

# **Dystrophia Myotonica (DM1) Scandinavian Consensus Program 2008**

Translated from the original document:

***“Dystrophia Myotonica (DM1) Skandinaviskt koncensuspogram 2008”***

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(with support from the Marigold Foundation)

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# 1

## Introduction

At the Brickless meeting in Aarhus in the fall of 2004, a joint Scandinavian reference program on Duchenne muscular dystrophy was presented. The program was the result of a Scandinavian cooperative project with the purpose of presenting common recommendations for the diagnostics and treatment of the disease.

The result was received positively and motivated the Scandinavian participants at the Brickless meeting to take on two additional diseases, myotonic dystrophy and spinal muscular atrophy, where common advice and recommendations seemed necessary.

The work in front of you, the reference program for dystrophia myotonica, is the result of mutual efforts for the purpose of finding basic advice and recommendations, based on science and experience, concerning diagnostics, evaluation, treatment, and care.

Myotonic dystrophy is

- the most common genetic muscle disease among adults
- a systemic disease engaging many organ systems
- a disease within which many complications can be treated
- a disease which should be familiar also to non-neurologists

The work in front of you is dated the spring of 2007 and since the knowledge base is forever changing, we count on regular updates of the material with the help from the authors responsible.

Dystrophia Myotonica occur in both children and adults. The disease profile and the problems associated with the disease are to an extent identical in both groups, but there are also some age-specific complications. We have therefore allowed the text to be introduced by two chapters dealing with adult patients and children respectively. As was the case in the reference program on Duchenne muscular dystrophy, there are then chapters on genetics, various organ manifestations, ergotherapeutic, physiotherapeutic, and neuropsychological aspects along with recommendations regarding dental and oral problems.

The individual chapters are introduced by brief recommendations followed by more detailed background information. The references for each chapter are collected at the end of the document, in chapter 17.

We have chosen to use the term 'dystrophia myotonica' for the disease, with the abbreviation DM, whereby we mean DM type 1, i.e. DM1. Several other spellings occur, but we have tried to use the same terminology uniformly. We could also have used the term Steinert disease or, in analogy with the English, 'myotonic dystrophy', but considering the abbreviation DM1, 'dystrophia myotonica', seems to be the most useful term.

As reference literature within more or less all relevant subject areas, we can mention P.S. Harper's book on myotonic dystrophy, its third edition published in 2001 by W.B. Saunders Co

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June 6, 2007

## 2

### Clinical Profile, Diagnostics, and Evaluation (Adults)

#### Background

The clinical profile of adult-onset DM is most often very typical and only rarely presents a neurologist with diagnostic difficulties. However, difficulties can occur in cases where the DM patient sees other specialists, such as specialists in internal medicine, cardiologists, or eye specialists. A contributory cause to these difficulties is the reluctance among DM patients to complain of or see a doctor about various symptoms, particularly muscular weakness. In many cases, this results in classic DM being diagnosed late.

The age of the onset of the symptoms is very hard to establish, but an average value of approximately 20 to 25 years of age is reported for the entire DM population [1]. As mentioned above, the patients themselves are often reluctant to consult a doctor about their symptoms, so the age at the time of diagnosis can be significantly higher than the actual age of onset of the disease. Many women with DM are diagnosed when they give birth to a child with congenital DM. Nowadays, some cases are diagnosed earlier because of active genetic diagnosis efforts in affected families.

The distribution of **muscular weakness** in DM differs clearly from other muscular diseases. Weakness and muscular atrophy in facial muscles, in temporalis and masseter muscles, are obvious and give DM patients a typical oblong face; in more severe cases, patients may also have a half open mouth. Most DM patients have symmetric, mild to moderate ptosis, which is rarely so severe that it affects the field of vision. There is an early occurrence of marked weakness in the sternocleidomastoideus muscle, which means that the patient cannot lift his/her head while lying down. The extremities are not as badly affected, and symptoms in distal muscle typically occur later – most prominent is a weakness in the distal muscles of the forearm, the small muscles in hands and feet, and the muscles that lift the sole of the foot. This means that most DM patients are able to walk their whole lives. The diaphragm muscle is affected, which leads to reduced breathing capacity [2].

**Myotonia** means a delayed relaxation of activated muscles. Most patients describe it as a “stiffness” and in many cases, they are not aware of myotonia symptoms. Myotonia is most noticeable in the hands, which are clinically examined by asking the patient to squeeze tightly for 2-4 seconds and then relax – if myotonia exists, the relaxation process is slow. Myotonia can also be detected via percussion of the thenar muscle with a reflex hammer, thereby releasing a tonic muscle contraction that often lasts 2-5 seconds. Hand myotonia decreases after a short period of muscle activity [2]. The diaphragm muscle is also affected by myotonia [3], which primarily contributes to the patients’ weak coughing exhalation. Also the tongue is affected by myotonia, which contributes to the patients’ unclear speech.

Several other organs and organ systems are affected, and this will be dealt with in later chapters. The effect on smooth muscles is more marked in DM than in any other muscular disease. The function of the gastrointestinal tract is affected (swallowing, esophagus, delayed emptying of the stomach, diarrhea, sphincter affected) [4, and chapter 8], as is the heart

(conduction disorders [5, chapter 6]), peripheral nerves (sensitivity disorder –rare), endocrine organs (testicle atrophy, insulin resistance, diabetes) [chapter 9], eyes (cataract, retinal degeneration, ptosis) and skin (frontal balding). Half of the patients with DM have levels of serum immunoglobulins that are lower than the bottom reference levels [6]. Skeletal dysplasia (feet, jaw, dentition) is not rare.

**Sleepiness** in various forms is common in patients with DM. This is partly due to the patients' reduced muscle endurance – physiological fatigue – and partly due to the patients' poor condition, brought on by lack of physical activity. Sleepiness, or excessive daytime sleepiness, is common and occurs in 33 % of the patients [7]. Excessive daytime sleepiness manifests itself as the inability to stay awake during the day and/or a need to nap in the afternoon. Excessive daytime sleepiness has weak correlation to the degree of muscular weakness and no correlation to the number of CTG repeats [7]. DM patients also have an increased need for nocturnal sleep [7]. Daytime sleepiness can be treated with Modiodal® (see chapter on treatment). Further, the apathy and lack of initiative in DM patients are often perceived as sleepiness.

While many patients with mild DM have no, or minimal, **cognitive impairment**, it is clear that there are, even among adults, patients with markedly reduced brain function. Symptoms include sleepiness, amotivational syndrome, and reduced cognitive function. These symptoms are progressive and, in many cases of classic DM, the one symptom that constitutes the greatest cause of disability. Via magnetic resonance imaging (MRI) we can detect marked changes in white matter [8, 9] and atrophy [10]. Neuropathological studies have shown changes in brainstem cores in the form of neurofibrillary tangles [11, 12], the same changes that are also seen in patients with Alzheimer's dementia. For details concerning cognitive function and personality changes, see chapter 10.

Patients with DM have an increased risk of narcosis (see chapter 13).

**Pregnancy and delivery** often involve complications. Infections of the urinary tract occur frequently. There is an increased risk of premature birth (19 %) – in most cases caused by polyhydramnios since the child has DM. The delivery itself is often complicated, leading to an increased frequency of Caesarean deliveries (34 %) [13].

## **Prognosis**

There is no easy rule of thumb to describe the course of the disease. Studies have confirmed that those with disease onset during the first year of life (Congenital DM) have marked reduction in cognitive functions and initially extensive – but later milder – muscular symptoms. Patients with onset of the disease in youth or as adults (Classic DM) have, as a rule, muscular symptoms as the major initial problem. Muscular functions decrease with age [14]. Older patients first present with cataracts and have mild, or no, muscular symptoms.

Patients with classic DM also have various degrees of other organ manifestations. These symptoms also get worse but it is not possible to give a detailed prognosis.

Impaired cognitive function is the main reason for DM patients to have lower work capacity than the rest of the population. Studies from Quebec[15], where DM is particularly prevalent, show that only 25 % of men with DM over 16 years of age are in the work force, compared to 74 % of the general population. Corresponding figures for women with DM are 6 %, as compared to 37 % for the general population. Over 20 % of the men with DM and 50 % of the women with DM had never worked.

The life span for people with DM is clearly shortened. The average age at the time of death has been found to be 54 and 53 respectively in two studies [14, 16]. Survival data for patients with classic DM show that 99 % are alive at 25 years of age, 88 % at 45 years of age (versus an anticipated 95 %), and only 18 % at 65 years of age. Heart arrhythmia and sudden death constitute up to 30 % of the deaths in this group, while 43 % died due to respiratory problems.

## 3

# Dystrophia Myotonica in Children

### Recommendations

- Annual check-ups with neuropsychiatricians.
- Close cooperation with other pediatric specialists, such as a cardiologist, gastroenterologist, endocrinologist, ophthalmologist, ear specialist, orthopedist, neuropsychiatrist and others since the children have a complex of problems full of nuances. *((This point should also be tied to chapter 14.))*
- Regular contact with the rehabilitation team.
- Special attention should be paid to the occurrence of neuropsychiatric problems and hypersomnia. Exhaustion and attention deficit disorders can be so extensive that medication should be initiated. Given the risk for arrhythmia, EKG during normal activity and 24-hour EKG should be carried out regularly, especially if treatment with central stimulants is considered.
- A neuropsychological evaluation should be performed before these children begin school, with follow-ups up to several times through the school years, primarily for children who have low intelligence or mild mental retardation since learning disabilities may increase over time. Pedagogical efforts must therefore be adapted over time. *((The need for a pedagogog was expressed but no direct change in the text was suggested.))*

### Background

#### History

Dystrophia myotonica (DM) was for a long time regarded as a disease occurring only in adult individuals. Symptoms of DM in children were mentioned sporadically in articles as early as the 1940s [1]. An overrepresentation of late abortions, stillbirths and increased infant deaths were noted in families with DM, but the problems were attributed to obstetric and social factors. Not until 1960 did Vanier describe the congenital form of DM as a separate form of the disease. During the following decades, several articles were published that contributed to the knowledge and recognition of DM in children. Little by little, it became more obvious that the congenital form of DM is the most severe form of the disease. Survival of children with congenital DM has increased with the expansion of neonatal intensive care, and today most, but not all, children survive.

In 1984, O'Brien and Harper [2] described children with the onset of symptoms prior to 16 years of age, who were not neonatally affected. Some had the typical facial diplegia and mental retardation associated with congenital DM. These individuals were siblings of children with the congenital form. In 1991, Koch et al [3] classified this form of DM as the childhood form, a form of its own, separated from the congenital form of the disease.

DM is a triplet repeat disease, where the trinucleotide CTG is repeated. Several studies have shown a connection between the size of the CTG repeat and the severity of the

disease [3, 4]. The largest mutations are found in the congenital group. However, it cannot be anticipated – for example through fetal diagnostics – which form of DM the fetus has based on the size of the CTG repeat, as there are considerable overlaps between the groups.

The congenital form is, with few exceptions, inherited maternally while the transmission of the childhood form occurs maternally versus paternally in near equal frequency.

It is an often recurring scenario that children with the congenital form are born without the disease being known in the mother despite the fact that she – at the time of delivery – has developed symptoms of the disease. Earlier, before the DM genetic defect was known or tested, the child was often diagnosed when the neonatal specialist shook hands with the mother and detected the typical hand myotonia. The diagnosis was later confirmed with an EMG test of the mother.

## **Clinical Forms of Dystrophia Myotonica in Children**

### **Congenital form**

The symptoms of muscular weakness can occur before birth and are due to a delayed maturity of the muscles. The fetal movements are weaker, contractures develop, and polyhydramnios is frequent. The child's condition at birth is characterized by various levels of hypotonia. In cases with the severe congenital form, the child is markedly floppy.

Joint dysplasia can occur, from talipes equinovarus to flexion contractures in several large joints, as with arthrogryposis multiplex congenita. The breathing insufficiency that often exists when the child does not reach satisfying spontaneous breathing can lead to grave asphyxia, which requires acute treatment with various forms of respiratory support, such as ventilators or CPAP. The respiratory problems are due to several factors, such as weakness in the diaphragm and the intercostal muscles, pulmonary immaturity, and deficient cerebral respiratory control. The condition can also be complicated by aspiration pneumonia. In X-rays, a typical image of a high, right-side diaphragm and thin ribs is present. Facial muscles are also affected, and the typical facial diplegia with a tent-shaped mouth and ptosis can be seen.

The muscular weakness also leads to sucking difficulties. Cardiovascular problems occur, and frequently open ductus arteriosus is seen. When the condition is life-threatening and requires intensive care, the form of the disease is termed severe congenital DM. A milder form of congenital DM with an onset during the infant period has been seen, where the infant has mild feeding difficulties but does not have asphyxia/breathing insufficiency [4].

### **Childhood Form**

With the childhood form of the disease, pregnancy and the neonatal period are uncomplicated. Psychomotor development during the first year of life is normal, but then symptoms begin before 10 years of age. The symptoms at onset are various levels of speech and learning disabilities. The muscular symptoms are less pronounced than in the congenital form, and are most often subtle .

## The Course of the Disease

### Congenital Form

The hypotonia improves gradually, often during the neonatal period. Breathing support can therefore gradually be removed after days or weeks. How long the child needs breathing support is an indication of the prognosis – the longer the treatment, the worse the prognosis.

Neonatally, the facial diplegia entails sucking and swallowing difficulties in addition to effects on the soft palate and esophagus. Neonatal feeding difficulties and the risk of aspiration are handled with tube-feeding. Most children can eventually feed themselves per os (*by mouth*), but some need gastrostomy. This is primarily an issue when there is a simultaneous, lingering chronic respiratory insufficiency.

Smooth muscles in the GI tract can also be affected, and constipation is a very common problem. The combination of weak abdomen muscles, the effect on smooth muscles in the colon, and constipation lead to a great many of the children developing inguinal hernias with a risk of ligation if they are not surgically treated.

The muscles in the urinary tract can also be engaged, with urinary tract infections arising as a result. Many children have frequent infections during their infant and toddler years, with otitis occurring most commonly. Many are treated with transmyringal drainage for any remaining hearing impairment due to conduction disorders.

Joint dysplasia requires early treatment with orthoses and regular physiotherapy. Pes equinovarus adductus joint dysplasia is treated conventionally during the first year using plaster. However, many children will later require repeated orthopedic interventions. The most common interventions are achillotenotomies. Contractures are found to increase over time according to a recently completed study [5]. Scoliosis is not rare and may have to be treated surgically. Muscular strength continues to improve during the early years, then reaches a plateau some time during puberty, and gradually deteriorates thereafter. A great majority of the children become independent walkers, while some may require walking aids. Remaining joint dysplasia can affect ambulatory ability. A few children become dependent on wheelchairs. Muscular weakness increases as the child grows to adulthood. Myotonia is not present during the early years, but arises during the teenage years.

Ductus arteriosus is the most common neonatal heart disease. Most close spontaneously, although some require medical ductus closure and others require sutures. Passing asymptomatic rhythm disorders and valve insufficiency can occur. Heart symptoms normally do not show up during the early years. The occurrence of symptomatic tachyarrhythmia requiring treatment triggered by physical activity has recently been described in patients between the ages of 10-18 years [5].

Signs of cataracts do not occur until closer to 10 years of age and do not require treatment until the child reaches adulthood, although there are a few documented cases where surgical intervention was required. During the early years, however, hyperopia requiring treatment is frequently occurring, as is strabismus.

Mental retardation is very common in the severe congenital form of DM and occurs from an early age [6, 7, 8, 9]. Neuroradiology has shown CNS pathology with ventricular dilation, among other things; these issues have been detected shortly after birth and sometimes even intrauterinely. Corpus callosum hypoplasia is also described, as well as white matter hyperintensity [10]. Much speaks for a prenatal cause of the mental retardation.

The effects of CNS also lead to – in addition to cognitive difficulties – hypersomnia and special behavioral deviations, such as ADHD, hypersomnia, autism and anxiety syndrome [7, 11, 12, 13].

There is an occurrence of excessive mortality in the congenital group. Reardon's study from 1993 shows 20 % mortality during the first month of life. Should the child survive this period, the mortality risk is low until late puberty. After that, there is a 50 % risk of dying before 30 years of age. Cardiac arrhythmia is the main cause of death, which is also the case with the childhood form of the disease and the classic adult form. Cognitive and behavioral problems primarily affect long-term treatment.

### **Childhood Form**

Pregnancy and delivery are normal. The children are born at term with a normal birth weight. The first year proceeds normally; passing mild muscular hypotonia can occur, as well as certain difficulties sucking, but this does not lead to any feeding problems. The children start to walk before 18 months of age, but a certain clumsiness can occur. No joint dysplasia is seen at birth, but it can develop later in childhood.

An indicated effect on the facial mimic muscles does occur, but no marked facial diplegia (facies myopatica) or tent-shaped mouth is seen. Unclear, nasal speech is a very common occurrence; often the children see a speech therapist. Dysarthry, in addition to various levels of learning disabilities, are the difficulties that lead to the diagnosis. Most children show no learning disabilities prior to school start, but these can appear later. The Die-Smulder [14] study shows an average IQ of 71 (range 48-94), where half of the children were of low intelligence (IQ 70-85).

The children have great difficulties with chronic fatigue, mainly after strenuous activities. They are slow and tire easily. Neuropsychiatric symptoms occur also in this group, and some patients get a neuropsychiatric diagnosis before being diagnosed with DM.

Unlike the congenital form, the childhood form of the disease does not show any delayed muscular maturity. Muscular weakness can occur, and distal muscles are more affected than proximal muscles. The weakness slowly gets worse and over time resembles the picture in adults, with weak dorsiflexors in hands and feet. The neck flexors are weak, especially the sternocleidomastoideus muscles; this is also the case in the congenital form of the disease. Myotonia can occur during the toddler years but often there are no symptoms until after the age of 10 [6].

Stomach/intestine problems are common symptoms and resemble those we see in the congenital form, as well as in adults.

The description of the eye symptoms agrees with that of the congenital group. The mortality risk is lower in the childhood form than in the congenital form. Mathieu et al [15] found that the average age at death was 44.7 years while Die-Smulder's study [14] shows an average age of 43.6 years.

## 4

### Differential Diagnosis

The clinical DM symptoms in adults are typical and do not often come with any differential diagnostic problems. In some cases, however, non-neuromuscular symptoms can dominate; in other cases, either muscular weakness or myotonia dominates, resulting in alternative neuromuscular diseases coming into question. Recently, more variants of DM have also been identified and we can probably count on more types being described in the future.

Muscular weakness in DM is of very varying degrees; it is progressive and can be significant. The weakness is distal in arms and legs, but also affects the facial muscles. In Proximal Myotonic Myopathy (PROMM or DM2) [1, 2, 3], the weakness is mainly proximal. Facioscapulohumeral Muscular Dystrophy (FSHD) [4] can be a differential diagnosis with regard to facial weakness and otherwise has a similar distribution of muscle symptoms as in DM1, but here myotonia and other organ symptoms are lacking.

In congenital myotonic diseases [5], the myotonia is usually general. In DM1, the myotonia is more pronounced in the hands. Myotonia is also, an early phenomenon in Myotonia Congenita (MC), unlike DM1. The myotonia in PROMM is discreet and can be clinically lacking even if it can be detected in an EMG test.

PROMM is much rarer than classic DM1. The symptoms are milder and the localization of the weakness also differs. Otherwise the diseases have many similarities, and the treatment and follow-up ought to be similar. Genetic analysis is now available to distinguish this disease from DM1 [6].

DM3 is an even more rare variant and the descriptions are still meager.

**Table 1**

Comparison of characteristics in some different myotonic diseases and FSHD.

	DM1	DM2	MC	FSHD	DM3
Facial diplegia	++	(+)	-	++	(+)
Shoulder weakness	±	+	-	++	+
Myotonia	+	+	+	-	+
Cataract	+	+	-	-	+
Heart effect	+	+	-	(-)	?
Systemic effect	++	+	-	-	(+)
Hereditary	AD	AD	AD/AR	AD	AD
Chromosome	19q	3q		4q	15q
Mutation	CTG-repeat	CCTG-repeat	Point mut	shrinkage	?
CNS	+	±	-	-	+

## 5

# Genetics in Dystrophy Myotonica

### Recommendations

- All cases where DM is suspected should be offered DNA analysis to guarantee the diagnosis.
- Everybody should have access to genetic guidance and study of their family history, testing for hereditary disposition, and information about the possibilities of fetal diagnosis.

### Background

#### Etiology/Mutation Mechanism

The cause of DM1 is a mutation in the gene *DMPK* (OMIM 605377), localized to the long arm of chromosome 19 (19q13.2-q13.3). The gene codes for a protein kinase localized to special cell structures in the heart and skeletal muscles, and is associated with impulse conduction and impulse transfer. In the 3' untranslated part of the gene, there is a DNA sequence with a trinucleotide repeat (a repeat of the three nucleotides CTG). The repeated CTG sequence is transcribed to RNA but is not translated into protein.

In a healthy individual, the number of repeated CTG is between 5 and 35. CTG repeats of higher than 50 are associated with symptoms of DM1. In classic forms of the disease, we often see repeats between 100-300. There is a certain correlation between the number of repeats and the level of severity in the symptoms; in the severe congenital form, the repeats can be 1000-3000.

Repeats between 35-49 are unstable but are not associated with symptoms. CTG repeats higher than 35 tend to expand when gametes are formed, primarily when oocytes are formed. This means that the number of repeats tend to increase with each generation. This is the molecular explanation of the disease showing anticipation.

As of today, we do not fully understand why expanded repeats cause disease. One possible explanation is that the expanded CTG sequence affects the chromatin structure in the region and in that way inhibits the transcription of *DMPK* and other, closely located genes. Another effect is that the mutated RNA molecule is kept in the nucleus and is therefore not translated to protein, which gives a reduced amount of protein kinase in affected individuals. The mutated RNA molecule also seems to interact with other protein splice factors and in that way inhibits their function. The effect of this mutation on several different genes correlates with the fact that so many different organs are affected.

#### Heredity/Repeat Risk

DM inheritance is autosomal dominant with a high level of penetrance. New mutations are probably very rare. An individual who has DM has a 50 % risk of transferring the predisposition for the disease in each pregnancy, and the child will then get the disease.

The level of symptoms is partly dependent on how much the CTG repeats expand. Women with DM1 have a high risk (25 – 30 %) of giving birth to a child with the severe congenital form. If a woman has given birth to a child with the congenital form, the risk increases to 40 % in the next pregnancy. In men with DM1, the risk of having a child with the congenital form is very low, but some isolated cases have been reported.

In certain cases, the trinucleotide repeat can also *contract*, i.e. decrease in size, and a child can then have milder symptoms than the parent. However, this is very rare. It is not unusual that a woman with mild DM is unaware of her disease until she gives birth to a child with the congenital type, and not until then does she get her own diagnosis.

### **Diagnostics**

A diagnosis can be guaranteed with *DNA analysis*. In a *PCR analysis*, the CTG repeat is amplified in the DMPK gene, and CTG repeats of up to 100 can be detected. Southern blot is used to detect higher CTG repeats. DNA analysis is recommended in all cases where DM1 is suspected. Also presymptomatic testing is possible when the family history is investigated.

### **Fetal Diagnostics**

Fetal diagnostics in the form of chorionic villus biopsy (CVB) may be offered to couples where one of the parents has DM1. The risk of the congenital form is high if the expectant mother has the disease. There is a correlation between the size of the repeat and the level of severity of the disease, but this is not absolute. It is therefore difficult to estimate how affected the expected child will be from the size of the repeat. Repeat sizes above 1000 however indicate a congenital form of DM1.

In *preimplantation genetic diagnostics* (PGD), the genetic analysis is done on a 3-day-old embryo before implantation in the woman. Thus, the method requires the couple to go through test-tube conception. This type of fetal diagnostics may be considered in families where the woman has DM1.

### **Differential Diagnostics**

In 1-2 % of the cases with a clinical picture of dystrophia myotonica, we do not find the typical DM1 mutation. Recently, a new form of DM was identified, dystrophia myotonica type 2 (DM2), also referred to as “proximal myotonic myopathy” (PROMM). DM2 (OMIM#602688) is caused by an expansion of a CCTG repeat in the gene *ZNF9*, located on chromosome 3. The disease inheritance is autosomal dominant and does show anticipation.

The level of severity and symptoms vary between affected individuals, but usually the symptoms are milder than in DM1, and the congenital form probably does not exist. Molecular testing for this mutation is available.

## 6

### Heart Disease in Dystrophia Myotonica (DM1)

- All individuals with DM1 should have a resting EKG as a reference at the time of diagnosis.
- Asymptomatic gene carriers with DM1 should be examined with EKG when experiencing heart related problems and – in case of deviating findings – be followed-up as a patient with muscular disability.
- All patients with a muscular disability and/or deviating EKG should – regardless of age – be checked with a resting EKG about once a year.
- A patient with AV block II or indicated/suspected tachyarrhythmia and/or unclear fainting/unclear fall trauma should go through a 24-hour EKG and echocardiography and – consulting a specialist – consider placement of pacemaker/arrhythmia protection.
- A patient with (the addition of) pathological Q wave in resting EKG should be evaluated for coronary disease/cardiomyopathy.
- Surgical operations should be carried out with increased observance of heart function.
- Avoid class 1 antiarrhythmia medications and adjust the dose of all medicines that affect heart function.

#### Background

While breathing-related disease dominates at the end of life, heart arrhythmia is seen to be the second most common cause of sudden and unexpected death in patients with DM1 [1-4]. Even before the disease was commonly approved as a separate entity, patient cases with deviating resting EKGs were reported [5]. During the following decades, observations of mostly small patient groups in various parts of the world confirmed that EKG changes are common, primarily in the form of conduction disorders that reduce the P wave and prolong the PR interval and QRS width [6, 7]. In a survey of the literature of the 1960s, abnormal resting EKG was noted in 86 % of the DM1 patients while only 16 % had reported heart-related symptoms, half of which were seen to be stemming from arrhythmia [8]. We found abnormal EKG in 63 % of the Norrbotten cohort of DM1 (65 patients) in a cross-section study, mostly AV block I and left front fascicle block (LAFB), common already among clinically mildly and moderately disabled, while the most severe cases (and older) also displayed abnormal Q waves and repolarization disorders without a history for coronary disease [9]. A later, large American multi-center cross-section study found abnormal EKG in 65 % of individuals, but arrhythmia diagnosis in only 5.6 %. PR interval and QRS width correlated to age, CTG repeat length, and male gender [10]. It is probable that a PR interval  $\geq 240$ ms indicates a greater risk of arrhythmia and sudden death, especially in an older patient [11, 12]. Longitudinal studies have confirmed that EKG changes (conduction disorders) in DM1, as a rule, gradually increase with age and increasing disability – but with variations from one person to the other – sometimes combined with a sudden need for a pacemaker [13-17]. Whether the progression of EKG change is different between the sexes or relates to the onset age of DM1 is unclear, but the speed of change possibly increases, along with the risk of sudden death in patients with larger CTG expansion.

Besides resting EKG, Holter EKG has indicated an increased occurrence of paroxysmal or permanent atrial flutter and tachyarrhythmia, particularly supraventricular, in various ages and levels of muscular disability [19-21]. Invasive electrophysiological studies have indicated conduction disorders even when the resting EKG is normal [22]. Common occurrences of late potentials have correlated well to QRS width and conduction disorders in His-Purkinje tissue, without a simultaneous notable tendency for chamber arrhythmia in Holter EKG or programmed intracardial stimulus [23]. An Italian study of 42 middle-aged patients with Holter EKG showed an increased occurrence of extra heartbeats in the chamber – including grouped ones – in the most disabled among the juvenile-onset DM1 patients with the longest CTG repeat and the most severe conduction disorders [24]. In a French study of a cohort of 204 DM1 patients, invasive electrophysiology was conducted on 83 individuals aged  $41 \pm 12$  from 73 families. They found superb correlation between standard EKG and invasive parameters (PR and AH intervals, and QRS width and HV interval respectively) and observed no malignant arrhythmia in Holter EKG or intraventricular stimulus [22]. The 49 patients who had HV interval  $\geq 70$ ms – regardless of any symptoms, such as heart arrhythmia or conduction disorders in resting EKG – were equipped with an arrhythmia-detection pacemaker which was followed for about 4.5 years. Paroxysmal AV block with bradycardia was registered in 21 of the 45 patients – most often short-term, and resulting in symptoms in only one patient – to which a bradycardia-protection pacemaker was seen to contribute. Most tachyarrhythmias were supraventricular, but self terminating chamber tachycardia was registered at some point in 13 patients. During the follow-up period, 10 patients died – 4 suddenly and unexpectedly – 2 documented as not of arrhythmia, one of asystolia due to respiratory insufficiency and decompensated ischemic cardiomyopathy, and one of unknown cause. Not unexpectedly, death correlated to high age, severe muscular disability, and reduced vital capacity – but also negatively correlated to treatment with amiodarone and beta blockers. Thus, the study indicated no arrhythmia death during the treatment with bradycardia-protection pacemaker (with or without simultaneous beta blocker/amiodarone), but this did not prevent unexpected, sudden deaths, which then seem to be triggered by other (breathing-related? author's remark) cause in DM1 [25].

Although histopathological studies of autopsy material and heart biopsy reveal that fibrosis, atrophy, and fat infiltration affect the heart as a whole, clinically significant cardiac insufficiency is unusual in DM1 [26-30]. Furthermore, the echocardiographic profile in various patient cohorts is so diverse that the occurrence of significant cardiomyopathy in the disease has been questioned [31-34]. Electron microscopy, modern MR technique, and echocardiography with tissue Doppler, however, speak firmly to the fact that the heart's contractural function is also directly affected in the disease, although seldom clinically marked in comparison with the EKG changes [35, 36]. The only notable valve change is usually said to be mitral valve prolapse [35]. However, no increased occurrence of coronary artery disease is indicated in DM1.

Newly discovered Q wave should instigate a coronary evaluation, but we should not be surprised to find DM1 patients with extensive conduction disorders and pathological Q waves in resting EKG who at the same time have normal coronary angiograms without anamnesis for coronary insufficiency or grounds for having gone through a transmural infarct

at echocardiography and who are without clinical cardiac insufficiency [37, own experiences].

All medical treatment of DM1 must take into account that the patient group has a different distribution of body mass and a disposition to habitual vascular hypotonia [38, 39]. It affects the dose tolerance and brings with it an increased sensitivity to medicine in general, as well as problems adhering to prescriptions. Special attention should be paid to the risks involving class 1 antiarrhythmia medications, which should probably be completely avoided regardless of DM1 phenotype and level of disability [20, 40]. Dose titration of all medicines affecting the heart function should be careful and continuous, with more frequent clinical and laboratory check-ups than is common in patients.

Earlier suspicions around the heart effects of certain anesthetics are weakened by the findings in a large retrospective study from Quebec (with the world's largest known concentration of DM1). In surgery with anesthesia, 16 out of 219 DM-patients had respiratory/lung related complications within a week of surgery, one of muscular hypotonia and one of a severe fall in blood pressure at the induction of the anesthesia. No serious arrhythmia or heart incident was reported, and these complications were not seen as associated with any specific anesthetics [41]. This still means that increased observance of the heart function in DM1 patients is necessary during all surgical operations and during deliveries [42, 43].

## 7

# Respiratory Aspects in Non-Congenital DM1

## Recommendations

- Ventilation capacity should be monitored by repeated examinations, including examinations of breathing frequency and breathing pattern, spirometry, arterial blood gases, blood tests, as well as EKG and ECHO examinations. Continuous monitoring can give valuable information.
- Secretion stagnation can be prevented by kinetic activity, resistance breathing, or alternatively by mechanically supported coughing, using a so-called cough machine.
- Choice of treatment is made as a result of the ventilation evaluation.
- Daytime sleepiness is a common phenomenon and should always be investigated.
- The patient is to be instructed about moderate intake of large meals and alcohol late at night, as well as the restricted use of hypnotics.
- An adequate diet is important, both for sufficient caloric intake and to avoid excessive weight.

## Background

As with a number of neuromuscular diseases (NMD) [1, 2], dystrophia myotonica (DM) is accompanied by respiratory complications. Early in the course of the disease, we can detect reduced strength in the respiratory muscles, primarily with an effect of the expiratory muscles until proximal muscle weakness appears, when the weakness in inspiratory muscles becomes more notable with an increased tendency for carbon dioxide retention [3]. In comparison with other NMDs, DM does not seem to have an equally clear connection between the level of weakness in the respiratory muscles and carbon dioxide levels [4], implicating other contributory factors to the respiratory disorders and symptoms [3, 4, 5]. Central components have been brought forth, based on sleep studies which indicated central apnea/hypopnea [5, 6] and on daytime sleepiness aspects which cannot be explained by nocturnal respiratory disorders [7, 8]. Indicated myotonia in the respiratory muscles does not seem to affect ventilation to any large degree, at least not during calm breathing at rest, but with a tendency to increase with forced breathing [9].

Various types of nocturnal respiratory disorders have been reported with DM. Most studies have focused on hypoxia and apnea registrations but only a few included carbon dioxide in the diagnosis of nocturnal hypoventilation. [10, 11].

A series of studies of NMDs, but only one specifically of DM, have indicated a positive effect of non-invasive assisted ventilation. Improvements in symptoms, nocturnal respiration, and daytime blood gases were indicated, but not to the same degree as in a control group of post-polio patients, and also with a lower usage degree of assisted ventilation. It was concluded that it is important to register the extent of the usage [11].

Beyond the risk of hypoventilation, DM patients, as well as several other NMD patients, run the risk of developing problems with secretion stagnation because of reduced coughing function and aspiratory complications as a result of a reduced ability to swallow [2].

Hypoventilation is as a rule defined as a condition where artery carbon dioxide (PCO<sub>2</sub>) levels extend 6.0 kPa and can have both central and periphery genesis. In most DM studies, focus is on the symptom of daytime sleepiness but for the NMD group as a whole, identified symptoms included difficulties concentrating, headache in the morning, orthopnea and sleeping disorders [2]. In my own experience, it is important to ask also about the occurrence of infections of the lower respiratory passages. Irregular breathing patterns are seen when the patient is awake or sleeping lightly, but not when in deep sleep [12, 13]. In normal circumstances, the breathing is adjusted during sleep to a lower volume per minute, the activity in the upper respiratory passages muscle tone is reduced and during phases of REM sleep, the activity in the respiratory muscles decreases beyond that in the diaphragm [14, 15]. These normal physiological processes bring with them, for the NMD patient, an increased risk of - respiratory dysfunction symptoms during sleep.

Although daytime sleepiness in DM patients does not necessarily indicate nocturnal respiratory disorders, this still has to be noted.

## **Evaluation**

### **Clinical Examination**

The patient is examined, if possible, both sitting up and lying down.

**The breathing frequency** is noted, as well as any usage of accessory breathing muscles, and this can be evaluated with visual or palpatory means. The patient's **breathing patterns** are noted. Normally there is an eversion of the abdominal wall in connection with inhalation, but with more marked diaphragm weakness, a paradoxal pattern can be inspected or palpated with inversion of the abdominal wall in connection with inhalation, mainly notable when the patient is lying down on his/her back.

### **Laboratory Examination**

Part of the basic laboratory examination is **spirometry**, which in cases of reduced breathing muscle function is characterized by reduced vital capacity (VC) and low total lung capacity. A decrease of the VC from sitting to lying down which extends 25 % is seen as an indicator of significant weakness of the diaphragm [16].

**Arterial blood gases** are characterized in NMD by raised carbon dioxide (PCO<sub>2</sub>) and a lowering of the arterial oxygen pressure (PO<sub>2</sub>), considering that oxygen saturation as a rule does not go below 90 % until PO<sub>2</sub> sinks below 8 kPa. Determination of oxygen saturation is therefore an awkward measure of the level of respiratory disorder in NMD. However, in my own experience, certain DM patients, unlike other NMD patients – except for those with pronounced scoliosis – often have a proportionately higher influence of PO<sub>2</sub> than is expected in pure hypoventilation.

Some patients have –prior to the respiratory evaluation – been identified because of **polycythemia** with high levels of hemoglobin, indicating chronic hypoxia. Different day parameters have been studied in order to predict nocturnal respiratory disorders. An increased **base excess**, or standard bicarbonate, gives an idea of PCO<sub>2</sub> over time and, as with normal or slightly increased PCO<sub>2</sub>, indicates higher PCO<sub>2</sub> values during parts of the 24-hour

period and suggests primarily nocturnal hypoventilation [17, 18, 19]. **EKG and ECHO cardiography**, justified by cardiological aspects in DM, can also provide secondary information about the patients' respiratory situation. EKG can show increased P wave amplitude, indicating cor pulmonale, and the ECHO examination is a non-invasive means to confirm the pressure conditions in the lung circulation. Considering the progressive course of DM, there is a need for **repeated examinations**, where the clinic and the level of deviations determine the intervals.

Nocturnal breathing registration with **continuous monitoring** of oxygen saturation and carbon dioxide levels are suggested with a broad range of indications. The carbon dioxide content can be determined with end-tidal or transcutaneous registration [20]. End-tidal determinations have a tendency to show falsely low values but usually reflect arterial levels well as long as there is not simultaneously an element of chronic obstructive lung disease. Transcutaneous determination, on the other hand, often provides falsely high levels. In order to validate nocturnal breathing registration, arterial blood gases are suggested the previous afternoon and the morning after, the latter while in a lying position with the patient still hooked up to the monitor. Further, it is desirable that breathing movements are registered and, if apnea is to be assessed, monitoring of the airflow is done. Nocturnal examinations may be required to be repeated before, as well as after, the placement of assisted ventilation. Complete polysomnography is not seen as indicated except in certain cases where special attention is paid to any sleep disorders despite adequate nocturnal respiration.

### **Treatment**

As a rule, the treatment consists of a mechanical breathing aid, a mask applied to the patient, a nose mask or a full mask that covers the nose as well as the mouth and, less frequently, only the mouth.

If the nocturnal breathing registration indicates a pattern suggesting an obstruction of the upper air passages, CPAP (continuous positive airway pressure) can be considered, unless significant restrictive ventilation limitation exists with a reduction of the patient's vital capacity. Considering that significant ventilation restriction with carbon dioxide involvement often exists at the time of treatment, use of a ventilator may be required.

There are a variety of brands of ventilators on the market, but there are in principal two different controls, pressure controlled and volume controlled [2]. Pressure controlled ventilators are designed to either only give a positive inspiratory pressure or a combined inspiratory and expiratory positive pressure, so-called bi-level ventilation, where the difference between inspiratory and expiratory pressure determines the given volume. Volume controlled ventilators are set to supply a given volume, which is obtained with varying pressure levels. Pressure controlled ventilators have the advantage that they compensate for mask leakage. Bi-level ventilation is advantageous if there is obstructive apnea/hypopnea. Volume controlled ventilators have the advantage that they, as needed, can increase the pressure levels to reach the required volume in situations of increased resistance in the air passages, as with secretion plugs. In volume controlled ventilators, a breath can be added to a breath, so-called air stacking. The patient receives a breath and closes the glottis, then receives another breath from the ventilator. By increasing the

inspiratory volume, the patient's opportunity to generate improved coughing increases. The best time to add assisted ventilation has to be determined by a combination of the patient's symptoms, clinical examination findings, and evaluation results. As a departure point, we can use the summary of a consensus conference published in "Chest" in 1999, based on symptoms,  $PCO_2 \geq 45 \text{ mmHg}$  (5.9 kPa) or nocturnal oximetry with oxygen saturation  $\leq 88 \%$  during 5 consecutive minutes or Forced Vital Capacity  $< 50 \%$  of the expected [21]. Once again, though, it is desirable to have information about nocturnal carbon dioxide levels. To summarize, it is important that the patients are identified in time so the need for assisted ventilation is in place before the patient needs to be exposed to intensive care efforts. The initial training can take place at the hospital, but preferably during a calm phase polyclinically where the patient can start using the device during the day. Daytime ventilation has, with NMD patients, proven to have similar effects on blood gases and symptoms as the same level of usage nocturnally [22]. Already limited usage can have positive effects. If non-invasive ventilation is insufficient, invasive ventilation via tracheotomy can be considered in accordance with the patient's general state of health, as well as the patient's cognitive status, which in and of itself can prevent the successful assistance of non-invasive ventilation.

### **Treatment of Secretion Stagnation**

The patient's weak expiratory muscles can lead to problems with secretion stagnation due to the patient's reduced coughing function. If the patient has enough strength in the upper extremities, it is suggested that the patient press his/her hands strongly against the abdomen while coughing, or, alternatively, that the caregiver is instructed to do so. The patient can get a BA tube, alternatively a PEP mask, as a breathing resistance device to facilitate secretion mobilization. Physiotherapy instruction or intervention in the form of active or passive movements that encourage chest movements contribute to secretion mobilization. The patient's ability to cough can be improved by using the Ruben breathing device to increase the inspiratory breathing volume. If significant secretion stagnation problems persist in spite of this, the usage of a cough machine can be considered [23, 24]. Positive pressure is applied via a full mask and is quickly followed by negative pressure. The maneuver is repeated a couple of times and the expectoration comes passively out in the mask or is manually evacuated from the mouth. After a pause, the procedure is repeated.

## 8

### Intestinal Effects of Dystrophia Myotonica

- The most common cause of diarrhea is the absorption of bile acid and treatment with cholestyramin (Questran®) often effective. Start with one bag (4 grams) per day with the morning meal, and the dose can be increased according to need. Should the patient experience constipation, ½ to ¼ of a bag per day is advised. If no effect can be seen with several bags a day, the effect can be strengthened with the addition of an antacid.
- Diarrhea caused by reduced function of the pancreas is treated with enzyme supplements, and bacterial overgrowth in the small intestines with intermittent antibiotic treatment.
- At the sign of disturbed motor functions in the upper intestinal tract, cisaprid was previously used. Considering the risk of serious heart arrhythmia, it is better to try erythromycin. The dose often does not have to be more than 50 to 100 mg per time. The medicine should be taken 30 minutes before a meal and watched for effect. It is often more practical to use single-dose-bags with a powder that is dissolved in water rather than a ready-mixed variant, because the latter has a limited storage time. As there is a risk of tolerance development, the patient should stop taking the medicine approximately one week per month.

#### Background

Near the turn of the last century, when the disease had just been described, it was reported that the intestinal tract could be affected [1]. As years progressed, infrequent reports followed about this connection, but no more systematic summary was made prior to an often quoted abstract published in 1962 [2]. The following summary is primarily based on the experiences gained in connection with thesis work at the DM center in Boden, Norrbotten, Sweden, during the 1990s. In a recent review, current knowledge was summarized and comparisons made with Duchenne muscular dystrophy and oculopharyngeal muscular dystrophy [3]. What is here written about dystrophia myotonica refers to DM type 1; at the present time it is not known whether DM type 2 has any affect on the intestinal tract.

#### Symptoms

Abdominal pain is a very common symptom and is reported in up to 55 % of the patients [4]. The symptom most often described in the literature is dysphagia, and it is common in a little over 40 % of the patients [4, 5]. This dysfunction is important to observe since aspiration and pneumonia are common and are a not infrequent cause of death [6]. Non-symptomatic swallowing disorders have also been described as a cause of unexplained fevers in a patient with DM [7]. Heartburn and regurgitation are common in this patient group, however here the patients do not differ from a control group.

Symptoms consistent with stomach disorders (nausea, an early feeling of fullness, and/or vomiting) can be conspicuous and appear in 1/3 of the patients[4].

Approximately one third of the Boden subjects suffered from diarrhea, more often intermittent than chronic in character. Constipation was also more common than in the control group but not as frequent as diarrhea. A very disabling symptom that was noted by 30 % was anal incontinence. This has been described as possibly leading to false suspicion of incest [8].

In 28 % of the patients, the gastrointestinal symptoms appeared before the actual disease dystrophia myotonica was known, and 25 % were of the opinion that these symptoms made up the dominant problem with the disease.

### **Pathophysiology**

Dystrophia myotonica is a systemic disease, so we can assume that several different organ systems can be the cause of the affected intestinal function. Earlier studies have focused on muscular disorders, but these have only seldom been proven [9]. It has been suggested that a disturbed electric control of gastrointestinal motor function might have a negative impact on the function [10], and this we have been able to prove when it comes to the stomach function [11]. Several endocrine deviations are known with the disease, and this has also been seen in studies that have been carried out from a gastrointestinal viewpoint [11, 12]. When we study the function on a physiological level instead of on a cellular and chemical level, we find, as expected, that motor function itself is disturbed [13]. An important pathophysiological finding is a disturbance of the enterohepatic circulation in patients suffering from diarrhea [14]. Of 20 patients examined with diarrhea, 12 had lowered retention of marked bile acid, signifying a defective absorption of bile in the terminal ileum. In the same study, a few cases were also shown with bacterial overgrowth in the small intestines and reduced function of the pancreas.

### **Treatment**

Diarrhea caused by the absorption of bile acid is successfully treated with cholestyramin [14]. In the same report, it is also said that treatment of bacterial overgrowth and pancreas insufficiency may help.

Metoclopramine has been shown to improve ventricular emptying [15], but whether this affects the symptoms is not reported in the article. From the same group, the experiences with cisaprid [16] are also reported. This medicine affects both studied physiological variables and a combined symptom score concerning the upper intestinal canal. Keeping in mind that it has been reported that cisaprid might give serious heart arrhythmia, much caution must be shown when this medicine is used [17] since these patients already have an increased disposition to arrhythmia (please see this chapter in this consensus). We have ourselves tested erythromycin in order to affect ventricular emptying in DM [18]. Neither clinical symptoms nor the ventricular emptying itself was affected, but a surprising side effect was that 5 out of 10 patients experienced improved intestinal functions. The effect of the medicine seems rather to depend on its similarity to the endogenous hormone motilin that stimulates motor functions than on its antibacterial effect, but a combination of effects cannot be ruled out.

The most common symptom, abdominal pain, is difficult to treat and no systematic studies of these have been accounted for. A case description reports that fenytoin can help [19], and several of the patients that have used previously mentioned gastrointestinal medicines have also experienced improvement when it comes to pain.

## 9

# Endocrine Disorders in Dystrophia Myotonica

## Recommendations

**Beta-glucose should be checked regularly. Raised Beta-glucose levels should be investigated and treated in the usual way.**

- Blood fats, cholesterol, and lipids should be checked approximately once a year and be treated in accordance with current guidelines.
- Electrolyte status should be checked in patients with heart arrhythmia.
- Other hormone tests should be done when there is an indication, and any deviations should be treated in the usual manner.
- Check weight, alternatively BMI, and encourage physical activity.

## Background

Endocrine disorders are well known and very common in DM1; disorders have been described within most of the body's endocrine system. The clinical relevance of these disorders is not always obvious and continued research is required to increase knowledge and understanding.

Historically, endocrine disorders have been part of the disease profile of DM1 since the 1880s. Impotence and testicular atrophy were among the earliest clinical signs described, and in 1912 Curschmann suggested that DM1 should be seen as a generalized endocrine disease. Despite this, only a few mapping studies were done during the rest of the 1900s, and not until the end of the century was the interest for endocrine research in DM1 awakened again. Most studies have focused on insulin and/or testosterone, but recently "newer" hormones, e.g. leptin have gained interest. Our group has focused on the stress hormone cortisol, its regulation and its relation to the metabolic syndrome and other hormone/cytokine systems.

The causes of the endocrine disorders may be connected to several different mechanisms, including the genetic defect, which in turn can affect the response to hormones and/or tissue-specific metabolism and production.

## Insulin Regulation and the Metabolic Syndrome

Hyperinsulinemia and insulin resistance are perhaps the most conspicuous and common endocrine disorders in DM1. A rapidly increasing amount of body fat with central distribution also commonly occurs [1, 2].

## The Metabolic Syndrome [3]

Glucose intolerance, reduced glucose tolerance (IGT), or diabetes mellitus and/or insulin resistance together with at least two of the following:

1. Impaired glucose regulation or diabetes
2. Insulin resistance
3. Raised arterial pressure
4. Raised triglycerides

5. Central fat distribution and/or BMI >30 kg/m<sup>2</sup>
6. Microalbuminuria

According to the above definition, a great number of our patients with DM1 fill the criteria for metabolic syndrome. The metabolic syndrome is further associated with an increased fat mass, increased levels of leptin, impaired fibrinolysis and disturbed cortisol regulation [4, 5], all commonly occurring disorders with DM1 [1, 6-9]. The most common blood fat disturbance in DM1 is hypertriglyceridemia [8, 10].

Despite all these disorders, the patients with DM1 do not have a heavily increased incidence of cardiovascular disease and/or diabetes [11]. The occurrence of diabetes in various DM1-populations is 0-6.5 % [11]. In our study of 109 DM1 patients, the occurrence of diabetes was 6.7 %, to be compared to 6.4 % in men and 5.8 % in women in the normal population in the same area [12]. Low, rather than high, blood pressure is also common in DM1 patients [13, 14]. This put together gives the profile of a regulation that is different from the classic metabolic syndrome, perhaps with a genetic background, and will require further research for better understanding.

### **Steroid Hormones**

The clinical profile of DM1 often includes sleepiness, apathy, sleep disorders, cognitive dysfunction, insulin resistance, body fat, and muscular dystrophy. Hormonal disturbances that may contribute to these symptoms in patients with DM1 include a disturbed regulation of the stress hormone cortisol and other steroid hormones from the adrenal cortex, among others dehydroepiandrosterone and its sulfate (DHEA/S). The disturbances include an abnormal metabolism and a disrupted circadian rhythm of cortisol as well as DHEA [7, 15]. The response to mediated stimulus of the corticotropin-releasing hormone (CRH) is also increased [15-18]. The levels of androgens are low, more pronounced in men [2, 7, 15].

### **Growth Hormone**

Disturbances in the regulation and secretion of growth hormone (GH) are common and include pulsatility, impaired response during sleep, growth hormone releasing hormone (GHRH), and insulin-induced hypoglycemia [19-22]. Treatment with GH and insulin-like factor-1 (IGF-1) have been tested without satisfying results [23, 24].

### **Gender Hormones**

One of the most common, and earliest known, symptoms is low testosterone levels. The levels of FSH (and to a certain degree LH) are raised; thus it has to do with a primary hypogonadism with a secondary over-production of gender hormones. Testicular atrophy is seen in 60-90 % [11, 25, 26], and impotence and poor development of secondary gender characteristics are also common occurrences. Lowered spermatogenesis has been reported, but fertility seems to be more or less normal in spite of this [1]. Treatment with testosterone has been tested without convincing results.

Women with DM1 show no signs of hypogonadism or other disturbances in the gonad system [11]. Lowered fertility has not been seen, but complicated pregnancies, an increased amount of miscarriages, bleeding disturbances, and early menopause are often seen [11, 27].

### **The Thyroid Gland and the Parathyroid Gland**

There are no clear connections between DM1 and disorders in the functions of the thyroid gland or parathyroid gland. Some studies have reported low TSH-response to TRH, normal thyroxine levels, and no antibodies or isolated lack of thyroid gland hormone [11, 28-30]. Several small studies (mostly case descriptions) have pointed to an association between DM1 and hyperparathyroidism. Raised calcium after oral calcium load has also been reported.

### **Cytokines**

Levels of the pro-inflammatory cytokines are raised in DM1 (interleukin-6 (IL-6) and tumor necrosis factor alpha patients [2, 9, 10]. Both cytokines may contribute to the muscular dystrophy in DM1 activity in the cortisol system. TNF [31] has been suggested as an important link in the development of insulin resistance and lipid disturbances [32] and may also affect the heart function by developing cardiac fibrosis [33]. Both cytokines can also affect the cognitive function [34, 35]. The cytokines are produced partly in the fat tissue, and the increased amount of body fat can therefore contribute to the raised levels in DM1 [2].

### **Electrolytes**

A few case descriptions have reported moderately raised potassium levels in DM1. Misra et al. have described three cases of hyperkalemia, discovered due to heart arrhythmia, and suggest that hyperreninemic hypoaldosteronism can be a more commonly occurring disorder than earlier thought [36]. Treatment with fludrocortison had no effect.

### **Recommendations**

A number of hormonal treatments have been tested in DM1, including testosterone, GH, IGF-1, and carnitine. No treatment has proven to be especially good. In 1998, a Japanese study was published where they treated a small group of DM1 patients with injections of the adrenal cortex hormone DHEA [37]. The results were good and showed an obvious improvement of muscular strength and ADL points, as well as reduced myotonia and a reduced occurrence of arrhythmia. DHEA is therefore a possible alternative to future treatment, but more research is required.

# 10

## Neuropsychology

### Recommendations (no comments)

- In the congenital and childhood forms of DM1, a complete neuropsychological examination should be carried out. This should include an assessment of cognitive development complemented by a prognosis of behavior-related deviations. The results should form the foundation for support in education and focus on maximizing independence and self-sufficiency in daily living.
- In classic DM1, cognitive and personality-related deviations should be paid attention to and evaluated in cooperation with the patient and those close to the patient. When needed, referral to a neuropsychological examination is recommended to form the basis of aid efforts and intervention. A neuropsychological examination should focus on explaining any cognitive impairment that may affect memory, attention, and the ability to concentrate, executive functions, problem solving, intellectual and motor processing speed, as well as visual-constructive solving. This examination should be complemented by an evaluation of the emotional status and personality. Secondary factors that may affect cognition and behaviour in the form of sleepiness, reaction to a crisis, and depression should be treated via medicine and supportive therapeutic conversation intervention.

### Background

The occurrence of cognitive disorders has been observed in Dystrophia Myotonica type 1 (DM1) since the first clinical descriptions of the disease [1]. Brain imaging with various techniques has shown pathological changes, such as widened ventricular system, cerebral white matter lesions, atrophy, and reduced blood flow [2]. Neurofibrillary tangles and a deviating tau protein pattern have also been documented in neuropathological examinations [2].

### Impaired Cognitive Function

Studies show varying degrees of impaired cognitive function in DM1, which only roughly correlate with the size of CTG repeats and clinical degree of severity. There is support for the assumption that impaired cognitive functions in classic DM1 are underreported and that these contribute to the individual's disability and opportunities to establish him/herself in a social context [1]. A marked impairment of cognitive function is associated with the congenital form (CTG-repeats > 1000) of the disease [3]. The adult form of DM1 is characterized by a great spread when it comes to neuropsychological competence. Classic DM1 (CTG-repeats 150-1000) is associated with impairment of limited executive functions [4, 5] and mild DM1 (CTG-repeats < 150) with impaired verbal memory capacity [5, 6]. Deviating results at the testing of visual-constructive and problem solving ability have also been identified in some studies of classic DM1 [7, 8]. Measuring of general intelligence (WAIS-r) has shown a moderate global impairment in combination with differences between lower results in visual-constructive tests than in verbal tests [1]. An age-related impairment of cognitive functions, resulting in a mild cognitive impairment, has been noted in the adult-onset form of DM1 [9, 10]. The occurrence

of cognitive dysfunction in classic DM1 varies in different studies, depending on the method used and the examined group, but has been assessed as 50-90 % [5]. A connection between cognitive impairment and brain deviation has been detected in the significant changes in the brain's white matter (above all in connection with cortex) and general intelligence, verbal flow, and attention [11, 12, 13]. A larger amount of CTG-repeats (> 1000) is related to a more substantial impairment of cognitive function [14].

### **Behavioral Deviation**

A marked over-representation of behavior-related disorders have been noted in the congenital form of DM1 [3]. This deviation is most obvious in social contexts (reserve and teamwork difficulties), but also in the lack of attention and control of behavior. Personality-related disorders are also associated with the classic form of DM1, mainly in the form of evasive personality traits and an overrepresentation of personality disorders [15, 16]. No personality disorder is noticeable in the mild form of DM1 [4]. There are no definite answers about the occurrence of depression and anxiety-related symptomatology in DM1, where studies have presented contradictory results [17]. Sleepiness and lack of energy are common phenomena noted with DM1, where the extent of sleepiness seems to affect motivation and depression [18, 19]. Several studies have pointed to the possibility of social consequences of a lack of facial motor functions and an indirect incapacity to express emotional facial expressions, however without these assumed consequences having been supported by research [16]. In this context, a lack of ability to read emotional facial expressions has been associated with increased CTG repeats as well as personality characteristics associated with a lack of social cognition and teamwork capability [20].

### **Summary**

To summarize, today there is research supporting the fact that impaired cognitive functions and personality-related disorders can be seen in DM1. In classic DM1, there is a successive progression of the impairment [5, 10]; at the same time as there may be a risk that the patient and his/her family do not notice the extent of the cognitive problems. It should be noted that the variation in performance and behavior is great in DM1, resulting in the individual patient possibly being free from these disorders at the occasion of the clinical examination. This possibility seems however to decrease when a large number of CTG repeats and a more extensive brain pathology can be identified. It is of great value to identify those DM1 patients who have these impairments since an explanation can be formulated regarding the patient's difficulties, and guidance on how to conquer the problems can be given to the patient and his/her family.

Finally, it should be stated that there is current data suggesting the direct relationship between neurocognitive impairment and the consequences these have in daily living. Mathieau et al [21] have indicated a substantially lower level of education and a higher rate of unemployment in DM1 as compared to the normal population which are social circumstances that are associated with disorders in cognitive functioning and personality.

# 11

## Oral Hygiene and Dental Development in Patients with Dystrophia Myotonica

**Recommendations (no comments)** (See more detailed recommendations regarding measures below.)

### Children with Congenital or Early DM1

- Early referral to pedodontist.
- Information focusing on diet, fluoride supplement, and hygiene instructions.
- Special toothbrushes that facilitate brushing.
- Cooperation between pedodontist and the district dental health care.
- The pedodontist should make arrangements for regular check-ups of the dental development and, together with the orthodontist, initiate orthodontic treatment
- Oral motor training methods may be implemented together with a speech therapist to try to prevent negative orofacial development.
- The pedodontist should also attend to examinations and any reparative therapy in cases where treatment constitutes a difficulty.

### Adults with the Mild or Classic Form of DM1

- Adapted prophylactic care focusing on diet information, oral hygiene measures, and fluoride supplement.
- Jaw joint problems can warrant referral to a dental physiologist.
- A jaw support while treating the teeth can be recommended to avoid tiredness in the jaw joint while the mouth is open for a long time.

### Background

Increasing hypotonia in the orofacial muscles is one of the typical symptoms of Dystrophia Myotonica (DM).

Hypotonia of the muscles of the oral cavity and face can affect the secretion of saliva, cause chewing problems, and reduce the self-cleaning of the mouth handled by the tongue, lips, and the chewing muscles, so-called oral clearance. This is impaired by reduced saliva secretion. The secretion of saliva in turn is partly affected by the ability to chew. Oral clearance is also affected by the coordination ability of the oral motor functions. Reduced oral clearance increases the risk of plaque accumulation and caries. Patients with weakened muscles around the oral cavity therefore have an increased risk of dental disease, especially caries and gingivitis. They have an increased need for good preventive dental care. This is particularly important if the muscles in the hands and arms are also weakened, making oral hygienic measures more difficult, such as toothbrushing, flossing, and cleaning with toothpicks [1]. Weakened orofacial muscles at an early age can also affect the orofacial growth pattern and dental development [2, 3, 4, 5]. A connection between jaw joint problems and bite problems have also been proven [6].

Four types of DM1 with varying orofacial effects can be discerned: congenital, early-onset, classic, and adult. The symptom profile varies between and within these groups, but typical features can be seen [7, 8].

The connection between muscle function and dental development has been studied. A vertical growth pattern and high occurrence of bite abnormalities such as postnormal relation, crossbite, and crowded teeth have been indicated among adult patients with the classic form of DM1, as well as difficulties to chew and swallow [2, 3, 4]. Problems with the jaw joint in the form of luxation and jaw locking are more common in adults with DM1[7].

We see more caries, plaque, and gingivitis in adult patients with DM1, and the explanation is the reduced oral clearance of sugar, saliva secretion, and oral muscular coordination ability, and an increased consumption of sugary products. Adult DM1 patients often complain of dry mouths and are tempted to frequently consume sweet drinks. They also complain about difficulties swallowing. Reduced ability to chew and prolonged chewing time have been detected in adult patients with DM1 and this can contribute to difficulties swallowing [9, 10].

Observations done in a current study of children and youth with congenital or early-onset DM1 agree with earlier studies of adults with the disease. The studied children have – compared to a control group – more caries, gingivitis, and plaque. This is particularly true when they reach the teenage years. They have more bite problems, mainly frontal open bites and crossbites. Jaw joint problems are also more common in the patients with DM1 even if it is not as marked as in adults with the classic form of the disease. They have more dental care than the children in the control group and are more often treated in specialist care. Treatment difficulties are common since neuropsychiatric diagnosis and developmental disorders are frequently occurring [8].

## **Measures**

### **Children with Congenital or early-onset DM**

Early referral to a pedodontist should be done as soon as there is a diagnosis. The pedodontist meets with the family for information and treatment planning. Support for the family is important since one of the parents always is more or less affected by the same disease.

The information should focus on diet, fluoride supplement, and hygiene instructions. Special toothbrushes, such as Collis Curve or Super Brush, that facilitate the brushing can be recommended and, from about 3 years of age, an electric toothbrush. Parents or other caregivers should help with the tooth cleaning longer than the 10 years that are recommended for healthy children. Toothpaste containing fluoride, an amount corresponding to the size of the child's nail on the little finger, should be used. Diet recommendations should focus on avoiding snacking on sweet foods and sweet drinks between meals.

The children who can manage it can be recommended to chew gum, preferably those containing fluoride, some time every day in order to stimulate the ability to chew, the secretion of saliva, and to add fluoride. For those children who have a neuropsychiatric diagnosis or retardation, the so-called TEACCH-method can be used during the training

period. Pictures are used to help the children understand and get used to different components of dental care [11].

Cooperation is recommended between the pedodontist and the district dental health care. Within the district dental health care, prophylactic treatment is preferably carried out in the form of tooth polishing and painting teeth with fluoride varnish at intervals that suit the individual. It is important to gradually get the patient used to this with many easy, structured visits with prophylactic measures and training. This prevents treatment difficulties that are otherwise commonplace.

The pedodontist should arrange check-ups every year or every second year in order to follow the bite development and, together with the orthodontist, put in place indicated orthodontic treatments. As it is not contraindicated to train muscles in patients with DM [12], oral motor training methods can be put in place in cooperation with a speech/language therapist in order to try to prevent negative orofacial development.

The pedodontist also arranges examinations and any reparatory therapy in the case of treatment difficulties. As DM1 brings with it great risks in the treatment with anesthesia, this should be avoided as far as possible but often becomes necessary for children who have serious developmental disorders and/or neuropsychiatric problems. Sedation with muscle relaxants, such as Midazolam, is contraindicated, but sedation with laughing gas can be tested in collaboration with the patient's own physician.

#### **Adults with the Mild or Classic Form of DM1**

Individually adapted, extended prophylactic care focusing on diet information, oral hygiene, and fluoride treatment is recommended.

Aids: Electric toothbrush and lip-and-cheek-support are appropriate aids to facilitate tooth cleaning. Plaque control with the help of chlorhexidin, perhaps in jelly spoons, can be recommended where conventional cleaning with toothbrush, dental floss, and toothpicks are not enough. Jelly that contains fluoride and chlorhexidin can be obtained at the pharmacy.

Jaw joint problems can cause referral to a dental physiologist for evaluation and any treatment in the form of dental splints and relaxation exercises. In cases where jaw joint problems exist, lengthy chewing, especially of foods that are difficult to chew, should be avoided. Diet anamnesis from patients with DM show that they often avoid such foods without the recommendations.

Dental supports to be used during dental treatment can be recommended to prevent tiredness in the jaw joint from having to keep the mouth open for a long time.

## 12

### Orofacial Functions

#### Difficulties with Swallowing and Speech in people with DM1

- When infants have feeding difficulties, the sucking reflex should be stimulated.
- When there is delayed speech and language development, we should aim at a stimulating language environment, perhaps via contact with the rehabilitation team's speech/language therapist.
- Dysarthria should be evaluated by speech/language pathologists or therapists, who decide on investigation and treatment.
- When there are signs of dysphagia (difficulty in swallowing), the patient should be referred for evaluation.
- When drooling is a problem, oral motor training should be initiated.

#### Background

Weakened muscles in the face, mouth, and throat are common in DM. Important orofacial functions – like being able to eat, speak, and express oneself with facial mimics – are often affected. Feeding difficulties during the infant period are part of the symptom profile associated with the congenital form of DM. Difficulties in swallowing can be detected during the fetal stage and lead to polyhydramnios (excessive embryonic water).

Many patients with DM have a characteristic appearance, giving guidance in the diagnosis of the disease. Most typical is *a long, narrow face, narrow temples, drooping eyelids (ptosis), expressionless facial mimics and a tent-shaped mouth*. In pronounced tent-shaped mouths, the mouth is triangular in shape, the upper lip pulled up and the lower lip rotated outward, flaccid jaw, and open mouth. The characteristic mouth has been detected already during the fetal stage with the help of ultrasound.

In the congenital form of DM and DM with childhood-onset, *delayed language development* is common as a result of learning difficulties and developmental disorders. Great difficulties with developing speech, language, and communication skills occur, mainly in people who have serious developmental disorders or some form of autism spectrum disorders as additional diagnosis.

In children with DM, there is an increased frequency of *intradental articulation*, which means that a sound normally articulated with the help of the tongue against the dental ridge instead is produced by the tongue tip between the front teeth. This articulation disorder is often associated with an open bite and does not affect the understanding of the speech to any great degree.

**Dysarthria** (speech motor disorder) of various kinds occurs frequently with DM and can be caused by:

- *Weak lip muscles* which specifically affect the pronunciation of bilabial

consonants (/m/, /b/ and /p/). In some cases the pronunciation of the labiodental consonants (/f/ and /v/) is also affected as well as the overrounded vowels (/y/, /u/ and /w/).

- *Hypotonic velopharyngeal muscles* lead to difficulties shutting the flow of air up toward the nose while producing oral sounds (all language sounds except /m/, /n/ and /ng/ in Swedish), which makes the speech hypernasal. Hypernasality can be an early symptom in the classic form of DM.
- *Tongue myotonia* (tongue cramp after muscle contraction) which occurs mainly in adults and temporarily renders articulation more difficult.

**The voice** may be affected by weakened breathing muscles and general fatigue so that the voice volume is weak, the voice quality “leaking” or “creaking”, and the sentence melody monotone.

Muscular weakness in DM can lead to **dysphagia** and can affect the whole swallowing sequence from the point where bolus is worked over in the mouth until it reaches the stomach via the pharynx and esophagus. Problems associated with the preparatory phase of the swallowing can be *leakage from the mouth* and *difficulty taking food from spoon and fork with the lips* due to weak lip muscles. It can be *troublesome to chew* and many describe *the meals taking an extra long time*. With the help of videofluoroscopy and manometry, we have been able to detect motor disorders in the throat and esophagus in adults with DM in the form of weakened contractions, hypotonic muscles, coordination disorders, and a lowered resting tonus in the upper esophageal sphincter. The symptoms are often subclinical, but also more marked *difficulties in swallowing* can occur in people with DM of all ages. The effect on the swallowing and open mouth result in an increased risk of *drooling*. Others may be troubled by *dry mouth* and *foaming saliva* associated with mouth breathing and a low production of saliva.

## **Treatment**

### **Feeding Difficulties in Infants**

If the child is mainly tube-fed, the sucking reflex is stimulated with a pacifier, breast feeding, or bottle to the extent the child’s general condition allows it. When tube-feeding continues for a long time (> 3 weeks), the family should be allowed the opportunity to see a speech/language therapist – or other staff familiar with early feeding – to get advice and support when it comes to aids, feeding techniques, and oral stimulation.

### **Delayed Speech and Language Development**

Children with DM must be allowed to develop at their own speed, but – as with other children – we must aim to create a linguistically stimulating environment both at home and at preschool/school. Signs as support for speech and language development can be introduced early via the rehabilitation team’s speech/language therapist or preschool consultant. Children with delayed language development should be evaluated and followed-up by a speech/language therapist who also decides if and when special training should be introduced. It is important to check the hearing regularly and immediately attend to any problems with hearing.

### **Dysarthria**

Dysarthria is evaluated by speech/language pathologists or therapists who will also suggest a treatment plan adapted to the individual. Measures that can come into play are articulation training, oral motor training, and various types of communication aids. If hypernasality is a problem, a surgical operation can be considered, whereby a velopharyngeal reconstruction is performed to facilitate the raising of the soft palate. A palatal lift treatment can also be considered, meaning that the patient is given a palatal plate which functions as a support for the soft palate and in that way facilitates the closure toward the inner pharyngeal wall. Patients with normal sensitivity in the throat, however, have a hard time tolerating this device. There is still no research that can guide us when it comes to treatment of dysarthria in DM. The treatment efforts and training programs should be followed-up and evaluated regularly in order to make sure that they have the desired effect.

All measures that contribute to a better breathing function and reduced sleepiness can be expected to have a direct positive impact on voice and speech.

### **Dysphagia**

Recurring pneumonia, coughing in connection with meals, and a gurgling voice after meals can be signs of aspiration. If aspiration is suspected, the patient should be referred to a dysphagia team, nutrition team or clinic for dysphagia evaluation. The swallowing sequence can be examined in detail with the help of videofluoroscopy (videoradiography). Fiber endoscope (FUS) and ultrasound can also sometimes be used to evaluate the swallowing. When difficulties in chewing occur, and other problems associated with the oral preparatory phase of swallowing, a speech therapist, occupational therapist, dietician, and dentist can contribute with advice and support from their individual areas of competence.

### **Drooling**

In order to get better lip closure and more effective swallowing, oral motor training is recommended. There are special training tools to strengthen the muscles in the lips and cheeks, so-called "mouth guards". Standard models of the mouth guards in soft or hard plastic can be purchased but can also be fitted at the dentist for a more individually adapted shape. Speech/language therapist and dentists evaluate drooling problems and are responsible for oral motor measures. Physicians are responsible for measures that are meant to reduce the amount of saliva via e.g. medicines or surgery. Since a reduced production of saliva can result in substantial risks for the oral health in DM, this type of treatment should only be considered in exceptions and then always in cooperation with a dentist.

Checking of facts, speech therapists Pamela Åsten, TACO- center, Oslo, and Eva Holmberg, child and youth rehabilitation, Mariestad.

# 13

## Anesthesia and Dystrophia Myotonica

### Preoperatively:

- Careful preoperative evaluation, including routine tests
- Heart examination and 12-lead EKG. Consider heart echo and 24-hour EKG with arrhythmia – a temporary pacemaker can be considered in certain cases.
- Lung function examinations.
- Use benzodiazepines with care in the premedication. Can be combined with oxygen-restricting medicine.

### Intraoperatively:

#### Induction

- Careful titration of intravenous medicine. Thiopental or propofol can be used.
- Inhalation induction with sevoflurane can be considered.
- Intubation is preferred in most situations.
- Modified RSI with cricoid pressure, propofol and alfentanil, either without neuromuscular blockade or with rocuronium has been suggested.

#### Maintenance

- Lowest possible level of the inhalation gases.
- TIVA with propofol and alfentanil one possibility, however with greatest caution.
- Opioids only to reduce the need for other anesthetics but use medicines of short duration.
- Muscle relaxants may not be necessary, but when there is a need, use non-depolarizing medicines of short duration.
- Neostigmin as needed – can result in depolarizing block or partial reversing.
- Normothermia important!
- Avoid solutions containing potassium.

### Analgesia and Postoperative Care

- Often prolonged postoperative recuperation
- Analgesia very important.
- Epidural anesthesia with local anesthesia and opiate can be very effective.
- Local nerve blockades good.
- Give paracetamol and NSAID to reduce the need for opiodes.
- PCA an alternative.
- TENS.
- Physiotherapy important.
- All patients should, if possible, be supervised in intensive care postoperatively.

## **Background**

Although most patients with DM1 receiving anesthesia are free of complications, the risk of serious complications is clearly increased and there are many examples of anesthesia with perioperative and postoperative complications that in the worst cases have led to death [1-7]. Most complications can be predicted and avoided through careful preoperative evaluation and planning of the anesthesia procedure, including the postoperative care.

## **Myotonia and Muscle Relaxants**

Myotonia affects, in addition to the extremities, also the masseter, tongue, and pharyngeal muscles. Myotonia is seldom a clinical problem with anesthesia but can be released by anesthetic medicine and create a problem with intubation [4, 8, 9]. Myotonia can be made worse by hyperkalemia, depolarizing relaxants (succinylcholine), and anti-cholinesterase (e.g. neostigmin), as well as of hypothermia, mechanical and electrical stimulation, shivering, or inhalation anesthesia [1, 3, 4, 7, 9-12]. Neither peripheral blockades or muscle relaxants prevent myotonia.

## **Respiratory Complications**

Respiration is reduced on account of general muscular weakness [8, 13, 14]. This brings with it a reduced breathing reserve, weak coughing, and often a tendency to central and/or obstructive apnea [12]. The respiratory drive in patients with DM1 is strongly affected by all the breathing depressive medicines (opiates, benzodiazepines, or barbiturates) and prolonged hypercapnea which gives apnea periods [5, 12, 14]. Delayed stomach emptying, esophageal dilation, gastroesophageal reflux [15], delayed relaxation of and increased secretion accumulation in the pharynx increase the risk of aspiration.

## **Cardial Aspects**

The risk of sudden heart death, even in young patients, is increased and has no connection with the clinical level of severity in the disease [16]. Arrhythmogenic substances, e.g. halothane, should be avoided. Certain drugs used to treat myotonia (e.g. phenytoin and procainamide) can cause hypotension, bradycardia, and heart failure in these patients.

## **Hypotension**

The blood pressure is as a rule 20-30 mmHg lower than in the normal population, perhaps due to reduced tonus in smooth muscles and/or a reduced minute volume of the heart due to bradycardia [15]. Hypotension can be made worse by the increased sensitivity to anesthesia medicines, e.g. halothane, isoflurane, and propofol [6]. Also keep in mind that a small amount of bleeding can become a big problem due to impaired compensation mechanisms [18].

## **Pregnancy**

Pregnancy increases the risk of anesthesia further [2]. The risk of aspiration is increased due to increased abdominal pressure and further reduced tonus in the esophageal sphincter [2, 9, 18]. High levels of progesterone lead to higher potassium levels which increase the risk of myotonia. Reduced uterine tonus together with bad contractility, further impaired by polyhydramnios accompanying a fetus with DM1, contribute to difficult and prolonged

labour. Intervention in partus and postpartum bleedings are more common in women with DM1. Local anesthesia is an alternative if the risk of hypotension is carefully considered.

## **Suggestions for Management**

### **Preoperatively:**

- Careful preoperative evaluation, including routine tests.
- Heart examination and 12-lead EKG. Consider heart echo if there is suspicion of myocardial dysfunction and 24-hour Holter-EKG with arrhythmia – a temporary pacemaker can be considered [17, 20].
- Examinations of lung functions to examine the level of lung effect, hypercapnea, and hypoxia.
- Avoid opiates in premedication and use benzodiazepines with care [15]. The pre-medication can contain oxygen-restricting medicines (ranitidine, omeprazole).

### **Intraoperatively:**

#### Induction

- Careful titration of intravenous medicines to minimize hypotension. Thiopental as well as propofol can be used [21, 22], however with care.
- Inhalation induction with sevoflurane can be considered – aspiration risk!
- Intubation preferable in most situations.
- Avoid succinylcholine.
- Modified RSI with cricoid pressure, propofol, and alfentanil, either without neuromuscular blockade or with rocuronium have been suggested [23.]

#### Maintenance

- Lowest possible level of the inhalation gases to reduce the risk of shivering – totally avoid halothane.
- TIVA with propofol and alfentanil a possibility [20, 22].
- Opioids only to reduce the need for other anesthesia medicines, but use medicines like alfentanil and remifentanil with short duration.
- Muscle relaxants perhaps not necessary because of general muscular weakness.
- When muscle relaxants are needed – use non-depolarizing medicines with short duration, like atracurium or vecuronium, titrated with the help of monitoring (reduces the need for neostigmin).
- Neostigmin as needed – can however in some cases lead to a depolarizing blockade or partial reversing.
- Normothermia important!
- Avoid solutions containing potassium if not especially indicated.

### **Analgesia and Postoperative Care**

- Often prolonged postoperative recuperation.
- Analgesia very important since pain further impairs the breathing and renders mobility more difficult, which leads to more thromboembolic complications.
- Epidural anesthesia with local anesthesia and opiat (f ex bupivacain and fentanyl) can be very effective. Remember to reduce the opioid dose.

- Local nerve blockade good.
- High opiate doses should be avoided because of the breathing depressive effect.
- Give paracetamol and NSAID to reduce the need for opiates.
- PCA an alternative.
- TENS.
- Physiotherapy important.
- All patients should, if possible, be supervised in intensive care postoperatively.

### **Alternative Methods**

Whenever possible, local or regional anesthesia is preferable, but myotonia may still occur [21]. Epidural and especially spinal anesthesia can make the hypotension worse and require careful supervision and aggressive treatment with vasopressor substances. Laparoscopic surgery is associated with fewer postoperative complications, especially with cholecystectomy [9, 21, 24].

Based on recommendations in “Myotonic Dystrophy – present management, future therapy” [19].

# 14

## Medical Treatment

### Recommendations

- Annual follow-ups via structured appointments.
- Regular, adapted muscular training.
- Consider medical treatment of myotonia.
- Regular heart function check-ups.
- Regular ventilation check-ups.
- Symptomatic treatment of other affected organs.
- Orthopedic technical consultation.
- Genetic advice.

### Background

There is at the present time no treatment that can affect the time of the onset or progression of DM. An important corner stone in the care of a DM patient is detailed and repeated information about the disease. This means everything from the genetic background and how the disease is inherited to which organ systems can be affected and what subsequently happens to the individual. A card or tag with the information about the diagnosis is good in emergency situations to avoid complications when given anesthesia in case of acute surgery.

**Structured follow-ups** of the patients with diagnosed DM are recommended considering that the patients clearly underreport symptoms and problems. Therefore, regularly occurring check-ups of heart and breathing functions are necessary, but even an active questioning of endocrinologic, gastrointestinal, and cognitive problems is often necessary.

**Myotonia** is seldom of the level of severity that the patient wishes to be treated. In some cases this is an issue, and then mexilitene Mexitil® in the dose of 50-100 mg 2-3 times a day is the most effective treatment.

Studies have shown that **strength training (body building)** does not lead to improved muscular strength [1].

**Dietary supplement** with Kreatin has shown to be without effect [2].

It is important to have **regular EKG** follow-ups to make sure that the patient does not have or is not getting any new conduction disorders.

The impaired **breathing function**, especially the coughing exhalation, in combination with difficulties in swallowing result in a risk of infections of the respiratory passages. Information about risks in connection with eating is important, as well as the recommendation that patients immediately see a doctor at signs of bacterial infection of the

respiratory passage. We also recommend **vaccination** against pneumococcal infection and influenza.

**Excessive daytime sleepiness** is common, and some of the patients benefit from treatment with modafinil Modiodal®[3]. Our experience is that most of those who respond to the treatment experience an effect with a dose of 100 mg morning and lunchtime; only a few patients need to increase the dose to 400 mg per day.

**Orthopedic surgical correction** can in rare cases be required, mostly in the form of Achilles tendon-lengthening, while scoliosis surgery is never an issue. Some patients with significant weakness in the muscles that lift the sole of the foot benefit greatly from ankle orthoses.

**Genetic guidance** is extremely important for patients who are about to become parents and it is, for the same reason, also important to identify the affected and the carriers in the extended family.

It is important that the information that the patient has DM is given to other caregivers. Our hope is that research will give us future treatments with the purpose of affecting e.g. the size of the CTG expansion and thereby the course of the disease. Recently published tests in cell culture show that the treatment with four different types of chemotherapy (mitomycin C, ethyl methanesulfonate, mitoxantrone, or doxorubicin) reduce the size of CTG expansion with 100-350 repeats [4].

# 15

## Occupational Therapy – Adults with Dystrophia Myotonica

### Recommendations

- Annual follow-ups in accordance with the suggested intervention program and good knowledge of the diagnosis group and the individual's needs. The occupational therapist focuses on supporting the patient in learning to use aids.
- All individuals affected by dystrophia myotonica should have access to an occupational therapist within the primary health care. There should be referral from a doctor.
- When complex problems arise, the individual should be referred to specialist health care to be evaluated in accordance with described guidelines. The occupational therapist within the specialist health care will then be able to support not only the individual user but also the district occupational therapist or others within the health care. It is important to coordinate services and measures.

### Background

The program deals with people who have been diagnosed with Dystrophia Myotonica (DM) as adults, but is also useful for adults who were diagnosed in childhood and youth. Individual needs differ, all the way from substantial loss of function to fairly good function. It is important to understand and consider the problems surrounding behavioural disorders that can exist in congenital DM and in the classic form of DM in order to be able to guide the individual.

Most patients have had symptoms for several years and have not been met with an understanding of their problems. Many have experienced that they are perceived as lazy and have had difficulties participating on the same physical level as others of the same age. In the family situation, it is often the case that relatives have the same diagnosis and the same problems. The result is that they are used to a certain appearance or behavior in the extended family. This contributes to the problems being detected late in life.

For those who have been diagnosed as adults, their whole daily living has been drastically changed and many functional losses are difficult to compensate. A common feature is that these individuals want to be able to maintain their independence in the home, at work, and socially. The lack of initiative, as well as physical and psychological fatigue, affect their daily living and make social exchange with other people more difficult. A social network, work opportunity, and family are often factors that decide whether or not a person feels isolated. Patients often face large obstacles in the public area. The degree to which this functional disability is perceived depends on which limitations there are in the environment and in society in general. The occupational therapist meets people in various phases with completely different needs and can help with arrangements [1].

The disease affects individuals differently depending on their own circumstances and needs [2], and it is necessary for the occupational therapist to do an individual evaluation with focus on activities associated with: personal hygiene, dwelling, work, leisure time, travels, transport, and communication.

## **Evaluation Guidelines**

The occupational therapist must focus on three areas in relation to the performance of actions.

### **Limitations – cognition:**

- Lack of initiative – to get going with planned actions.
- Impaired endurance – difficulties completing the task.
- Mental fatigue/exhaustion – fatigue, lack of motivation
- Memory difficulties – difficulties getting to meetings and appointments on time
- Orientation issues – insecurity when it comes to orientation in the immediate and external environment
- Reduced attention span and concentration – loss of focus

### **Limitations – physical functions:**

- Physical sleepiness – difficulties executing actions.
- Hand function – the ability to grip and reach items
- Movement in the hand and finger joints – distal stiffness, diastasis, myotonia
- Weakened hand strength – can be measured with the Grippit instrument [3]
- Weakened pinch and key grip – can be measured with Pinch Gauges [4]
- Fine motor skills and coordination – can be measured with the Perdue Pegboard [5]
- Sitting – maintaining body position in actions.
- Standing – reduced muscular function and balance.
- Movement while walking – the risk of falling.
- Reduced oral motor skills – difficulties chewing, limits the choice of food, and can result in extended meal duration.
- Pain – in the throat, neck, shoulder, and back muscles, resulting in limitations while participating in activities in all areas.
- Sight problems – disturbances in eye motor skills and cataracts result in activity limitations. Can lead to tension in certain head positions, e.g. while reading and writing.
- Driving – focus on this because of the risk associated with sleepiness, pain, impaired endurance, and attention. Furthermore, the ergonomic conditions to drive well and safely in traffic must be present.

### **Limitations – social functions:**

- Feeling insecure and unsafe in social contexts.
- Mental and physical fatigue – difficulties performing actions.
- Lack of initiative – both short-term and long-term consequences. This might lead to the disappearance of a social network.
- Reduced mimic muscle functions and difficulties interpreting other people's facial expressions can lead to limitations in social communication.
- Poor sight – can contribute to isolation and reduces ability to stay oriented.

- Stomach/intestines – reduced control of bowel functions can be an obstacle in social activities.
- The eating situation – can prevent the individual from participating in social meals.
- Lack of motivation – can prevent the individual from participating in activities.
- Pain – limits the desire and opportunity to participate socially.
- Memory – difficulties being on time for meetings and appointments.

## Goals

This should be tied to the individual's needs and desires to perform actions, taking into account the identified problem areas. What is important for the individual to master on his/her own, and what can be adapted in the environment? What is possible? Can an assistant or a family member execute any of these activities?

Three different compensatory intervention areas can be suggested [6]. The individual needs must be considered. A combination of all three areas is often necessary.

1. Learn to use new strategies
2. Adaptation of the environment
3. Evaluate the need for and the testing/adaptation of technical aids.

## Guidelines for Intervention

### Cognition:

- Acquire new strategies in relation to the execution of actions.
- Energy budgeting, to distribute strength and find a balance between work and rest.
- Teach the individual to structure and adapt to his/her limitations.
- Inform and give practical advice to family members.
- Adapt activities by planning and structuring daily living.
- Provide help to get started.
- Give motivation to perform actions.
- Make sure the individual realizes the need to maintain function in activities and distribute strength in a purposeful way.
- Reduce the demand for how much the individual can do in relation to work at home and outside the home. Pay attention to the importance of creating opportunities to rest. Where there are small children in the family, there might be a need to increase their time at daycare and after-school care
- Be rested before driving and before performing more demanding work tasks for the sake of safety.
- Learn memory strategies, use day-timers, electronic aids, telephone, and alarm systems.
- Give information and guidance to those around the patient about individual needs for adaptation and arrangement of e.g. work hours.

### Physical function

Consideration must be given to the extent the individual can improve on and/or keep his/her level of function. Compensatory efforts are often necessary:

- Adaptation of the indoor environment and the environment in the immediate surroundings of the home, the work place, and the school. The choice of leisure time activities, and necessary adaptations, is an important area. It is important to map out communication in the immediate environment.
- NB - safety and adaptation when using a privately owned car.
- Evaluate the need for technical aids.
- Where there is a need for a personal assistant and/or home-based services, the occupational therapist can contribute with factual statements about issues surrounding daily living.
- Sitting – difficulties getting up from chairs, the bed, the toilet, the car seat, etc.
- Is there a need for an electric lift/elevator?
- Weakness in the neck, shoulder, and back
- Is there a need for an ergonomic adaptation of the work place? E.g. the chair by the computer and/or the chair used while doing house work. It may also be necessary to adapt the computer.
- Standing – endurance and balance.
- Is there a need for a support chair, work chair, shower chair, support railing?
- Walking – safety while walking, risk of falling.
- Is there a need for a wheel chair or adaptation via support, walker, guardrail, or a lift between the floors?
- Pain – the affect on activity performance in the environment.
- The need to test alternative devices, such as wrist orthoses, grip build-up?
- Sight problems – the effect of the choice of activities.
- Is there a need for impaired vision aids and adaptation of the environment?
- Reduced speech function – the effect on the individual's speech. Is it hard to hear or understand what is said?
- Is there a need for communication aids?
- The eating/food situation – the effect on meal content and duration. Does the individual eat enough and within a reasonable amount of time?
- Is there a need for medically adapted utensils or other aids for daily living?
- Problems with stomach/intestines – access to a toilet and possibility for personal hygiene.
- Is there a need for a bidet?

### **Social Function:**

- Decisions about the individual's social functioning depend on what conditions there are, physically and cognitively. By combining the individual's needs and desires for change, an evaluation can be done about how and in which way social function can be affected. Often another person or a personal assistant is a condition for participation in social contexts.
- Structural changes can facilitate daily living. You must also look at in which way the performance of an action is possible and adapt to it via other ways/methods, or that another person helps out.

- Inform family members, friends, colleagues, and others the individual is in contact with about the consequences of the disease, especially when it comes to taking the initiative, about the sleepiness, and any behavioural problems.

### **Evaluation Tools to be Used as Necessary**

Can also be used to compare results from year to year. Can follow the development in the individual and be in the foreground when it comes to making early intervention possible.

#### **Evaluating Activity:**

Sunnås ADL Index, ADL instrument [7].

ADL-Taxonomy. The device comprises defined daily living activities organized into actions from the easiest to the most demanding one [8].

AMPS, the Assessment of Motor and Process Skills – when the intention is to measure the quality of a person's performance of specified actions [9].

#### **Assessing Function:**

Gripping force meter – measures maximum values, average values during 10 seconds, and final value [3]

Pinch Gauges – measures the maximum pinch grip and the key grip [4]

Perdue Pegboard – measures the fine motor skills and coordination in the right, left and both hands as well as in an assembly task [5]

There are age-related value references in all.

#### **Assessing what Activities the Individual Wishes to Prioritize:**

COPM, The Canadian Occupational Performance Measure [10], an individualized, client-centered measure that identifies problems with occupational performance, assesses the individual's self-perception and detects change over time.

The device deals with performance and participation limitations and classifies them in accordance with ICF taxonomy of functional characteristics and disabilities and contains the categories Function, Performance and Participation.

#### **Theoretical Frame of Reference**

MOHO, The Model of Human Occupation: Reports on motivation, performance and organization of daily living, Explains what happens in case of dysfunction and points to what can be done [2].

OTIPM, The Occupational Therapy Intervention Process Model: Reports on the process: the mapping, the intervention and the assessment from an ergotherapeutic perspective [6].

CMOP, The Canadian Model of Occupational Performance: Reports on basic activity areas (personal daily activities, productivity and leisure time) [10].

# 16

## Physiotherapy

### Recommendations

- Physical activity and medium intensity training recommended as scheduled activities of daily living.
- Physical activity must be part of the energy budgeting involving all of daily living.

### Introduction

This reference program concerns all groups of people with dystrophia myotonica (congenital, juvenile, classic, and mild adult form of dystrophia myotonica) where we see a great spread in age, functional condition, and functional disabilities. The goal of this section is to inform about physiotherapeutic intervention by:

- pointing out/identifying the reasons for the problems people with dystrophia myotonica experience.
- showing the areas that need to be considered specifically and where the people with dystrophia myotonica need more support.

People with dystrophia myotonica can have cognitive impairment in functions that affect their daily living and that should be considered also in connection with instruction in physiotherapy. Examples of factors affecting physiotherapy are:

- reduced initiative, attention, and endurance
- memory problems, ability to concentrate
- physical and psychological fatigue

A holistic access to management/treatment, considering all of the individual's problems, is important if the treatment is to be beneficial. In order to get best possible result, it is necessary for the physiotherapeutic intervention that consideration is given to the completeness of the individual's daily living.

In the reference program, we are using International Classification of Functioning, Disability and Health (IFC) [1] as a model and a structure to describe how people's function and health are affected by the disease. With IFC the functional situation and/or functional disability are described based on bodily function, bodily structure, activities and participation, and the effect of environmental factors.

## Measurement and Intervention

General suggestions based on function. The measuring methods are to be seen as suggestions of tests that may be used.

<b>Body function/body structure</b>	<b>Measuring method</b>	<b>Intervention</b>
Myotonia	have/ have not	
Muscle strength	Manual muscle strength testing, e.g. MRC [2] Myometer [3] Muscular Impairment Rating Scale (MIRS) [4]	Strength training/ endurance training [5] Activity guidance
Facial motor skills		Stimulus, training, and guidance
Sink function/swallowing	Bulbär	Attention and
Speech motor skills, articulation	functional evaluation (modified after Brooke) [6, 7]	advice Articulation – refer to speech therapist
Respiratory	Spirometry measuring Breathing anamnesis	Pursed-lip-breathing [9] Deep respiration [10] Manual cough help Ventilator [8, 11]
Daytime sleepiness	Epworth sleepiness scale [12] Fatigue severity scale (FSS) [13]	
Pain	Visual Analog Scale (VAS) [14] Borg CR10 Scale [15]	Traditional methods (e.g. warmth, TENS)
Back and joint function (including foot deformities)	Describe back from fixed positions and chronology Joint measure relevant joints	Muscle extension (stretching) Mobility training Guidance Orthopedic technical aids
Heart		Attention and Advice
Endurance-condition	Perhaps 6 minutes walking test [16]	Condition training Guidance

Advice on physical activity (energy budgeting - customize plan)

<b>Activities and Participation</b>	<b>Measuring Method</b>	<b>Intervention</b>
Level of motor skills	Hammersmith Scale [17, 18] Graded evaluation of function, lower and upper extremities (modified after Brooke) [6, 7]	Motor training
Mobility	Rivermead Mobility Index [19] Timed up-and-go (TUG) [20]	Mobility training with/without aids
Walking patterns/ Walking function	Walking test 10 m [21] Two or six minute walking test [16] Walking analysis	Walking training Advice (shoes and splints) Test dorsal flexion aids
Balance	Stand on one foot [22] Walk in an 8-figure [23]	Balance training
<b>Environmental Factors</b>	<b>Measuring Method</b>	<b>Intervention</b>
Factors in the environment Need for aids		Testing of orthopedic technical aids (aids worn on the body) Testing of walking and mobility aids (cane, walker, scooter)

Persons with DM1 often have a need for physiotherapy throughout the course of the disease. The degree of therapy varies depending on the level of function and disability and may consist of advice and individual training and treatment, as well as testing of adequate aids [24-27].

### **Training and Dystrophia Myotonica**

The scientific proof of the effects of conditioning and strength training in Dystrophia Myotonica type 1 (DM1) is limited, both when it comes to the number of studies and the quality of the studies [5, 26, 28-30]. Most studies are neither randomized nor controlled, and it is the norm that the study population consists of adults with varying types of neuromuscular diseases [31-37]. In regards to moderate intensity conditional training however it seems – at least in the short-term perspective – as if a training-related improvement may take place without any detected negative effects [32, 38].

High-load strength training with DM1 has, in a pilot study, shown an increased muscular strength in the trained leg [39], but in a randomized and controlled study [40] neither positive nor negative effects could be proven. In other studies of persons with a variety of neuromuscular diseases, strength training with light/moderate as well as high loads have been carried out and resulted in some improvement of muscular strength [34-36]. It appears there is a connection between the trainability and initial strength such that weak muscles have bad trainability [35, 40].

It has been debated whether people with DM1 have an increased risk of getting secondary diseases, heart-coronary diseases as well as diabetes, on account of a reduced physical activity level as a result of both the disease in itself and a sedentary lifestyle [30, 41-43]. A program consisting of dietary advice and individually adapted advice of increased physical activity in the form of walks showed positive change, but not enough to affect the risk factors of secondary disease [44].

Another form of training studied with DM1 is Qigong. After three months of training, a tendency was seen to preserved balance function, increased well-being, and reduced stress [45, 46].

Breathing gymnastics, in the form of pursed-lip breathing and deep breathing, have shown improved breathing function in two smaller studies [9, 10].

Despite a lack of evidence, it appears that condition/muscular strength/endurance training with light to moderate intensity (i.e. 35-69 % maximum pulse in condition training and 15-50 repeat maximum (RM) at muscular strength/endurance training) could be recommended for people with DM1. It is also important to stimulate daily physical activity for improved health and life quality. The purpose of all training with DM1 is to contribute to an improved or preserved function capacity and prevent secondary complications [25, 29].

### **Energy Budgeting and Strength Accounting**

For people with DM1 it is often difficult to find a balance between physical activity and rest. The structure of the day can vary with different projects. To combine school/work with an active social life is demanding for many. To take the initiative and get started and to persevere over time is for many DM1 patients a daily problem both when it comes to small tasks and big ones. To make the strength last, it may be necessary to ration the strength/budget one's energy. This may mean a shortened work day those days when there is a scheduled training program. Or it may mean the use of technical aids with some activities in order to save strength for other activities. As is pointed out earlier in this article, physical

activity and training may lead to improved health and increased life quality for persons with DM1. For it to be the case, the training has to be part of a completely adapted day. The choice of activity and form of training should be determined by the individual's motivation and interest.

# 17

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