSA and are recommended for all patients with DS by 4 years of age, regardless of symptom history. Marcus et al. found overnight PSGs to be abnormal in 100% of children with DS including OSA (63%), hypoventilation (81%), and desaturation (56%) [7]. Because children and adults with DS do not present with typical signs and symptoms of OSA, screening for SDB should be done annually.

Treatment of should be individualized based on patient's age, developmental status, comorbid conditions, and acceptance to treatment. Options include positive airway pressure (PAP), upper airway surgery (most often tonsillectomy and adenectomy), dental appliances, nasal steroids, oral leukotriene modifiers, and weight-reduction strategies. Tonsillar adenectomy is the mainstream treatment for children with OSA. Unfortunately, almost two-thirds of children with DS have residual OSA after undergoing adenotonsillectomy [9]. This emphasizes the need for postsurgical PSG and possibly evaluation of the upper airway via drug-induced sleep endoscopy.

Cerebral Palsy

CP is one of the most common childhood disabilities with an occurrence rate of 2–2.5 per 1000 live births [10]. It encompasses a group of permanent, non-progressive disorders of movement, posture, and muscle tone, resulting from cerebral damage. Although it is not a progressive disorder, clinical expression of the disease can change with time as the nervous system matures. Even though it is

primarily a motor abnormality, there are a variety of other symptoms including altered sensation or perception, ID, behavior and language difficulties, seizure disorders, and musculoskeletal complications [11].

SD are commonly found in children with CP (23–46%) when compared to typically developing children (20–30%) [12]. These include difficulty initiating and maintaining sleep, sleep-wake transitions, SDB, sleep bruxism, nightmares, sleep talking, and EDS [11]. Additionally, sleep deficiency due to pain, mobility impairment, uncontrolled seizures, and gastroesophageal reflux disorder (GERD) are common [13]. Visual loss commonly seen in CP causes dysregulation of melatonin production, leading to abnormalities in their sleep-wake cycles. This not only negatively affects the child's emotional, cognitive, and physical well-being but also has extensive impact on their families and caregivers.

Early recognition and treatment of SD are imperative in improving their quality of life, cardiopulmonary consequences, seizure control, and neurobehavioral consequences [14]. PSG remains the gold standard for diagnosing OSA with treatment options similar to the general population with PAP, dental appliances, upper airway surgery, and medical management with nasal steroids and leukotriene modifiers. In treating dyssomnias, providers should not overlook other comorbidities such as pain. Some tricyclic antidepressants (amitriptyline, nortriptyline, trimipramine) and serotonin modulators (trazodone) have been studied and proven effective in treating both chronic pain and SD. Gabapentin and pregabalin are also often used to treat CP and dyssomnias [15].

Neuromuscular Disease

Neuromuscular diseases (NMD) are a group of acquired or hereditary disorders caused by a defect in a portion of the lower motor neuron-anterior horn cell, peripheral nerve, neuromuscular junction, or the muscle. These disorders have varying anatomic distribution of weakness, patterns of muscle weakness, rate of progression, and age of onset. Many are multisystem disorders causing abnormalities in the skeletal muscles, smooth muscles, myocardium, brain, and ocular systems. Children often present with infantile floppiness or hypotonia, delayed motor milestones, feeding and respiratory difficulties, frequent falls, or abnormal gait. Adults often present with muscle cramps, loss of strength and endurance, fatigue, breathing difficulties, or bulbar symptoms, relating to speech and swallowing difficulties.

SDB is commonly found in NMDs due to weakness in their respiratory and diaphragmatic muscles, increased risk for obesity starting earlier in life due to loss of ambulation, and other comorbidities such as GERD. Although the rate of respiratory failure varies from disease to disease, physiological changes occurring in rapid eye movement (REM) sleep (intercostal inhibition, loss of accessory muscle tone, reduction in ventilatory drive, and diminished arousal response) result in REM-related SDB, before appearing in non-REM sleep. Most commonly hypoventilation occurs due to decreased tidal volume, but nocturnal desaturations may also present

secondary to sleep-related hypoventilation, apneas, or hypopneas. SDB, including OSA and sleep-related hypoventilation, in NMD is found in 27–62% of children and 36–53% of adults [16]. If not recognized and addressed early, nocturnal ventilatory failure leads to daytime ventilatory failure, causing significant morbidity and mortality.

In addition to respiratory muscle, other factors contribute to disruptive sleep including upper airway and craniofacial weakness, impaired cough mechanism, difficulty with secretion clearance, and limitation of posture causing discomfort due to weakness [16]. Not only is sleep subjectively disrupted, alteration in objective PSG findings includes a decrease in total sleep time, sleep efficiency, and REM sleep with increased sleep fragmentation, arousals, and stage 1 sleep [16]. Depending on the type of NMD, they may present with other comorbidities associated with sleep disorders such as ID, learning disabilities, seizure disorders, and accompanying environmental and psychosocial stressors.

Disorders of the Anterior Horn: Spinal Muscular Atrophy (SMA), Types 1–4

SMA is an autosomal recessive (AR) disorder characterized by degeneration of the motor neurons in the anterior horn cells due to a mutations of the survival of motor neuron gene (SMN1) on chromosome 5. There are four different phenotypes based on severity of disease, age of onset, and maximum motor function achieved (see Table 14.1) [17]. Introduction of new disease-modifying treatments in the pediatric population has reshaped the natural history of the disease, care pathways, and outcomes associated with SMA in adulthood. Ongoing research is needed to develop guidelines for standard of care and advance health policy to ultimately reduce the burden associated with adult SMA.

Sleep disorders in SMA have had increasing attention over the last decade with past research porting sleep apnea and sleep-disordered breathing found commonly in this population. Patients were also found to have abnormal sleep architecture with reduced arousal in those with SMA 1 and SMA 2.

Table 14.1 Classification of SMA [17]

Type	Age of onset	Survival	Maximum muscular function
SMA type 1 (severe)	Before 6 months	Ventilation by 2 years of age	Severe hypotonia and unable to sit or roll
SMA type 2 (intermediate)	6–18 months	Survival until adulthood	Proximal muscle weakness
SMA type 3 (mild)	Early childhood—Early adulthood	Normal	May lose ability to walk
SMA type 4 (adult)	Adulthood (20–30 years of age)	Normal	Mild motor impairment

14.2 Neuromuscular Junction Disease

Currently, we have a very good understanding of how autoimmune processes and genetic disorders affect the neuromuscular junction. In infants and children, they can be either acquired or congenital, causing fluctuating muscle weakness, hypotonia, and fatiguability, either transiently or permanently. Other symptoms are respiratory distress, feeding difficulties, and flaccid tone following delivery.

Neonatal Myasthenia Gravis

Maternal IgG autoantibodies against acetylcholine receptor (AChR) can freely cross the placenta and cause transient neonatal myasthenia gravis (TNMG) in 21% of infants born to mothers who have clinical myasthenia gravis [18, 19] and in some cases may have no symptoms or are in remission [20, 21]. Passively transferred AChR antibodies in some infants did not cause myasthenic symptoms [18], and one case described delayed-onset hypoxia [20]. Usually, the symptoms are transient and resolve after maternal antibody clearance generally after 2–4 weeks. Neonates may manifest difficulties in sucking, swallowing, and respiration, which predisposes them to aspiration and respiratory compromise. Polyhydramnios can also be a sign antenatally [22].

TNMG should be highly suspected in infants with myasthenic symptoms born to a mother with known myasthenia gravis or in remission after successful treatment. In the setting where maternal status is uncertain, a challenge of an acetylcholinesterase (AChE) inhibitor, usually neostigmine and in some cases pyridostigmine [23], may be attempted in an appropriate clinical setting, after which, clinical response is assessed. There are suggestions that repetitive motor nerve stimulation may be a much more reliable diagnostic tool than acetylcholinesterase challenge, especially in the setting of hypoxia and poor respiratory effort [23, 24].

A multidisciplinary supportive approach is of benefit, which includes nasogastric and orogastric feedings and assisted ventilation when necessary. Neostigmine can be given prior to feedings, though side effects such as diarrhea, oropharyngeal secretions, and weakness limit its use. In rare cases, plasma exchange has been used [22] as well as IV immunoglobulins. Disease course may be monitored by nerve studies and serum levels of AChR antibodies. Majority of affected infants will recover with early diagnosis and prompt treatment.

Congenital Myasthenic Syndrome

Unlike the autoantibody nature of TNMG, congenital myasthenic syndromes (CMS) are a rare heterogeneous group of disorders brought about by genetic mutations of proteins in the presynaptic, synaptic, and postsynaptic regions of the neuromuscular junction or defects in protein glycosylation and serine peptidases involved in post-translational protein modification [25]. As a result, there is dysfunction in

neuromuscular transmission, leading to muscle weakness, which is worse with sustained exertion. Most symptoms such as hypotonia, variable eyelid ptosis, bulbar weakness, dysphagia, and respiratory distress are evident during birth, but mild forms may cause symptoms during adulthood. Feeding difficulties and respiratory failure are of concern. Severe episodic apnea has been reported as well as sudden death and anoxic brain injury [26, 27].

The advent of low-cost massively parallel and next-generation DNA sequencing resulted to rapid discovery of the 30 genes currently implicated to CMS [28, 29]. Almost all cases of CMS are inherited through AR pattern, except the autosomal dominant (AD) classic form of slow-channel congenital myasthenic syndrome (SCCMS) [30]. Prevalence in the UK is 9.2 cases per million under 18 years of age [31]. Initial diagnosis includes fatigable exertional weakness pronounced on ocular and cranial muscles, pediatric onset, negative autoantibody testing, and supportive electrophysiologic data [32].

Fortunately, treatment for most CMS are available currently, though extra care should be exercised since some treatment for a certain genetic type may be ineffective and/or detrimental to another such as using pyridostigmine in DOK7, acetylcholinesterase deficiency, and SCCMS. Present approach to therapy is to determine which CMS is responsive to either cholinergic agonists, long-lived open-channel blockers of the acetylcholine receptor ion channel, and beta-adrenergic agonists [32, 33]. Such approach will be dependent on accurate genetic testing. When there is decreased synaptic response to acetylcholine (ACh), pyridostigmine, an AChE inhibitor, and 3,4-diaminopyridine (3,4-DAP) increase ACh in the synaptic cleft. In SCCMS with increased synaptic response to ACh, fluoxetine and quinidine are used as long-lived open channel blockers of the AChR. Beta-adrenergic agonists like salbutamol and ephedrine are adjunctive treatment for CMS due to glycosylation defects, fast channel syndrome, AChR deficiency, and choleacetyltransferase deficiency. Respiratory support, such as noninvasive ventilation, may be needed as all CMS forms can cause hypoventilation. Unlike in TNMG, there is no role for immunotherapy or plasma exchange.

14.3 Disorders of the Muscle

Muscular Dystrophy

Muscular dystrophies (MD) are a group of genetic conditions characterized by muscle weakness and atrophy, each affecting different muscle groups and presenting with onset of symptoms at varying times. In addition to SDB, MDs are strongly associated with SDs including periodic limb movements (PLMS), central hypersomnia, and REM sleep dysregulation, including high REM density and a narcoleptic-like phenotype [34]. In this section, we will discuss Duchenne's muscular dystrophy (DMD), Becker's muscular dystrophy (BMD), congenital muscular dystrophy (CMD), and myotonic dystrophy (DM) (see Tables 14.2 and 14.3).

Table 14.2 Muscular dystrophy [35]

Type	Age of onset	Progression	Affected muscles	Symptoms
Congenital muscular dystrophy (CMD)	Infancy or early childhood (<2 years)	Variable. Can shorten life span	Voluntary muscles	Muscle weakness with possible joint stiffness
Becker's muscular dystrophy (BMD)	2–16 years old. Up to 25 years of age	Slowly progresses Can live into adulthood	Arms, legs, and spine. Can affect cardiac muscles	Weak muscles. Affects males only
Duchenne's muscular dystrophy (DMD)	2–3 years of age	Worsens rapidly. Life expectancy into 30s–early 40s	Proximal muscles then distal muscles. Legs then arms	Muscle weakness Ambulatory stage: Preschoolers who are clumsy, can't climb stairs, run Children: Walk on their toes, waddling gait Early non-ambulatory stage. Wheelchair by 12 years Late non-ambulatory stage. Teens with weakness of arms, legs, and trunk. Require mechanical support Death: 20s–early 30s
Myotonic dystrophy (DM)	DM type 1 ages 0 years to adulthood DM1, mild DM1, adult onset DM1, early childhood DM1, congenital	Slow progression. Decreases life expectancy	Myopathy early adulthood and disabling at age 50 years. Can also affect the central nervous system DM type 1: Facial and distal muscle weakness. Grip myotonia DM type 1, variation (congenital myotonic dystrophy): Global hypotonia, clubfoot	Stiffing and spasms of the muscles. Prolonged muscle contractions (myotonia) and are not able to relax muscles after use Insomnia: Prominent
	DM type 2: 8–60 years	Milder than DM1with normal life expectancy	Proximal muscle weakness. Variable mild grip myotonia	Myotonia present <50% Muscle weakness onset at age 50–70 years. Respiratory muscle weakness is exceptional Insomnia: Infrequent

Table 14.3 Muscular dystrophy and associated sleep disorders [34, 36–38]

Type	Age of onset (years) [37]	Clinical manifestation	Progression	Respiratory and sleep disorders
Congenital	Birth	Birth: Severe hypotonia, respiratory distress/failure, clubbed feet, feeding difficulties Childhood: cognitive defects, motor developmental delay, muscle weakness (distal>proximal), muscle atrophy [37]	Mortality of 30–40% in neonatal period from respiratory failure [39] Mean life expectancy: 45 years [37]	Muscular weakness causing respiratory distress/failure at birth [37] Impaired central respiratory control leading to SDB (OSA, CSA) Hypersomnolence and fatigue
Childhood	1–10	Facial weakness Generalized muscle weakness Recurrent infections (weak cough) Myotonia (first decade of life) Muscular atrophy Cognitive defects Psychosocial issues Incontinence [37]	Mortality: Similar to adult onset Mean life expectancy: 60 years [37]	EDS (50%) in childhood [38] Hypersomnolence and fatigue Features of adult-onset subtype present in adulthood: SDB (OSA, CSA, hypercapnia, hypoxemia) RLS and Periodic Limb Movement of Sleep (PLMS) (38% have PLMS >5/h on PSG [38] REM sleep dysregulation [36] – Increased density and frequency of REM sleep – Narcoleptic-like phenotype with increased Sleeponset Rapid Eye movement Periods (SOREMPs) during time [34]

(continued)

Table 14.3 (continued)

Type	Age of onset (years) [37]	Clinical manifestation	Progression	Respiratory and sleep disorders
Adult-onset	10–30s	Myotonia Muscle weakness Cataracts Conduction defects Insulin resistance Respiratory failure [37]		EDS (70–80%) [Hilton] Hypersomnia (HLA haplotype DRW6-DQW1) [34] SDB (OSA, CSA, hypercapnia, hypoxemia) RLS and PLMS (61.1% had PLMS >5/h on PSG [34] REM sleep dysregulation [36] – Increased density and frequency of REM sleep – Narcoleptic-like phenotype [34] with increased SOREMPs during Multiple Sleep Latency Test (MSLT)
Mild/late onset	20s–70s	Mild myotonia Cataracts [37]		

Congenital Muscular Dystrophy

CMD infants usually have dystrophic features (hypotonia, arthrogryposis, and contractures) within the first few months of life. There are more than 30 different disorders affecting various muscle groups with different ages of onset, severity of disease, and inheritance patterns. Muscle weakness may improve, remain stable, or worsen with time. Some forms of CMD are associated with ID, seizure disorders, and cardiac dysfunction. As disease progresses, all types of CMD develop respiratory failure, and some may be severe at birth. Management for CMD must be individualized to help treat specific symptoms, and ongoing multidisciplinary care is required for optimization of care.

Duchenne's and Becker's Muscular Dystrophy

DMD and BMD are X-linked recessive disorders found exclusively in males. They are caused by reduction or absence of function in the dystrophin protein, particularly in the cardiac and skeletal muscles, leading to muscle weakness. Although they present with similar signs and symptoms, they vary in age of presentation, severity, and rate of progression. DMD is the most common form of MD in childhood with a

prevalence of 4.78 per 100,000 males [40]. Compared to BMD, they present earlier in childhood with signs and symptoms of difficulty walking, calf hypertrophy, and progressive muscle weakness, which rapidly progresses to loss of ambulation and premature death. BMD has a milder in presentation with a prevalence of 1.53 per 100,000 males worldwide [40].

Duchenne's Muscular Dystrophy

Previous studies report SDB (frequency of 31%) in patients with DMD with OSA (31%) in the first decade of life and sleep-related hypoventilation (32%) in the second decade of life [41]. Despite prolonged survival with corticosteroid therapy and noninvasive ventilation (NIV), the major cause of death is respiratory failure, with one quarter of deaths occurring unexpectedly during the night [42]. Patients with DMD also have high rates of ID (17–27%), learning disabilities (26%), autism spectrum disorder (15%), attention-deficit hyperactivity disorder (ADHD) (32%), and anxiety (27%), which are all associated with SDs [43]. Daily care, including the need to be turned by a career associated with immobility, muscular-skeletal pain, medications, and behavioral and psychological problems, also affects their quality of sleep [44].

Evaluation of sleep problems includes assessing for symptoms of fatigue, morning headache, frequent awakening, hypersomnolence, tachycardia, and frequent nightmares. According to the American Thoracic Society consensus statement on respiratory care of patients with DMD (2004), patients should be evaluated by a physician specializing in respiratory care once between ages 4 and 6 years and before they are wheelchair bound. Baseline pulmonary function testing should be obtained, and anticipatory guidance regarding respiratory complications of DMD should be offered. Simple oximetry can be used in the home to screen for sleep-related oxyhemoglobin desaturations, but annual awake CO_2 monitoring and evaluation for SDB should also be performed with PSG and capnography. In areas where PSG with capnography is not available, continuous pulse oximetry and CO_2 monitoring can help provide limited information regarding nighttime gas exchange. Because disorders of maintaining and initiating sleep (30%) are often a side effect of steroid use and disorders of excessive somnolence (11%) are common, a comprehensive clinical assessment of sleep should be obtained at every patient encounter [44].

Interventions for SDB and sleep-related hypoventilation include nocturnal assisted ventilation (preferably NIV) with a backup rate. Assisted daytime ventilation is added when despite nocturnal ventilation, daytime pCO_2 are >45 mmHg or symptoms of dyspnea while awake are present. To decrease the risk of SDB, clinicians should create ongoing nutritional plans to help maintain an ideal body weight. Adaptation of the dosage of steroids should be considered if sleep initiation or maintenance insomnia is present. Medications with central nervous system depressant effects should be avoided due to potential further respiratory compromise. As a replacement, melatonin, in particular the slow-releasing form, may be considered for sleep initiation and maintenance disorders [45].

Myotonic Dystrophy

Myotonic dystrophy (DM), an AD progressive myopathy with myotonia, is divided into two clinically distinct diseases (type 1 DM and type 2 DM), both caused by a repeat expansion mutations. Although there is limited research on DM type 2 (DM2), we know it presents as a milder form of DM type 1 (DM1), with proximal rather than distal weakness and less prominent muscle wasting. Additionally, DM1 includes facial weakness, ptosis, respiratory insufficiency, and a congenital form, which are generally absent in DM2.

DM1 is the most common form of MD in adulthood, affecting about 1 in 8000 people worldwide presenting with varying phenotypes including congenital, early childhood, adult onset, and late/asymptomatic onset [46]. Although adult onset is well understood, congenital and childhood phenotypes require further investigation to help optimize outcomes and develop standards of care. DM1 has prominent propensity to SD including SDB, resulting in nocturnal hypoxia and hypercapnia, PLMS, REM sleep dysregulation, and EDS [34, 47].

Classic adult-onset DM1 is a relatively slow progressing disease with primary symptoms of fatigue. EDS, and SD including PLMS, SDB, and REM sleep disturbances. Prior studies suggest selective loss of serotoninergic neurons of the dorsal raphe nucleus and low cerebrospinal fluid orexin A levels. This may directly affect sleep regulatory circuits in the CNS, causing sleep dysregulation and abnormality in central control of ventilation. As a result, symptoms of EDS that are out of proportion to degree of SDB, fatigue, and REM sleep dysregulation are present. Patients also present with symptoms similar to idiopathic hypersomnia with long, nonrestorative sleep and diurnal sleep episodes [36]. REM sleep dysregulations have been described with sleep-onset REM periods frequently with short sleep latencies found on MSLT and hypocretin CSF deficiency to support the diagnosis of narcoleptic-like phenotype [36]. Like other NMDs, SDB is commonly found with associated nocturnal hypoxemia, sleep-related hypoventilation, OSA, and CSA [34].

Congenital myotonic dystrophy (CDM) is considered the severe early form of "classic" DM1 with a biphasic course, whereby symptoms stabilize in surviving neonates before adult-type symptoms present [37]. Individuals present at birth with severe hypotonia, clubfoot, respiratory weakness, cerebral atrophy, and ventricular enlargement with a high mortality rate from respiratory failure. Those individuals who do survive show gradual improvement in motor function with almost all CDM children having the ability to walk, swallow, and independently ventilate until the third and fourth decade of life, when cardiorespiratory complications arise [48, 49]. Like those who survive CDM, early childhood DM presents first with cognitive deficits and learning abnormalities and then with progressive muscular weakness in early adulthood. EDS is the most common non-muscular-related sleep symptom and reported in 50% of children with DM1 [38]. Patients with mild-/late-onset DM generally have minimal clinical manifestations with myotonia, weakness, and EDS rarely present [37].

Myotonic Dystrophy Type 2

Scarce research has been done on DM2; therefore, little is known regarding the occurrence of SD in these patients. The most common symptom mentioned is pain-induced nocturnal awakenings, and in contrast with DM1, fatigue, not EDS, is a prominent clinical feature of DM2 [50]. The clinical spectrum of DM2 includes similar but milder form of sleep problems as seen in DM1, including SDB, PLMS, RLS, insomnia, and REM sleep dysregulations. More research is needed to help understand the prevalence and pathophysiology of this disease.

Management of DM1 and DM2 emphasizes having a multidisciplinary team to provide supportive care, reduce complications, and optimize health and quality of life [37]. Although muscle weakness in DM1 is rarely progressive in childhood, it is important to provide ongoing therapies to limit and manage complications such as contractures, pain, and scoliosis and to maximize muscle function [39]. Diagnosis of EDS is the same for the general and DM population with thorough assessment using questionnaires, actigraphy, MSLT, and a maintenance of wakefulness testing. Evaluation for SDB includes overnight pulse oximetry testing and PSG with capnography, and treatment remains standard with NIV (continuous PAP or bilevel PAP) with a backup rate. Management of DM2 is similar to DM1 but with less need for supportive care and respiratory needs.

Congenital Myopathy

Congenital myopathy defines a heterogeneous group of congenital muscle disorders characterized by genetic defects affecting skeletal muscle fibers, resulting in generalized muscle weakness, poor muscle tone and bulk, hyporeflexia, and dysmorphic features, with intelligence mostly intact. Symptoms may present subtly or profoundly at birth, in early life, and in rare cases adulthood [51, 52]. The abnormal genes code for proteins, making up the sarcomere or involved in Ca^{2+}-mediated myofibrillar contraction. Different forms are based on predominant pathologic features such as presence of rods or nemaline bodies, oxidation-deprived cores, abnormally located central nuclei, and type I fiber hypotrophy [53]. These may overlap, making classification challenging. Creatine kinase levels are usually normal, though maybe mildly elevated. Electromyography and nerve conduction studies are normal most of the time, except in severe disease. Muscle biopsy is done in specialized centers along with light and electron microscopy for identification of specific subtypes [54]. Genetic testing using parallel, whole exome, and genomic sequencing currently is needed for accurate diagnosis and guide management [55].

Nemaline Myopathy

This group of congenital myopathies is identified microscopically by distinct Z line-derived red rods against a blue-green myofibrillar background with modified

Gomori trichrome staining. Various clinical phenotypes exist and may occur at birth or later during childhood with some reported cases presenting as respiratory failure in adults [51, 52]. Severe congenital cases may manifest as profound generalized weakness and hypotonia in bulbar regions and in muscles of respiration, contractures and fractures at birth, and swallowing difficulties. Childhood-onset symptoms are commonly delayed motor milestones, gait abnormalities, and poor exercise tolerance. A North American and Australian clinical study of 143 patients from infancy to adults reported 17 out of 23 deaths from respiratory failure in infants, 12 of which were ventilator-dependent until death and 30% of surviving group requiring mechanical ventilation during first few months of life [56]. During the same study, ventilatory failure was associated with mortality in the first year of life, but not after. Conflicting electromyography results from patients with nemaline myopathy were reported, showing normal-to-mild myopathic changes in action potentials [57].

At least 12 genes have been identified, and some are still being under investigation due to increasing use of parallel sequencing methods and whole exome and genome sequencing. Inheritance may be either AR or AD, and associated features reported were presence of cores, zebra bodies, fiber-type disproportion, actin accumulation, excess connective tissue, ophthalmoplegia, arthrogryposis, and cardiomyopathy, among many others [58].

No current treatments exist, but patients will benefit from a multidisciplinary approach involving muscle strengthening, mobility exercises, physiotherapy, and regular respiratory assessment and care.

X-Linked Myotubular Myopathy

X-linked myotubular myopathy (XLMTM) is one of the forms of the genetically heterogeneous group of centronuclear myopathies (CNM) whose distinct pathologic features involve one or more centrally placed nuclei, instead of the usual peripheral location brought about by the absence of myofibrils. It has been described as a disorder of muscle development as a result of the expression of pathogenic variants in the MTM1 gene. In an investigation of nine CNM patients, there was persistence of fetal cytoskeletal proteins vimentin and desmin, as well as intracytoplasmic dystrophin, indicating evidence of maturation arrest [59].

While other forms of CNM have AD or AR pattern of inheritance, XLMTM occurs almost in males, is much more common, and has severe phenotypes. Estimated incidence is at 1 in 5000 live male births [60]. The multicenter RECENSUS study reviewed 112 XLMTM patients in 6 sites. They reported a mortality of 44% with 90% of patients requiring respiratory support at birth, spending 35% hospital stay, and requiring an average of 3–4 surgeries during the first year of life [61].

Reduced fetal movement and polyhydramnios are signs of antenatal onset. Infants appear with macrosomia, cryptorchidism, elongated facial features, high-arched palate, and ophthalmoplegia. An Italian cohort during 2010–2014, involving 352 CNM patients, reported 15 patients with the pathogenic MTM1 gene variant. The patients' age ranges from a month old to 45 years old. All except one had

respiratory issues at birth with three requiring tracheostomy during the first year of life and two requiring noninvasive ventilation. Almost all had feeding problems and hypotonia at birth, with about half developing delayed motor milestones and extraocular muscle abnormalities [62].

Clinical characteristics at birth warrant a muscle biopsy showing histopathologic features as well as genetic confirmation of the pathogenic MTM1 variant. As with other congenital myopathies, there is currently no treatment, and care should be focused on optimizing functional capacity and managing medical complications through a multidisciplinary team.

Mitochondrial Disease

Mitochondrial diseases (mtD) comprise a group of inherited or spontaneous nuclear (nDNA) and mitochondrial DNA (mtDNA) mutations, causing defects in oxidative phosphorylation, resulting in impaired adenosine triphosphate production. It is known that proteins of the oxidative phosphorylation must be translated before being imported to the mitochondria and finally inserted into the mitochondrial membrane. Any mitochondrial and nuclear gene mutations may cause defects in the mitochondrial respiratory chain. Additionally, defects in the mitochondrial membrane phospholipid bilayer as well as in the mitochondrial movement, fusion, and division cause failure of the respiratory chain [63–65].

Epidemiological studies in childhood approximate the prevalence of mtDNA disease and minimal risk of developing mtD to be greater than 1 in 5000 and estimate prevalence of pathogenic nDNA mutations at 1 in 35,000 [66]. Primary mtD are the most common inborn errors of metabolism.

PSG changes, periodic movements, and SDB have been observed [67, 68]. Muscular weakness and decreased ventilatory drive to $PaCO_2$ have been elucidated in various case series and case reports as causes of SDB in patients with mtD [69–71]. The prevalence of SDB in patients with mtD has not been clearly defined. A retrospective chart review by Mosquera et al. of 18 patients with mtD aged 1.5–18 years showed SDB in 56% of the sample [68]. Hypotonia ($P = 0.043$) and being overweight and obese ($P = 0.036$) were shown to be significantly associated during the same study.

Manifestations vary and can be limited from isolated myopathy, exercise intolerance, fatigue, or diplopia to more serious multisystem involvement, which can be fatal. High-energy-demand organs such as skeletal, cardiovascular, renal, and endocrine are usually affected, but virtually any organ system may exhibit findings (Fig. 14.1) [72]. Some degree of overlap exists between and among the known phenotypes (Table 14.4) [73]. A retrospective, multicenter cohort in Austria and the Czech Republic consisting of 75 pediatric patients who had either biochemically or molecularly diagnosed mitochondrial disease revealed a predominance of nonspecific encephalomyopathy and Leigh syndrome [74].

The diagnosis of mtD is complicated by varying clinical phenotype, dual genomic origins, and symptomatology as well as the lack of a definitive biomarker. Maternal

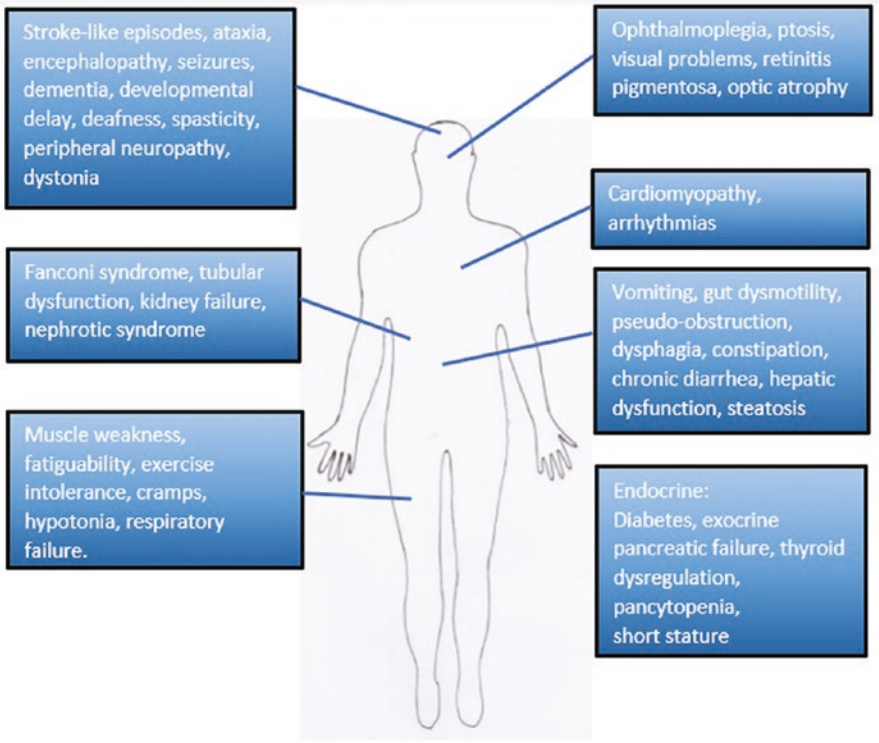

Fig. 14.1 Clinical systemic presentations of mitochondrial disease

pattern of inheritance is a clue that a provider should not miss since the disease is mainly transmitted by females, though diagnostics may not be evident in heteroplasmic mutations. The approach is different between patients who present with classic versus a non-classic phenotype. It is of prime importance to gather an extensive family history that spans 3–4 generations. For multisystem involvement, high-energy-demand organs are prone to be affected though atypical presentations and single-organ disease can range from usual fatigue, exercise intolerance to abnormal eye movements, retinopathy, and cardiomyopathy, among many others. Generally, noninvasive tests such as genetic testing should be considered initially and muscle biopsy be reserved for equivocal genetic testing results or when ruling out other differential diagnosis. In 2014, a consensus statement from the Mitochondrial Medicine Society on the diagnosis and management of mitochondrial disease was released [75].

Next-generation genetic sequencing techniques have revolutionized the way we identify specific mutations underlying mitochondrial dysfunction, which is by far the gold standard for diagnosis as it can test for deletions and duplications of the mitochondrial genome [76]. Although equivocal results of genetic studies necessitate the need for muscle biopsy analysis, the invasive nature of performing open muscle biopsy over percutaneous route is limiting but useful in confirming

Table 14.4 Clinical phenotypes of mitochondrial diseases including pattern of inheritance and signs and symptoms

Clinical phenotype	Pattern of inheritance	Onset	Signs and symptoms
Alpers syndrome	Autosomal recessive	Youth	Neurodegeneration Seizures Hepatopathy
Congenital lactic acidosis (CLA)	Multiple etiologies	Youth	Lactic acidosis Seizure Infection Organ failure
Kearns-Sayre syndrome (KSS)	Sporadic, maternal, autosomal dominant, or autosomal recessive, mtDNA and nDNA	Youth	Retinitis pigmentosa External ophthalmoplegia Short stature Cerebellar ataxia
Leber's hereditary optic neuropathy	Maternal (mtDNA)	Young men	Bilateral acute loss of central vision
Leigh syndrome (LS)	nDNA and mtDNA	Infancy or early childhood	Seizure Blindness External ophthalmoplegia Psychomotor regression Hearing loss Dementia Ataxia Hypotonia Lactic acidosis
Maternally inherited deafness and diabetes (MIDD)	Maternal (mtDNA)	Third and fourth decade	Insulin dependence Sensorineural hearing loss
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)	Maternal (mtDNA)	Variable	Stroke-like episodes Seizures Migraines Diabetes Hearing loss Psychiatric problems Dementia
Mitochondrial neuro-gastrointestinal encephalopathy (MNGIE)	nDNA, autosomal recessive	First to fifth decade	Early satiety Nausea Dysphagia GERD Postprandial emesis Episodic abdominal pain Diarrhea Neuropathy
Myoclonic epilepsy with ragged red fibers (MERRF)	Maternal (mtDNA)	Childhood	Dementia Generalized epilepsy Ataxia Myopathy Optic atrophy

(continued)

Table 14.4 (continued)

Clinical phenotype	Pattern of inheritance	Onset	Signs and symptoms
Peripheral neuropathy, ataxia, and retinitis pigmentosa (NARP)	Maternal (mtDNA)	Youth	Sensory neuropathy Seizures Dementia Lactic acidosis
Progressive external ophthalmoplegia (PEO)	Maternally (mtDNA)	Any age	Bilateral ptosis
Pyruvate dehydrogenase complex deficiency (PDC)	nDNA, X-linked, autosomal recessive	Youth	Hypotonia Psychomotor retardation Seizures Lactic acidosis

diagnosis and ruling out other causes. Histochemical stains, traditionally Gomori trichrome stains, aid in visualizing the subsarcolemmal and intermyofibrillar accumulation of mitochondria, which appears as bright red masses, coined "ragged red fibers," against a blue background of muscle fibers. Other stains such as SDH, NADH-TR, COX, and SDH/COX combination are being utilized by different institutions depending on their availability and operator experience.

In 2014, a systematic review of 1335 abstracts published in the Cochrane Database concluded no clear evidence supporting the use of any intervention in mtD [77]. Management remains as symptomatic interventions and supportive treatment. Noninvasive positive-pressure ventilation is a life-sustaining modality for those suffering from chronic respiratory failure and sleep-disordered breathing [78]. Acute treatment of stroke and seizures is a priority especially in patients with MELAS. A multidisciplinary approach that includes speech, physical and occupational therapy, genetic counseling, and nutritional support needs to be coordinated [73, 79, 80].

14.4 Conclusion

With the advancements in medicine, individuals with neurodegenerative and neuromuscular disorders have longer life expectancy leading to a larger population of adults with health issues related to their premature aging, neurocognitive disabilities, and neuromuscular weakness. This highlights the importance of future research, aiming to further evaluate neurocognitive outcomes, characterize OSA, and improve treatment efficacy for these patients. There is a need to provide ongoing evidence-based, specialized care to this vulnerable population, who are at risk for medical conditions at an early age that are otherwise low risk to the general population.

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