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Core myopathies – a short review

Haluk Topaloglu

Yeditepe University Department of Pediatrics, İstanbul, Turkey
Correspondence Haluk Topaloglu Yeditepe University Department of Pediatrics, İstanbul, Turkey. E-mail: htopalog@hacettepe.edu.tr

Conflict of interest

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Abstract

Congenital myopathies represent a clinically and genetically heterogeneous group of early-onset neuromuscular diseases with characteristic, but not always specific, histopathological features, often presenting with stable and/or slowly progressive truncal and proximal weakness. It is often not possible to have a diagnosis on clinical ground alone. Additional extraocular, respiratory, distal involvement, scoliosis, and distal laxity may provide clues. The “core myopathies” collectively represent the most common form of congenital myopathies, and the name pathologically corresponds to histochemical appearance of focally reduced oxidative enzyme activity and myofibrillar changes on ultrastructural studies. Because of the clinical, pathological, and molecular overlaps, central core disease and multiminicore disease will be discussed together.

Key words: core myopathies, central core, multiminicore, malignant hyperthermia

Introduction

The scope of this short review is pure core myopathies: central core disease and multiminicore disease often associated with mutations in the skeletal muscle ryanodine receptor 1 (*RYR1*) and selenoprotein N1 (*SEPN1*; also known as *SELENON* according to new nomenclature).

Mutations in the skeletal muscle ryanodine receptor 1 (*RYR1*) gene are associated with dominantly inherited central core disease and subgroups of recessively inherited multiminicore disease, centronuclear myopathy (CNM), and congenital fiber type disproportion. Malignant hyperthermia susceptibility trait is a dominantly inherited allelic trait and is described as a pharmacogenetic predisposition to severe and potentially life-threatening reaction in response to halogenated anesthetic agents and depolarizing muscle relaxants.

RYR1-related malignant hyperthermia susceptibility is allelic to central core disease and has also been described as a common cause of induced and episodic phenotypes such as exertional rhabdomyolysis or periodic paralysis, which present throughout life. Late-onset presentations in the adulthood period highlight relevance of the congenital myopathies for adult neuromuscular practice.

A number of distinct phenotypes are seen in multiminicore disease, which is most commonly caused by recessive mutations in the *RYR1* and *SEPN1* genes. It has been linked to dominant mutations in the gene for beta-myosin heavy chain protein (*MYH7*) and autosomal recessive mutations of titin (*TTN*). Recessive mutations of satellite cell gene (*MEGF10*) are defined in patients with early-onset myopathy, areflexia, respiratory distress, and dysphagia (EMARRD) [1].

Central core disease is probably the most common form of the congenital myopathies[2]. Recessive *SEPN1*-related minicore myopathy is the second most common core myopathy[3]. The exact prevalence of the condition is unknown. In prevalence study of congenital myopathies in a representative pediatric United States population, overall point prevalence of congenital myopathies was 1 out of 26,000, with mutations in *RYR1* being the most common cause of congenital myopathies at 1 out of 90,000 [2].

History

In 1956, Magee and Shy described "a new congenital nonprogressive myopathy" characterized by a distinctive microscopic appearance on skeletal muscle biopsy[4]. It was the first recognition of the congenital myopathies, the diagnosis of which was based on the distinct structural or histochemical changes in biopsied skeletal muscle, as a distinct group of diseases.

This disorder was then named central core disease [5], and an absence of oxidative enzyme and phosphorylase reactivity in the cores were demonstrated on muscle biopsy in these patients [6].

In 1971, Engel and colleagues described a patient with multiple small cores within muscle fibers [7], which were later renamed as "multicores," "minicores," "focal loss of cross-striation," "target-like lesions," and "miniature cores;" multiminicore disease is now the preferred terminology [8].

Clinical manifestations

There is a wide clinical spectrum of core myopathies, with severity ranging from mild to severe. Hypotonia, joint laxity, developmental delay in motor milestones, hip girdle or axial weakness, and congenital hip dysplasia may be among early clinical presentations. Arthrogryposis represents the severe end of the spectrum. There may be a variability even within the same family; some of the individuals being asymptomatic and others presenting with hyperCKemia, exertional myalgia, rhabdomyolysis or periodic muscle stiffness, and paralysis (Fig. 1).

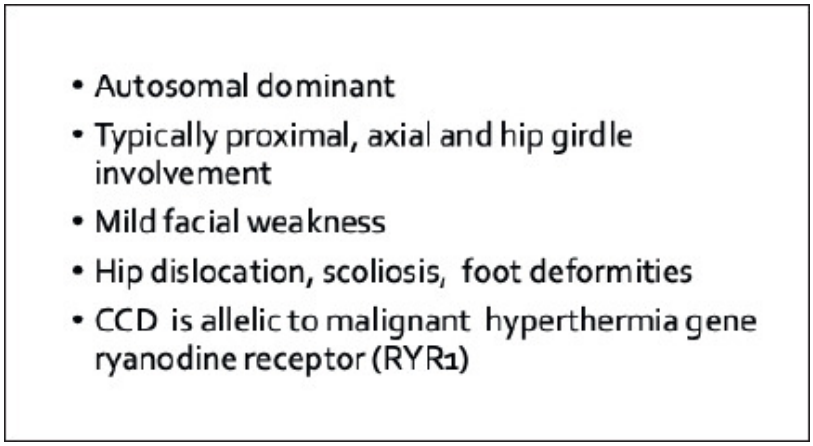

Figure 1.

Central core disease (CCD).

Typical central core disease patients present with mild and symmetrical weakness, hypotonia, and delayed motor milestones, and although late, patients achieve independent ambulation. The course is usually nonprogressive or slowly progressive. Patients presenting with severe neonatal weakness, arthrogryposis, and respiratory failure require early respiratory support and corrective scoliosis surgery. More significant respiratory muscle weakness is seen in infants with recessive core disease [9]. Extraocular muscles are spared in the dominant forms. Because of musculoskeletal deformities including congenital hip dislocation, kyphoscoliosis, pes cavus, pes planus, and thoracic deformities, patients are frequently referred from orthopedic clinics. Heart disease is not considered as a part of the typical "core myopathy" spectrum. Some cardiac abnormalities described include mitral valve prolapse, arrhythmias, and asymptomatic right bundle branch block[10]. Intelligence is generally normal in central core disease.

Genetic resolution of core myopathies in recent years further lead to "mutation-specific" clinical presentations and phenotype-genotype correlations. Availability of next-generation sequencing (NGS) techniques lead to improved detection rate for mutations and expanded the clinical spectrum [3,11].

Central core disease is associated mainly with dominant *RYR1* mutations, and multiminicore disease is genetically a more heterogenous condition [12].

Dominantly inherited *RYR1*-related central core disease is characterized by mild to moderate muscle weakness presenting from infancy to childhood. Congenital hip dislocation, scoliosis, and generalized joint laxity are common. In contrast to the recessive forms with a more severe clinical phenotype, there is no extraocular muscle involvement. Bulbar, respiratory, and cardiac involvement is uncommon. Myalgia may be prominent. Central core disease tends to be stable over long periods with a possible progression in adulthood, and due to intrafamilial variability, there may be a delay in diagnosis [13].

Malignant hyperthermia is a disorder of calcium metabolism. Central core disease is associated with an increased risk of malignant hyperthermia. Most patients with malignant hyperthermia have normal muscle biopsy features, and less than 30% of the patients with central core disease have malignant hyperthermia susceptibility [14]. Two well-known malignant hyperthermia-related syndromes are King-Denborough syndrome and Native American myopathy (NAM).

The association between malignant hyperthermia and central core disease patients was first described in 1973 and has since been confirmed in many other reports [15,16]. King-Denborough syndrome is characterized by facial and skeletal dysmorphism, malignant hyperthermia susceptibility, and myopathy. All genetically solved patients to date are due to *RYR1* mutations.

Native American myopathy is characterized by mild facial dysmorphism, skeletal abnormalities, and mild extremity weakness. All individuals to date are from Lumbee Native Americans in North Carolina, with recessive mutations in *STAC3*, coding a protein regulating excitation-contraction coupling [1,17].

In a retrospective cohort study including 277 pediatric and adult patients referred for malignant hyperthermia and inherited myopathies, *RYR1* mutations were detected in 77 unrelated patients with a detection rate of 28%, and exertional rhabdomyolysis phenotype was prominent in this Dutch series [18].

RYR1-related malignant hyperthermia susceptibility is allelic to central core disease, and some patients with central core disease may also have malignant hyperthermia susceptibility. Exertional rhabdomyolysis and periodic paralysis may present throughout life [3]. Late-onset presentations in the adulthood period highlight relevance of the congenital myopathies for adult neuromuscular practice (Fig. 2).

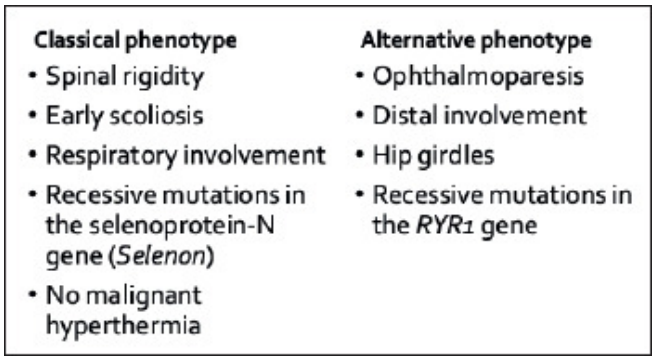

Figure 2.

Multi-minicore disease.

Multiminicore disease is a clinically heterogeneous disorder. Four major clinical subgroups are recognized [4,8]. Core phenotype due to *SEPN1*-related myopathies can be defined as predominant axial weakness, early spinal rigidity, scoliosis, and respiratory involvement. There is a disproportion between axial and skeletal muscle weakness. This is the most common (approximately 75% of all cases) "classic" form, which presents in the neonatal period or first year of life. Affected infants are hypotonic and weak and have delayed motor development. Some children have associated congenital abnormalities such as cleft palate, dislocated hips, or arthrogryposis [19]. Physical examination reveals generalized hypotonia, joint hyperlaxity, and asthenic phenotype with decreased muscle bulk. Short stature and failure to thrive are common in children with significant weakness. Intelligence is normal. Weakness in the classic form is predominantly axial. The neck flexors are usually the most affected muscles, with poor or absent head control in infancy being characteristic of this disorder. There is mild to moderate weakness of the proximal limb muscles. Facial weakness is common but of variable severity, whereas the extraocular muscles are spared. The deep tendon reflexes are absent or diminished. Extremity weakness may be static or slowly progressive or may even appear to improve

slightly with increasing age. Paraspinal rigidity and kyphoscoliosis frequently lead to early-restrictive respiratory dysfunction with progressive respiratory insufficiency, which may be rapid in onset. Weakness and spinal deformity are usually static after adolescence. Because limb weakness is often relatively mild, most patients are ambulant well into adulthood, even in the presence of significant respiratory compromise. Up to two thirds of patients with the classic form of minicore disease develop respiratory insufficiency in late adolescence or early adulthood [8]. Cardiac involvement is usually in the form of cor pulmonale secondary to respiratory insufficiency, rather than primary myocardial involvement. About 50% of cases of "classic" multiminicore disease are caused by recessive mutations in the *SEPN1* gene [20].

The moderate form of multiminicore disease with hand involvement is relatively rare (fewer than 10% of all cases) and is characterized by relatively mild distal weakness of the upper limbs with hand amyotrophy and marked joint hyperlaxity. The lower extremities are mildly affected with proximal pelvic girdle weakness. Scoliosis and respiratory involvement are minimal or absent [8,18].

Fewer than 10% of cases of multiminicore disease are of the ophthalmoplegic form, in which there is external ophthalmoplegia in addition to proximal limb weakness [21]. This form of minicore disease may be associated with recessive mutations in *RYR1* [22].

There is a huge phenotypic variability in multiminicore disease. Spanish kindreds with a dominantly inherited distal myopathy with weakness of the great toe and ankle dorsiflexors and often associated neck flexor, finger extensor, and mild facial weakness were found to have minicore myopathy caused by the common mutation in the *MYH7* (beta-myosin heavy chain protein) gene, which is more commonly known to cause Laing distal myopathy [23]. A report described 2 kindreds with minicore disease caused by dominant mutations in *MYH7*, presenting in childhood with proximally predominant weakness with progression in adulthood to distal weakness and dilated cardiomyopathy [24].

Recessive mutations of a satellite cell gene (*MEGF10*) are also implicated in multicore disease [25]. Clinical phenotype is characterized by early-onset myopathy, areflexia, respiratory distress, and dysphagia (EAMRDD).

In 2015, a single case with a severe congenital myopathy, ophthalmoplegia, and recessive variants in the gene encoding the alpha-1 subunit of the dihydropyridine receptor (*CACNA1S*) is described [26].

At the beginning of 2020, *TRIP4* mutations leading to loss of the coactivator protein ASC1, which direct binds to transcription factors, have been shown to cause multiminicore disease with a contractural phenotype [27].

Prognosis and complications

The course is static or slowly progressive in most central core disease patients. Involvement of the respiratory muscles may be of insidious onset and may remain subclinical until unmasked by intercurrent illness or anesthesia. Lung function should be monitored with serial pulmonary function tests, and where indicated, polysomnography. Cardiac complications are uncommon, but baseline electrocardiography and echocardiography are appropriate in most cases of suspected myopathy. Children should be monitored for the development of scoliosis and other skeletal deformities [28]. Many patients with central core disease are at risk of developing malignant hyperthermia during a general anesthetic. As the first exposure to trigger substances elicits an event in only 50% of malignant hyperthermia susceptibility patients, a previous history of tolerance of halogenated anesthetic agents or depolarizing muscle relaxants does not guarantee that these agents can be used safely in future anesthetics. Appropriate anesthetic precautions should be taken in all instances [28].

Minicore myopathy follows a variable course. In many patients, the condition remains benign with static or slowly progressive weakness of the extremities and retention of independent mobility. In some, spinal rigidity becomes a clinically predominant feature in late childhood or adolescence. Severe progressive scoliosis is apparent in a minority. Surgical fixation of the spine is required in most such cases. Minor contractures of the elbows, knees, and hips may develop after infancy and are generally amenable to physiotherapy.

Progressive scoliosis or respiratory insufficiency is seen in up to two thirds of patients with the "classic" form of multiminicore disease, although the ability to walk independently is often preserved even in adults with respiratory failure. There is a marked discrepancy between profound respiratory impairment and preserved ambulation [4]. Mortality from multiminicore disease is usually related to complications of respiratory disease. Mortality related to cardiac involvement is uncommon but has occasionally been reported [16,24].

Pathogenesis

Central core disease is caused by mutations in the *RYR1* gene on chromosome 19q13.1. The *RYR1* gene encodes a protein product, the calcium release channel ryanodine receptor (RyR1), which is highly expressed in skeletal muscle sarcoplasmic reticulum, B lymphocytes, and lymphoblastoid cells [29].

The *RYR1* gene is large (containing 106 exons), rendering genotype-phenotype correlation difficult. Mutations in the ryanodine gene can be identified in more than 90% of patients with central core disease when all parts of the *RYR1* are carefully sequenced [30]. Mutations causing central core disease and malignant hyperthermia cluster to 3 regions of the *RYR1* gene. Approximately 50% of patients with clinical evidence of a myopathy and central cores on muscle biopsy have a mutation in region 3 in exons 93 to 104 of *RYR1* [31]. Recessive *RYR1* mutations may cause a marked decrease in sarcoplasmic reticulum calcium release during excitation-contraction coupling [32].

Central core disease has traditionally been regarded as an autosomal dominant disease with variable penetrance. De novo mutations are relatively common [31]. The new mutation rate is estimated to be about 10%.

Autosomal recessive inheritance of central core disease has been recognized in a number of families [33,34]. Recessive central core disease links to *RYR1* but demonstrates more clinical and pathologic heterogeneity than that is seen with dominant inheritance. Protein expression studies variably suggest a correlation between specific mutations, protein levels, and phenotype. Recessive core disease may be more common than has previously been recognized.

The pathological hallmark of central core disease is the presence of well-demarcated cores (round or oval shaped regions within a muscle fiber that lack oxidative enzyme activity on histochemical stains) within type 1 muscle fibers (Fig. 3). There is usually type 1 fiber predominance, which may be most marked in those with *RYR1* mutations at the C-terminal [30]. Cores usually extend along most or all of the length of the fiber. There may be 1 or more cores within a fiber. Although the biopsy may show other myopathic features such as fiber size variability, increased internal nuclei, and fiber splitting, the presence of cores as the predominant pathological feature in the biopsy establishes the diagnosis of central core disease. Necrosis and significant fiber regeneration are uncommon, but extensive fibrosis and fatty infiltration are seen occasionally [35].

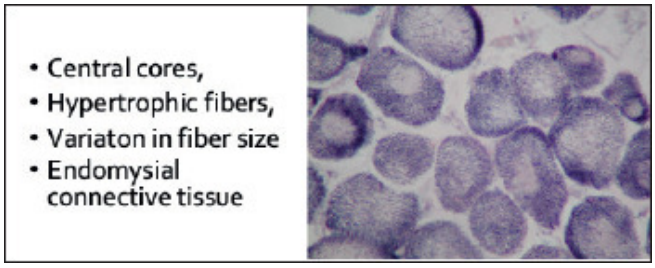

Figure 3.

Central core disease muscle biopsy findings (courtesy of Dr. Beril Talim), NADH staining.

Cores may be centrally or eccentrically placed and, in a minority of cases, may resemble minicores, raising the possibility of the separate but related disorder minicore myopathy, which is generally autosomal recessive in inheritance. In such cases, microscopic evaluation of cross sections may not distinguish between central core disease and multiminicore disease, whereas longitudinal sections reveal the cores of central core disease to run the whole length of the fiber (Fig. 4). Those of multiminicore disease are usually shorter and are seen in both type 1 and type 2 fibers. Diagnosis is also difficult in the small number of patients whose muscle biopsy demonstrates uniformity of type 1 fibers without cores. This entity, now known as congenital neuromuscular disease with uniform type 1 fiber and *RYR1* mutation (CNMDU1), is caused by mutations in *RYR1* in 40% of cases [36].

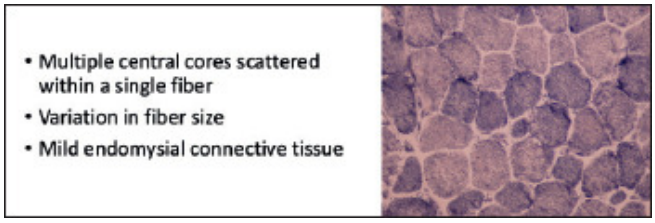

Figure 4.

Multiminicore disease biopsy findings (courtesy of Dr. Beril Talim), NADH staining.

Desmin (an intermediate filament protein found in muscle fibers) reactivity, detected by an indirect immunofluorescence assay, is abnormal in cores [37]. Accumulations of desmin are seen in many other myopathies. Myotilin, a Z-disc protein that binds alpha-actinin, gamma-filamin, and F-actin, is also present in central cores [38]. Immunocytochemistry is helpful in demonstrating cores but shows no other specific abnormalities in central core disease [35].

Electron microscopic examination of cores shows an absence of mitochondria, the anatomical correlate to the loss of oxidative enzyme activity in histochemical reactions [39].

Muscle MRI may help to define distinct pattern of involvement and can be used as a potential biomarker for disease severity in neuromuscular conditions [40].

Selenoprotein N, a glycoprotein, localizes to the endoplasmic reticulum and is found at low levels in virtually all body tissues. Selenoprotein N mutations have also been implicated in myogenesis, with work suggesting a possible role in muscle sarcomeric organization and myofiber attachment [41]. *SEPN1* mutations cause 40 to 50% of cases of classic minicore myopathy [20].

Mutations in 2 genes are responsible for approximately 50% of cases of minicore disease. In a study from Italy, mutations of *SEPN1* represented 6% of congenital muscular dystrophy patients [42].

Recessive mutations in the gene for *SEPN1* account for 30% of all multiminicore disease and represent 40 to 50% of all “classic” form (20). Homozygous mutations of the same gene were originally described in congenital muscular dystrophy with rigid spine (rigid spine muscular dystrophy) [43], an entity that is now felt to represent severe “classic” minicore myopathy presenting in early childhood [33].

Minicore myopathy is described in subjects with mutations in *MYH7*, a gene for beta-myosin heavy chain protein usually associated with Laing distal myopathy [23,24,44]. Weakness in such cases may be of childhood or adult onset, may be proximally or distally predominant, and may be associated with an adult-onset cardiomyopathy.

Diagnostic work-up

The traditional approach to the diagnosis of a congenital myopathy is combining detailed clinical and family history with physical examination findings in order to recognize clues to clarify a phenotype. The International Standard of Care Committee for Congenital Myopathies provides a diagnostic approach and highlights the fact that other than muscle biopsy investigations are rarely specific for congenital myopathies but are widely used to exclude other possible diagnoses. Evaluation of muscle biopsy is important; however, one should also keep in mind the overlap and morphological abnormalities seen in these conditions, marked variability in their clinical progression, and severity [45].

Serum creatine kinase is usually normal or mildly elevated.

Electromyography (EMG) and nerve conduction studies (NCS) are useful to exclude denervation disorders. EMG is typically normal or shows myopathic features, with short-duration, small-amplitude, polyphasic motor unit potentials.

Muscle imaging (ultrasonography and MRI) may be useful in diagnosis demonstrating a characteristic pattern of selective muscle involvement, which may be used in conjunction with clinical features to guide genetic testing. Muscle biopsy and analysis of muscle histology, histochemistry, immunohistochemistry, and ultrastructure by light and electron microscopy (EM) have been the mainstay of reaching the diagnosis of a specific form of congenital myopathies [46].

From a few laboratories worldwide offering diagnostic mutational screening, there is a shift in paradigm, from invasive procedures to the new era of NGS strategies [47]. Cost-effectiveness and increasing availability of these techniques in different centers give the opportunity to directly perform molecular analysis.

Diagnostic work-up finally includes molecular genetic testing. In a patient with a phenotype consistent with core myopathy first *RYR1* mutations, minicore myopathy first *SEPN1* mutations and second *RYR1* mutations should be screened. In case of associated cardiomyopathy, *MYH7* and *TTN* analysis is recommended [46].

Whole-exome sequencing and whole-genome sequencing approaches, wherever available, may help diagnosis in a cost-effective way [46].

Management

Core elements of treatment include physical therapy, orthopedic interventions, management of respiratory complications, and feeding problems.

Involvement of the respiratory muscles may be of insidious onset and may remain subclinical until unmasked by intercurrent illness or anesthesia. Respiratory function should be monitored with serial pulmonary function tests, and where indicated, sleep studies.

Cardiac complications are uncommon in central core disease, but baseline electrocardiography and echocardiography are appropriate in most cases [16].

Children should be monitored for the development of scoliosis and other skeletal deformities. Scoliosis may develop quickly and may be of a severity disproportionate to that of limb weakness. Congenital dislocation and dysplasia of the hip require orthopedic treatment. Gamble and colleagues reported a higher number of treatment failures and hip contractures after surgery in children with central core disease than in other myopathies [48].

Because malignant hyperthermia susceptibility is common in central core disease, all patients subjected to general anesthesia require preoperative anesthetic consultation and planning to ensure that a nontriggering anesthetic technique is used. Individuals with multiminicore disease are usually able to care for themselves in all activities of daily life. Schooling is unaffected. A regime of physical therapy wherein muscle strength is maintained, and range of motion preserved is generally appropriate. Minor contractures of the elbows, knees, and hips may develop after infancy and may respond to physical therapy or splinting. Surgical release is rarely necessary.

One study examined the effect of salbutamol, a beta-2 agonist, on effect on muscle strength in central core and minicore disease. Five children with minicore myopathy (average age 13.6 years) received 2 mg salbutamol orally 4 times a day for 6 months. One stopped the medication because of tremors and palpitations. The other 4 completed 6 months of therapy, at the end of which, they reported improved stamina and had a small but significant improvement in strength measured by myometry and MRC scores, and in their vital capacity, relative to baseline [49].

The 2 major complications of multiminicore disease are the development of progressive kyphoscoliosis and progressive deterioration of respiratory function. Monitoring of spinal growth is important, especially during growth spurts. Given the possibility of “malignant” kyphoscoliosis, it is advisable to obtain a surgical opinion as soon as kyphoscoliosis becomes evident, and early spinal operation should be considered in those with progressive respiratory involvement [50]. The possible predisposition to malignant hyperthermia should be kept in mind in all patients with multiminicore disease [51].

Respiratory function should be monitored in all affected children, but especially those with significant scoliosis and spinal rigidity. The degree of respiratory insufficiency seen in minicore disease is often disproportionate both to the extent of peripheral weakness and to the severity of scoliosis, and in those with significantly diminished reserve, there is potential for life-threatening decompensation of respiratory function with intercurrent illness. Polysomnographic evaluation should also be undertaken in order to evaluate for subclinical nocturnal hypoventilation.

Evaluation of cardiac function, in the form of a clinical assessment, ECG, and echocardiogram, should be undertaken at baseline and in patients with progressive skeletal weakness or respiratory insufficiency. Cardiac involvement in multiminicore disease is most commonly in the form of cor pulmonale as a sequela of progressive respiratory failure, but occasional cases have been associated with primary cardiomyopathy [52,53].

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