13. Myotonic dystrophy type 1

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Summary. Myotonic dystrophy type 1 (DM1) is a distal myopathy and a multisystem disease occurring with an incidence of 1/8000, as a result of a CTG trinucleotide repeat expansion in the serine-treonine-protein kinase (DMPK) coding gene on chromosome 19q13.3. In DM1 patients the length of the CTG expansion ranges from 50 to 4000. Disease severity correlates with repeat length and the phenomenon of genetic anticipation is frequent. DMPK mRNA disturbs splicing of pre-mRNA of a vast number of other genes coding for chloride channels, insulin receptor, muscle and cardiac troponine T, tau protein etc, resulting in a multisystem character of the disease. DM1 patients often exhibit cataracts (>80%), cardiac disturbances (up to 90%), respiratory failure, central and peripheral nervous system dysfunction, endocrine and other disturbances. These patients often present with apathy, hypersomnia, dysexecutive syndrome, visuo-spatial deficit and attention disturbances. Brain MRI in DM1 patients frequently demonstrates diffuse white matter hyperintense lesions, while voxel-based morphometry shows marked reduction of both white and grey matter.

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Introduction

Myotonic dystrophy type 1 (DM1) or Steinert’s disease is an autosomal dominant, slowly progressive multisystem disease, clinically presenting with muscle wasting and weakness, myotonia, cataracts, cardiac conduction defects and arrhythmias, endocrine, gastrointestinal and respiratory disturbances, as well as peripheral and central nervous system involvement (1). DM1 is the most frequent form of muscular dystrophy in adults with a prevalence of 1 to 20/100000 in Caucasian population (1). DM1 is caused by CTG trinucleotide repeat expansion in the 3’ untranslated region of the myotonic dystrophy protein kinase (DMPK) gene on chromosome locus 19q13.3 (2). Normal individuals have 5 to 37 CTG repeats in the DMPK gene, while patients with DM1 have 50 to 4000 CTG repeats (3). Longer CTG repeat expansions are associated with a more severe disease (3) and earlier age at onset (4, 5).

Molecular genetic mechanisms in DM1

It is broadly accepted that the basic mechanism of DM1 pathogenesis is the formation of toxic RNA which is considered to compromise processing of various pre-mRNAs and that reduced expression of the DMPK gene and neighboring genes such as SIX5 and DMWD is of less significance.

Due to increased CTG repeat size in the DMPK gene, transcription results in formation of mutant RNA (6). Mutant RNA containing expanded CUG repeats accumulates in nuclear inclusions, the so called RNA foci (7), subsequently interfering with RNA-binding proteins, particularly the transcription factors and splicing regulators such as muscleblind-like-1 (MBNL1) (8). Therefore, aggregated mutant RNA has a toxic gain-of-function effect (9).

MBNL1 protein sequestration in RNA foci reduces its activity in the nucleus (10). Conversely, increased steady-state levels of CUGBP1 protein due to hyperphosphorylation by different kinases has been demonstrated in DM1 patients (6). Reduced MBNL1 activity and increased CUGBP1 activity in DM1 results in predominance of embryonic isoforms of various proteins and missregulation of splicing of pre-mRNA of a vast number of different genes. To date, more than 30 transcripts have been found to be missspliced in DM1 (6); thus DM1 is termed as spliceopathy (11). This mode of inheritance in which mutations in non-coding regions of one gene damage proteins coded by other genes is known as trans dominant inheritance. This phenomenon may account for the multisystemic character of DM1 (8).
Misregulated splicing of pre-mRNA for CLCN1 protein produces dysfunctional transcripts of muscle-specific chloride channels and causes myotonia (10-12). Splicing defects for insulin receptors account for insulin resistance in DM1 (11,13). Cardiac troponin (TNT) in DM1 patients is of fetal type with preferential inclusion of exon 5 which could cause arrhythmogenic cardiomyopathy (11,14). Deranged splicing in genes for tau protein, beta amyloid and NMDA receptor could, in part, explain cognitive disorders, while disruption of splicing in the gene for myotubularin-related protein 1 is speculated to be pathogenetic for muscle wasting and weakness in congenital DM1 (14,15). Missplicing of exon 11 of amphyphysin gene is associated with a myotubular defect, appearance of central nuclei in myocytes and with developmental weakness and hypotonia in congenital DM1 (4). Misregulated splicing of exon 29 for calcium channel CaV1.1 is associated with altered channel conductance and muscle weakness (16).

Splicing defects have also been identified for other muscle proteins such as ryanodine receptor 1 (skeletal), ZASP protein of Z-band, the sarcoplasmic/endoplasmic reticulum Ca\(^{2+}\) ATPase 1 and 2 (SERCA), LIM domain-binding protein 3, myomesin and nonmuscle myosin heavy chain 14 (10,17,18). Splicing defects of MBNL1 protein itself with more frequent isoforms containing exon 7 have also been demonstrated in patients with DM1 (11). A clear clinical correlation for missplicing of other proteins has not been established so far (4), and splicing defects for proteins which could account for some DM1 phenotypic characteristics, such as cataracts and gonadal dysfunction, have not been identified yet (19).

In transgenic DM1 mouse models with over expression of CTG repeats in the DMPK gene, toxic RNA accumulates in nuclear foci with subsequent modification of MBNL1 and/or CUGBP1 protein function and misregulation of splicing events which, in turn, lead to many, but not all clinical symptoms and signs of DM1 (8,10). Over expression of MBNL1 protein in HSA\(^{LR}\) mice with 250 CTG repeats in the DMPK gene reduces myotonia and restores normal splicing patterns for different proteins, but does not improve histological findings in skeletal muscle, suggesting that reduced function of MBNL1 protein is insufficient to cause myogenic defects (20). Interestingly, transgenic mice with five CTG repeats in the DMPK gene and increased levels of CUGBP1 protein, reproduced RNA splicing deficits, and characteristic DM1 phenotype including myotonia, myopathy and cardiac conduction abnormalities in the absence of detectable toxic RNA nuclear inclusions (21). Transgenic animal models with over expression of CUGBP1 protein, as well as knock-out models with MBNL1 or MBNL2 protein deficiency also exhibit altered splicing for various proteins and reproduce DM1-like phenotypes in the absence of toxic RNA nuclear foci (22-24). Recent studies show that other
RNA-binding proteins play a critical role in the pathogenesis of DM1 in addition to the MBNL family and CUGBP1 (21).

It should be noted that inappropriate regulation of alternative splicing is not restricted to myotonic dystrophy since it has been identified in other neuromuscular diseases and in traumatic lesions of skeletal muscle (25, 26).

The DM1 mutation is a dynamic mutation since expanded CTG DNA repeats in the DMPK gene exhibit a marked tendency to further repeat gain in intergenerational transmissions. Mitotic instability results in allelic size heterogeneity in various cells and tissues - somatic mosaicism (27). In addition, the length of CTG repeats shows a propensity to expand through successive generations, termed genetic anticipation, most pronounced in DM1 (28) (Figure 1). This phenomenon is mainly a consequence of meiotic instability of expanded CTG repeats in germ cells (3). Longer CTG repeats lead to earlier onset and more severe phenotype of DM1 (29).

Figure 1. Anticipation phenomenon in one of our DM1 families. Anticipation phenomenon results from increasing CTG repeat expansions in the DMPK gene with transmission to successive generations causing more severe phenotype and earlier onset in offspring.
MDN163 – woman from the first generation with approximately 90 CTG repeats on Southern blot analysis, her only symptom of DM1 was a cataract in her sixties;
MDN164 – daughter of the patient MDN163, with approximately 800 CTG repeats, onset of symptoms at age 25;
MDN165 – son of the patient MDN164, with approximately 1000 CTG repeats and juvenile form of DM1 with onset at age 7 and mental retardation.
DM1 is inherited from both parents with similar frequency with the exception of congenital DM1 which is most often inherited from an affected mother due to the sex differences and instability of CTG repeats in germ cells (30). If the mother has less than 300 CTG repeats, her risk to born a child with congenital DM1 is 10% (31). If the mother has more than 300 repeats, the risk of a congenital DM1 child increases to 60% (31,32). Conversely, mild forms of DM1 with less than 100 CTG repeats are more often inherited from the father. Intergenerational contraction (reduction of CTG repeat length) and reversion (reduction of number of CTG repeats to normal range) occur very rarely and are almost exclusively of paternal inheritance (29).

Only a few cases of congenital DM1 with paternal transmission have been reported (33). It is assumed that males do not normally pass on more expanded CTG repeats (greater than 1000), due to a possible toxic effects of CTG repeats on spermatozoids or negative selection (34).

Clinical features of DM1

In relation to age at onset and number of CTG repeats, DM1 is classified into four categories: congenital DM1, childhood/juvenile onset DM1, adult (classical) onset DM1 and late adult onset (oligosymptomatic) DM1 (35).

Congenital DM1 (cDM1) is the most severe form of the disease (4). These children have more than 1000 CTG repeats (4). The first symptoms appear in the prenatal period as reduced fetal movements, polyhydramnios and various deformities (3). Affected infants exhibit pronounced hypotonia at birth (floppy baby) (1,3). Many of them do not survive infancy due to the weakness of respiratory muscles and respiratory failure (1,3). Children with longer survival exhibit mental retardation of various degree, while cognitive and motor milestones are delayed. (1,3,4). Progressive symptoms similar to those of classical DM1 begin in the second or third decade. Mean lifespan of these patients is approximately 45 years if neonatal deaths are excluded (34).

Childhood/juvenile onset DM1 (jDM1) becomes manifested between ages 1 and 20, and the affected children have 50-1000 CTG repeats. The initial symptoms are not typical for muscular dystrophy; the principal problems are often inadequate functioning in school (36). As in cDM1, progressive symptoms similar to those of classical DM1, appear in the second or third decade. Muscle weakness causes the same degree of physical disability as in severe adult onset DM1 (36).

Adult DM1 (aDM1) is the most frequent form of the disease (4). The onset of disease is between ages 20 and 40, and affected individuals have 50-1000 CTG repeats. Mean lifespan is 48-60 years (34). Three cardinal
symptoms of aDM1 are muscle weakness, myotonia and eye cataract (4). In addition, cardiac disturbances, central nervous system dysfunction, intestinal and endocrine disturbances and skin changes are frequent (4,37).

Late adult, oligosymptomatic DM1 (oDM1) becomes manifested in the late adulthood, most often after age 40. These individuals have between 50 and 200 CTG repeats. Those with 50-99 CTG repeats are most frequently asymptomatic apart from 38% who had cataract as the only manifestation of the disease (34). In patients with 100-200 CTG repeats, myotonia, muscle weakness and hypersomnia are more common (34). Patients with oDM1 have a mean lifespan of over 60 years or a normal lifespan (34).

Muscular manifestations of DM1

The predominant muscular symptoms in DM1 are myotonia and distal myopathy with slowly progressive weakness and wasting (1).

Myotonia represents a delayed muscle relaxation after voluntary (active myotonic reaction) or evoked (percussion myotonic reaction) muscle contraction (Figure 2) and can also be demonstrated on electromyographic examination (electrical myotonia) (28,38). Myotonia may improve or disappear with continuing exercise which is known as the warm-up phenomenon (39).

Electrical myotonia is caused by a high resting membrane potential rendering the sarcolemma vulnerable to depolarizations. It is characterized by high-frequency repetitive muscle fiber discharges with a firing rate between 20 and 80 Hz (Figure 3) (38). The amplitude and frequency of myotonic discharges wax abruptly to a maximum and then gradually wane (crescendo-decrecendo phenomenon), producing characteristic sound of a dive bomber, or, in modern days, an accelerating and decelerating motor engine (38).

Figure 2. Active and percussion hand myotonia in DM1. Upper row images – active myotonic reaction of hand muscles representing delayed relaxation after hand grip; Lower row images – percussion myotonic reaction of hand muscles representing delayed relaxation (adduction of thumb) after percussion of the thenar.
Weakness and wasting of facial, neck and distal limb muscles is typical of DM1. The characteristic *facies myopathica* is caused by weakness and wasting of the facial, levator palpebrae and masticatory muscles (34). Involvement of pharyngeal and laryngeal muscles and the tongue, frequently produces rhinolalia, dysphagia and dysarthria. Weakness and wasting of neck muscles is present from onset of the disease; always prominent weakness and wasting of the sternocleidomastoid muscles gives rise to a characteristic *swan neck*. Distal limb weakness and muscle wasting is initially present. As the disease progresses, proximal muscles are also involved.

**Ocular manifestations in DM1**

Eye cataract is the most common manifestation of DM1 and in some patients remains the only manifestation of the disease (19). Initially, presenile dust-like polychromatic opacification of lens occurs, commonly located in the posterior subcapsular region (Christmas tree cataract) (1,19). As the disease progresses, confluent, and finally total lens opacification appears.

**Otologic manifestations in DM1**

Premature mild to moderate sensorineural hearing loss is noted in over 60% of DM1 patients (40).

**Cardiac disturbances in DM1**

Conduction defects and arrhythmias are the most common cardiac disturbances in DM1 (37,41,42). Cardiomyopathy, valvular and ischemic heart disease are significantly less frequent (37,41).
Conduction disturbances occur in 30-75% of DM1 patients (41,42). The most frequent are the first degree AV block, left anterior fascicular block, left or right bundle branch block, and prolonged QT interval (41-43). Conduction disturbances may progress to complete AV block with a fatal outcome (28,43). Supraventricular arrhythmias are more common than ventricular arrhythmias, although ventricular tachycardia and fibrillation may seriously jeopardize the patient’s life (43).

Structural alterations of the heart are present in approximately 20% of DM1 patients (left ventricular hypertrophy, left atrial and ventricular dilatation, regional myocardial dyskinesia), while heart failure occurs in only 2% (4). Mitral valve prolapse is found in 13% to 40% in DM1 patients (37,44). Histopathological analyses of myocardial biopsy specimens in DM1 reveal fatty infiltration, fibrosis and focal myocarditis (45).

Patients with DM1 commonly have low blood pressure (46).

Cardiac disturbances account for more than one third of all deaths in DM1 patients (43, 44). It should be stressed that cardiac abnormalities are not always correlated with the severity of the disease and the length of CTG repeat expansion (47).

Respiratory complications in DM1

Respiratory complications in DM1 are the result of multiple peripheral and central disturbances (19). Peripheral factors include severe wasting, weakness and myotonia of thoracic wall muscles, pharyngeal muscles and diaphragm and skeletal abnormalities (19). Due to weakness of pharyngeal and esophageal muscles and consecutive dysphagia, aspiration pneumonia is frequent in DM1 patients and can be fatal (19,28). Central factors such as brain stem, hypothalamic and hypophyseal dysfunction, can lead to alveolar hypoventilation, hypercapnia, hypoxemia, sleep apnea and daytime sleepiness (19).

Endocrine disturbances in DM1

The most frequent endocrine abnormalities in DM are insulin resistance and gonadal dysfunction, while the thyroid, parathyroid, hypophyseal and adrenal disturbances are less frequent (19).

Insulin resistance, insulin overproduction and/or glucose intolerance are common (19,48). A few studies have revealed a four-fold greater risk of diabetes in DM1 patients in relation to controls (19).
In 60-80% of men affected with DM1, progressive testicular atrophy with oligospermia is present (49). Almost one half of these men exhibit compensated hypogonadism or primary hypogonadism (49). Tubular (spermatogenic) testicular dysfunction with elevated levels of follicle stimulating hormone (FSH) occurs in 60%, and impotence in two thirds of affected male patients (49).

Reproductive dysfunction in women with DM1 is less specific and appears in 15-20% of patients (43). Complications in pregnancy and labor are more frequent in relation to the general population.

**Gastrointestinal disturbances in DM1**

In 28% patients with DM1 gastrointestinal disturbances are noted before the diagnosis of the muscular disease and a quarter of DM1 patients state that their most severe symptoms were related to bowel function (34). Involvement of striated and smooth muscles of the gastrointestinal tract causes numerous symptoms such as dysphagia, regurgitation, pyrosis, vomiting, early satiety, slow gastric emptying, bloating, abdominal pain, constipation, pseudoobstruction, diarrhea, fecal incontinence and propensity to form gall bladder stones (50).

**Urinary tract dysfunction in DM1**

Urinary dysfunction has been described in DM1 patients (frequent and urgent micturition, urinary incontinence, stress incontinence) and is caused by altered function of affected striated and smooth muscles of the urinary tract (19).

**Skeletal disturbances in DM1**

Various skeletal abnormalities are described in DM1 patients. The most common are cranial hyperostosis, enlargement of paranasal sinuses, deranged craniofacial morphology, sella turcica morphological abnormalities, prognathia and pectus excavatum (28,51).

**Skin manifestations in DM1**

Frontal alopecia is frequent in affected males (34). In addition, pilomatricomas occur both in men and women, most often in the scalp region (52).
Carcinogenesis in DM1

It has been established that patients with DM1 have a twofold greater risk of developing malignancy in relation to the general population (53). The relative risk is sevenfold greater for endometrium, ovary, brain and colon malignant tumors (53).

Risk of anesthesia in patients with DM1

The anesthetic management of patients with DM1 is challenging. General anesthesia in these patients is associated with the possibility of numerous complications. It has never been proven that anesthetic medications cause malignant hyperthermia in DM1, but it is certain that depolarizing muscle relaxants leads to myotonic spasms (54). The sensitivity of these patients to anesthetic drugs increases the risk of respiratory failure (54). In addition, patients with DM1 are at greater risk of paroxysmal arrhythmias and hypotension in response to anesthetic medication and opioids (1).

Peripheral neuropathy in DM1

A vast number of studies have demonstrated electrophysiological and histopathological peripheral nerve impairment in 14% to 54% patients with DM1 (55, 56).

Central nervous system involvement in DM1

Disturbances of the central nervous system have been noted in the earliest descriptions of DM1. These disturbances include cognitive and behavioral manifestations (57).

Post mortem histopathological examination of the brain tissue of patients with DM1 reveals neuronal cell loss in the brainstem nuclei as well as in the cortex and subcortical nuclei (58,59). In addition, eosinophilic intranuclear inclusions have been detected in thalamic neurons, in the substantia nigra and caudate nuclei (58, 60). Neurofibrillary tangles were found in the hyppocampi, entorhinal and temporal cortex, subcortical nuclei and in the infratentorial region. (60). In one of our studies, transcranial sonography showed significantly more frequent hypoechogenicity of the raphe nucleus and altered echogenicity of the substantia nigra in DM1 patients in relation to controls (61).
T2-weighted MR brain images of patients with DM1 reveal hyperintense white matter lesions (WMHL) which are most commonly diffuse and appear in both hemispheres and less frequently occur in the infratentorial regions and basal ganglia (15,62-64) (Figure 4). Voxel-based morphometry (VBM) demonstrates reduction of both grey and white brain matter (62,64). Regional grey matter loss in the frontal and parietal lobes is the most common finding (62-64). Positron emission tomography (PET) scans in DM1 patients have shown reduced glucose metabolism predominantly in the frontal brain regions.

Patients with cDM1 are mentally retarded (1,3,4). In patients with jDM1 and aDM1 cognitive screening tests and intelligence tests show lower scores in comparison to healthy age and sex matched controls, although still within normal range or slightly below the lower limit of normal (1,65,66). One of the most significant neuropsychological findings in aDM1 patients consists of defective executive and visuospatial abilities (64-66). Some authors have described attention, arithmetic and language deficits (65).

Mild depression and marked anxiety with a clear impact on quality of life were found in approximately half of the investigated DM1 patients by several authors (65,67). Others suggest that depression in DM1 patients correlates with their preoccupation with somatic health and that it is not a direct expression of the disease (68). In the last thirty years, several studies have stated that DM1 patients preferentially exhibit a certain personality profile, including avoidant, dependent, depressive, hypochondric, obsessive-compulsive, passive-aggressive and aggressive-sadistic features,
while others have found patients with paranoid, schizotypal and schizoid personality traits (68,69). Daytime sleepiness is very common in DM1 patients and is often reported only by family members and not the patients themselves (64). Fatigue is more frequent in DM1 than in patients with hereditary neuromuscular diseases without cognitive disturbances (70).

**Diagnosis of DM1**

Diagnosis of DM1 is established on the basis of a typical clinical presentation and electromyographic (EMG) findings with a molecular genetic confirmation in the proband or a first-degree relative.

Muscle biopsy is not mandatory for the diagnosis of DM1 (34). Histopathological findings in muscle specimens are typical but not pathognomonic of DM1 (19). These findings include type 1 fiber atrophy, preferential type 2 fiber hypertrophy, markedly increased number of central and/or internal nuclei, ring fibers, polydimensional fibers, sarcoplasmatic masses and general myopathic changes (1,19).

**Differential diagnosis of DM1**

If the result of a molecular genetic testing for mutation in the DMPK gene is negative, genetic analysis for mutation in the ZNF9 gene should be performed, since 1-2% patients with a clinical presentation of DM1 carry a mutation typical of myotonic dystrophy type 2 (DM2) (34).

Myotonic dystrophy type 2 (DM2) is caused by CCTG repeat expansion in the ZFN9 gene on chromosome locus 3q21.3. Affected individuals have 75-11000 CCTG repeats. The onset of DM2 is typically later than DM1, ranging between ages 20-60 (4,28). In patients with DM2 clinical manifestations of the disease are less severe than those in DM1 and prognosis is better. DM2 most frequently presents as proximal myotonic myopathy (PROMM), less frequently as proximal myotonic dystrophy (PROMD) with wasting of proximal muscles in addition to weakness, and least frequently as distal myotonic dystrophy (dDM2) which cannot be distinguished from DM1 phenotypically (4,34). Myotonic phenomena are milder in PROMM than in DM1. Congenital form of the disease has not been described for PROMM and the number of CCTG repeats does not correlate with the severity of the disease. DM2 children often have a smaller number of CCTG repeats than their affected parent, since retraction of CCTG repeats is frequent while anticipation occurs rarely. Nevertheless, this fact should be accepted with caution since the number of CCTG repeats in DM2 tends to increase by even
2000 in an individual within the period of three years, contrary to DM1 where it increases only by 50 to 150 repeats (4,11,28). In contrast to DM1, patients with DM2 often complain of muscle pain and cramps and inspection reveals hypertrophy of calf muscles. DM2 is a spliceopathy, similarly to DM1 (11,28). However, the multisystem character of the disease is less prominent than in DM1, the most frequent disturbances being cataracts, insulin resistance and cardiac abnormalities. Intellectual deterioration is less pronounced in DM2 (4,28). Histopathological examination of muscle biopsy specimens in DM2 reveals predominantly type 2 fiber atrophy, central nuclei and nuclear chains in type 2 fibers in contrast to DM1 where atrophy and central nuclei are typical for type 1 fibers.

Differential diagnosis of DM1 also includes other hereditary diseases with myotonia, the so-called nondystrophic myotonias, such as congenital myotonia with a mutation in the chloride channel gene and congenital paramyotonia and hyperkalemic periodic paralysis with mutations in the sodium channel gene (34).

Schwartz-Jampel syndrome (chondrodystrophic myotonia) is a rare disease characterized by prominent myotonia, short stature, muscle hypertrophy, diffuse bone disease and joint contractures. It is caused by mutation in the gene coding for perlecan, a basement membrane protein.

Some acquired diseases such as hypothyreosis should also be considered in differential diagnosis of DM1. Hypothyreosis may be associated with myotonic phenomena which is known as Hoffmann’s syndrome. Another cardinal sign of DM1 - myopathy, may also be present on EMG examination of patients with hypothyreosis, additionally complicating the differential diagnosis.

**Prenatal diagnostics and genetic counseling in DM1**

Since DM1 is inherited in an autosomal dominant manner with a markedly expressed anticipation phenomenon, prenatal diagnosis of the disease is essential. The most common procedure is molecular genetic testing by analysis of DNA extracted from fetal cells obtained by chorionic villus sampling or amniocentesis in the first trimester of pregnancy (32).

Presymptomatic genetic testing in DM1 is a complex issue due to large variability in clinical expression and age at onset with consecutive vague prognosis (72). On the other hand, individuals carrying a mutation with less than 100 CTG repeats may be asymptomatic, but at high risk of disease transmission to offspring (72). Presymptomatic testing of healthy children is not recommended until they are old enough to understand and voluntarily give an informed consent; consensus holds that the appropriate age for this is 16 (72).
Therapeutic approach in DM1

While still anticipating efficient and safe gene therapy, the treatment of patients with DM1 is restricted to symptomatic therapy and screening for critical symptoms.

Symptom management and screening

The therapy of choice for severe myotonia is mexiletine, given 150-200 mg 3 times daily (73). Mexiletine was found to be effective in a double-blind, placebo-controlled study (73).

According to the Cochrane review article, creatine monohydrate treatment with doses 5-10 g daily for a period of two to six months clearly improved muscle strength and functional performance in patients with muscular dystrophies without significant side effects (74). This review also showed that muscle strength training and aerobics are of no harm to patients with muscular diseases, and may even slightly improve muscle strength in patients with facioscapulohumeral muscular dystrophy (75). It has been demonstrated that mild aerobic exercise may help DM1 patients feel better and improve oxygen consumption.

Wearing adequate shoes, as well as ankle-foot orthotics may be useful in patients with peroneal gait and foot drop (76). In advanced disease, mobility aids and adaptive equipment are needed, including a wheelchair for most severe cases (76).

At least yearly ECG, echocardiographic and ophthalmologic examinations and spirometry are recommended.

Permanent cardiac pacemaker should be implanted in DM1 patients with a HV (Hiss-ventricle) interval longer than 100 ms or AV block of any degree, regardless of the presence or absence of symptoms (77). Implantable cardioverter-defibrillators are indicated in patients with ventricular tachyarrhythmias (77,28).

Monitoring of respiratory function in supine position is essential in order to detect early signs of respiratory insufficiency (76). Respiratory infections should be treated aggressively with antibiotics, and vaccination is recommended (78).

In patients with insulin resistance, glucose intolerance and diabetes, lifestyle modifications such as exercise and a balanced diet are advised. Some patients may require medication including metformin and, in selected cases, insulin (19).
Statins should be avoided in the management of hyperlipidemia since they could cause rhabdomyolysis, muscle pain and weakness, adding to the symptoms of the disease (79).

Gonadal dysfunction can be treated with substitution therapy when necessary (4). Before considering treatment of erectile dysfunction, substitution therapy should be attempted in patients with a low level of testosterone (4). Another option is administration of sildenafil (78).

It is imperative to closely monitor gastrointestinal function in order to prevent the most serious complications such as aspiration and acute colon pseudo-obstruction. Patients with severe dysphagia and frequent aspiration may be candidates for percutaneous gastrostomy (76).

Modafinil at 200-400 mg/daily has been shown to be effective in DM1 patients with daytime sleepiness (28).

Gene therapy

Research on efficacy and safety of gene therapy in DM1 has, so far, been restricted to in vitro and animal experimental models.

Potential gene therapy interventions are targeted towards mutant DNA, toxic RNA, RNA-binding proteins and pre-mRNA which gives the final protein products (80). Targeting DNA repeat expansion would be of greatest therapeutic benefit, although this approach is technically most difficult and, for the time being, remains a theoretical possibility. Potential therapies targeting products of splicing abnormalities are easier to design and implement, however, only a subset of symptoms of this multisystem disease would be treated (80).

Prognosis of DM1

Mortality rate of children with cDM1 reaches 25% in those requiring ventilatory support longer than three months, while the mean lifespan of those who survived infancy is approximately 45 years (34). No precise data as to prognosis of jDM1 exist (34). The mean lifespan of patients with aDM1 is between 48 and 60 years, which is significantly shorter in comparison to the general population (34,81,82). Patients with oDM1 have an average lifespan of more than 60 years and usually do not differ from the general population (34).

Mortality rate in patients with DM1 is sevenfold greater than in the age- and sex-matched general population (81). The most common causes of death are respiratory failure and cardiac disturbances (81,82).

In a recent retrospective study conducted in all patients from our institution hospitalized from 1990 to 2009, average age of death was 56, and
the most frequent causes of death were sudden death (42%) and respiratory failure (29%) (82).

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