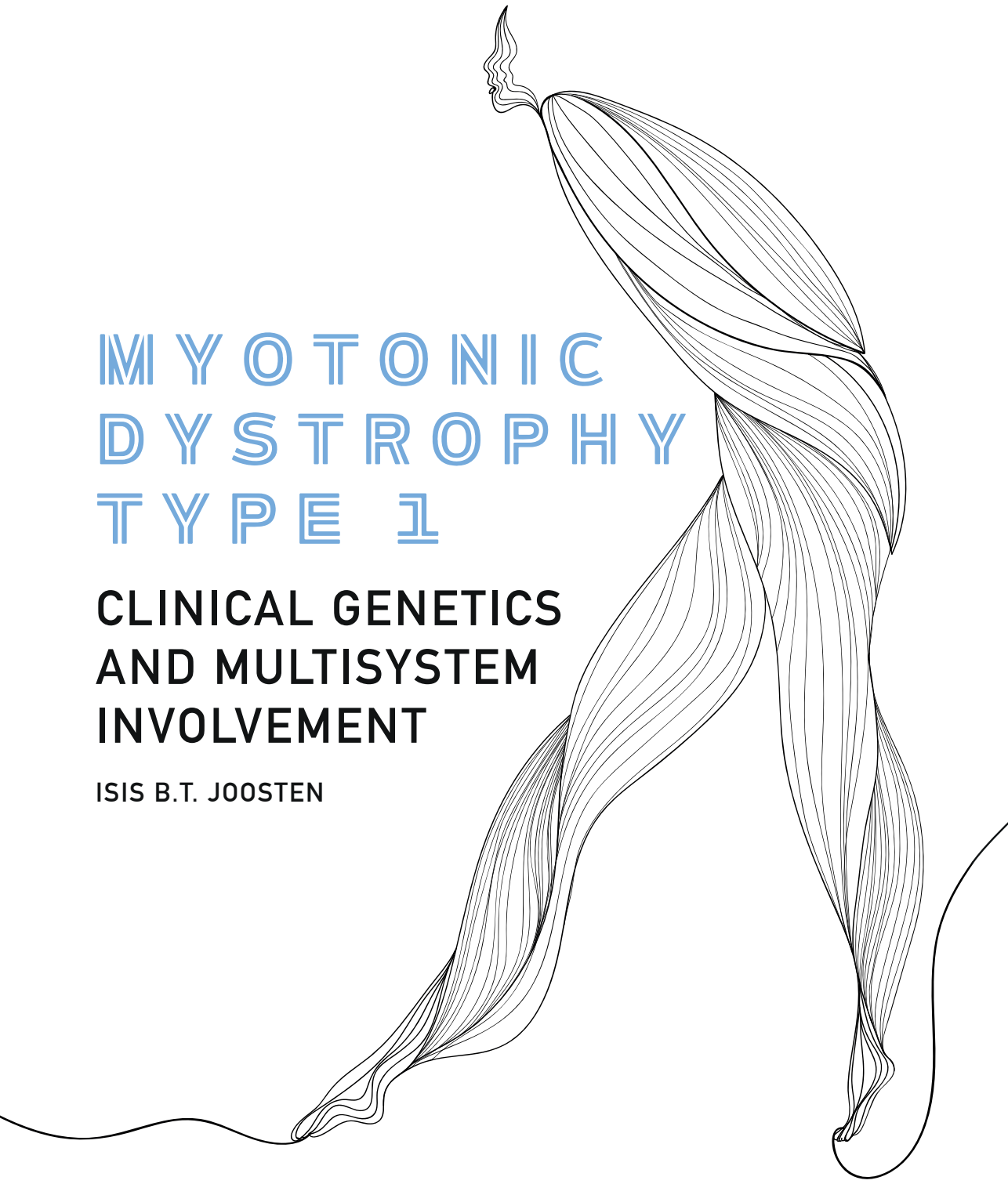
Myotonic dystrophy type 1

MYOTONIC DYSTROPHY TYPE 1

CLINICAL GENETICS AND MULTISYSTEM INVOLVEMENT

ISIS B.T. JOOSTEN



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Clinical Genetics and Multisystem Involvement

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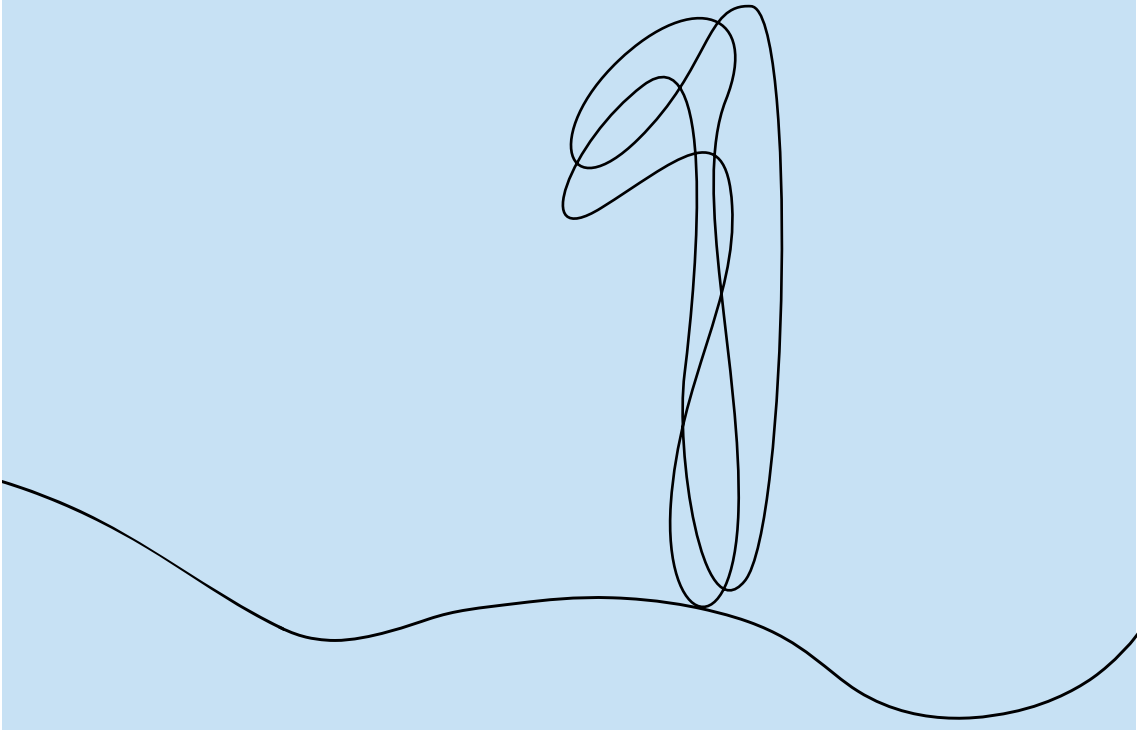
Chapter 1

General Introduction



General introduction

Myotonic dystrophy type 1 (DM1) is classically known as a muscle disease affecting patients of all ages. Despite the fact that muscle weakness and myotonia (inability to relax muscles) are the two main symptoms of disease, DM1 is a highly variable disorder able to affect almost every organ system in the human body. Consequently, the term multisystem disorder seems more suitable and is being used more often in both research and clinical practice. Due to the broad range of possible symptoms, disease management in DM1 requires multiple specialties for patient follow-up, as is reflected in the current thesis. Since a curative treatment for DM1 is not yet available, patient management also requires frequent screening for possible disease complications. Moreover, informing and managing patients' expectations is an important part of DM1 care. In the current thesis, we aim to improve DM1 patient management by adding to the current knowledge of clinical genetics and multisystem involvement.

Genetic background

DM1 (formerly known as Steinert's disease) is caused by an autosomal dominantly inherited repeat expansion on chromosome 19.[1] More specifically, the cytosine-thymine-guanine (CTG) trinucleotide expansion is located in the dystrophia myotonica protein kinase (DMPK) gene. Whereas the number of CTG-repeats in healthy individuals range from 5 to 35, repeat expansions larger than 50 are associated with DM1.[2] Repeats between 36-50 (premutations) only rarely cause DM1-related symptoms, but may become unstable when transmitted to offspring.[2] This phenomenon of unstable transmission to the next generation is known as genetic anticipation, which is a characteristic feature of DM1. As CTG-repeat lengths increase during transmission to successive generations, this also results in an earlier age-of-onset and increased symptom severity.[3] Consequently, it is quite common for DM1 to be first discovered in families upon the birth of a severely affected neonate. In these cases, the disease has unknowingly been transmitted over multiple generations, as carriers of shorter repeats were asymptomatic or only mildly affected at a reproductive age.

Pathogenesis

The mechanism by which CTG repeat expansions cause DM1 manifestations is not completely understood. Most support has been given to the toxic RNA gain-of-function hypothesis[4]: mutant DMPK transcripts carrying expanded CUG repeats, accumulate in nuclear foci and interfere with several RNA-binding proteins. Two specific proteins have been demonstrated to play an important role in the DM1 pathogenic process, namely

CUG-binding protein 1 (CUGBP1) and muscleblind-like protein 1 (MBNL1). While sequestration of MBNL1 in DMPK RNA foci causes a loss of function, CUGBP1 is upregulated by the same foci.[4] Eventually, this leads to deregulation of global splicing events and to changes in gene expression, protein translation and micro-RNA metabolism causing DM1 specific symptomatology.[5]

Disease prevalence

DM1 is the most common type of muscular dystrophy among adults, yet disease prevalence is highly variable in different regions of the world. While the prevalence is estimated at 10-18 per 100.000 in Europe[6-8], the prevalence is as low as 0.46 per 100.000 in Asia.[9] Variability in prevalence is mainly due to the so-called founder effect, which describes a loss of genetic diversity when a new colony is formed by a small number of ancestors, carrying a DMPK repeat expansion in case of DM1. Additionally, genetic anticipation and autosomal dominant inheritance play a role in locally increased prevalence.

Disease subtypes

Clinical symptomatology, age of onset and CTG-repeat length are used to divide DM1 into four subtypes: congenital, childhood/juvenile, adult-onset/classic, and late-onset DM1.[3] Patients affected by late-onset DM1 presumably have a milder phenotype consisting of early-onset cataract and mild muscle weakness, yet data on the true prevalence of multisystem involvement in this subtype is scarce. In the three remaining subtypes, severe muscle weakness, myotonia, multisystem involvement and neuropsychological deficits are of frequent occurrence. An overview of associated symptoms per subtype is presented in **Table 1.1**. Although CTG repeat size is part of DM1 subtype differentiation, it is known that there is an overlap in repeat lengths between different subtypes, and that CTG repeat lengths can be tissue-specifically expanded and unstable throughout life.[10,11]

Multisystem involvement

Survival in DM1-affected individuals is significantly reduced, primarily as a result of multisystem involvement.[12] Median survival was found to be 60 years for males, and 59 years for females affected by adult-onset DM1, with the main causes of death being of pulmonary and cardiac origin.[12] In patients affected by the congenital subtype, only 50% survive beyond the age of 30.[13]

As described in **Table 1.1**, disease manifestations are diverse and different combinations of symptoms can arise in each DM1 patient. Complications in organ systems that are a topic of the current thesis, are described in more detail below.

Table 1.1 Myotonic dystrophy type 1 disease subtypes.

Subtype	Age of onset	Early manifestations	Later manifestations	CTG repeat length
Premutation		most often asymptomatic	risk of transmitting expanded allele to offspring	38-50
Protomutation		most often asymptomatic, but can become symptomatic later in life	comparable to late-onset DM1 risk of transmitting expanded allele to offspring	51-80
Late-onset	>40 years	cataract	myotonia mild muscular weakness	50 – 150
Adult-onset	20 – 40 years	muscular weakness myotonia gastrointestinal disorders	severe muscular weakness apathy excessive daytime sleepiness fatigue cardiac conduction delay and arrhythmias	100-1000
Childhood/juvenile	1 year – 20 years	intellectual disability behavioral problems gastrointestinal disorders	comparable to adult-onset DM1	100-1000
Congenital	<1 year	hypotonia bulbar weakness respiratory deficits intellectual disability orthopedic complications	comparable to adult-onset DM1	>1000

Cardiac involvement

Cardiac complications mainly consist of cardiac conduction delay and/or arrhythmias, which may result in sudden cardiac death. Conduction abnormalities such as atrioventricular (AV) blocks and bundle branch blocks (BBB) are observed in 17-45% of the DM1 population, while atrial fibrillation/flutter and ventricular arrhythmias are described to be present in respectively 5-13% and 1-4% of patients.[14-16] Moreover, DM1-affected individuals are at risk for cardiomyopathy and heart failure. Even though left ventricular ejection fraction (LVEF) may decrease over time, an LVEF <50% is present in less than 10% of DM1-affected individuals.[14]

Cardiac involvement in DM1 seems to be a direct result of CUGBP1 upregulation, as mice in models with expanded CUG expression can have PR prolongation, QRS widening and arrhythmias.[17] Moreover, histopathological evaluation of cardiac tissue of DM1-affected individuals reveals fibrosis and fatty infiltration into the conduction system.[18]

Respiratory involvement

Respiratory dysfunction, predominantly of a restrictive nature, is present in approximately 30% of the general DM1 population[19-21] and is associated with alveolar hypoventilation and chronic hypercapnia.[21] Moreover, sleep related breathing disorders are common, yet the noted prevalence is highly variable among different studies reporting percentages between 16-75%.[20,22]
Respiratory involvement likely originates from both peripheral respiratory muscle weakness and central respiratory drive dysfunction.[21] Studies have demonstrated a reduced amount of serotoninergic and catecholaminergic neurons in the brainstem of DM1-affected individuals[23], presumably causing subsequent central CO_2 insensitivity.[24]

Metabolism

Established metabolic consequences of DM1 consist of insulin resistance and dyslipidemia (increased serum total cholesterol, low-density lipoprotein and triglyceride concentrations).[25,26] Furthermore, overweight and obesity are common in the DM1 population in combination with alterations in body composition, such as increased fat mass, decreased lean body mass and visceral obesity.[27-30] It remains unclear however, if weight and body composition alterations are a direct result of DM1 on muscle metabolism, or results from a sedentary lifestyle due to muscle weakness and neuropsychological involvement.

Patient management

Since a curative treatment for DM1 is not yet available, disease management focusses on monitoring progression and early detection of possible complications. Due to disease complexity, multisystem involvement and neuropsychological manifestations, it is recommended to follow-up DM1 patients on an annual basis.[31] Follow-up is carried out by a coordinating physician, preferably by a neuromuscular neurologist, referring to other specialists when appropriate. Although the neuromuscular neurologist may serve as the coordinating physician[32], a multidisciplinary team approach is imperative in DM1 patients, as is reflected in the current thesis. Moreover, providing adequate information on disease progression to the patient and their caregivers, including expectation management, is also of great importance.

Genetic counseling

Genetic counseling takes place in case of suspected DM1 or after a family member has received a DM1 diagnosis. Due to the autosomal dominant inheritance pattern and expected genetic anticipation, it is essential to inform patients about possible reproductive outcomes and options to prevent the repeat expansion from being transferred to the next generation. In short, there are two possibilities to prevent DM1 in offspring: (1) natural pregnancy followed by prenatal testing through chorionic villi or amniocentesis and possible termination of pregnancy, or (2) in vitro fertilization (IVF) combined with pre-implantation genetic testing (PGT). Even though DM1 can be maternally or paternally inherited, congenital DM1 in offspring is most often the result of maternal inheritance with a large intergenerational expansion of the CTG repeat.[33] This maternal bias is generally described in mothers affected by the adult-onset subtype of DM1 with CTG repeat expansions >100.[33,34] For small-sized CTG repeat expansion carriers (pre- or protomutation carriers), a reversed sex effect has been suggested in which paternally transmitted CTG repeats are more unstable.[35-37] As data on the inheritance of small-sized repeat expansions is scarce, genetic counseling of small-sized CTG repeat carriers with a desire to conceive offspring remains challenging.

Screening for multisystem involvement

Even though strict guidelines on the cardiac management of DM1 are still lacking, consensus-based care recommendations describe the necessity of annual screening through history taking (most importantly palpitations, dizziness, syncope) and electrocardiogram (ECG).[31,38] Apart from ECG, regular echocardiography and 24 h Holter monitoring are commonly carried out, while the exact role of both of these screening modalities in DM1 has not yet been validated.[38] In case of symptomatology, (severe) conduction disturbances or objectified arrhythmias, an invasive measurement of the cardiac conduction system called an electrophysiological study (EPS), with subsequent device implantation, may be necessary. Nevertheless, ECG criteria predicting the need for an EPS have not yet been established.

For respiratory analysis, attention should be paid to possible dyspnea, orthopnea, recurrent pulmonary infections and signs of sleep-related breathing disorders. Yearly pulmonary function testing is advised, as well as regular blood gas analysis and polysomnography.[39] In case of symptoms suggestive of chronic respiratory insufficiency in combination with (1) daytime hypercapnia, (2) forced vital capacity <50% of predicted, or (3) evidence of nocturnal hypoventilation on polysomnography, non-invasive ventilation (NIV) is indicated.[39,40]

Screening for involvement of, for example, the eyes, gastro-intestinal system or neuropsychological involvement is primarily done through history taking by the

coordinating physician, after which the patient can be referred if considered necessary. Bloodwork for metabolic abnormalities is advised at diagnosis and every three years, including fasting glucose, lipid levels, and thyroid hormone levels, even though evidence for these measurements is sparce.[31] While patients are commonly referred to a rehabilitation specialist and/or physical therapist, DM1-specific exercise interventions are not yet available. Previous research has demonstrated that exercise capacity increases when combined with cognitive behavioral therapy in DM1-affected individuals.[41]

Outline of this thesis

The current thesis aims to improve DM1 patient management by adding to the current knowledge of clinical genetics and multisystem involvement. The thesis is divided into four sections, of which the General Introduction (**Chapter 1**) belongs to **Section 1.**

Section 2 focuses on clinical genetics. First, **Chapter 2** gives a comprehensive overview of DM1 including information on diagnostic testing, physical manifestations and disease management. In **Chapter 3** we aimed to evaluate the intergenerational instability of DM1 pre- and protomutation alleles, focusing on the influence of parental sex, in order to improve genetic counseling for small-sized repeat carriers.

Section 3 focuses on multisystem involvement in DM1. To improve cardiac management, **Chapter 4** aimed to determine ECG criteria predicting abnormal infrahissian conduction in patients with DM1. In **Chapter 5**, we evaluated the clinical effectiveness of routine 24 h Holter monitoring to screen for conduction disturbances and arrhythmias. Thereafter, we compared the clinical phenotype of adult-onset versus late-onset DM1 in **Chapter 6**, focusing on the prevalence of cardiac, respiratory and muscular involvement.
In **Chapter 7**, we aimed to determine the presence of possible metabolic abnormalities in DM1 affected-individuals, by comparing energy expenditure and body composition between DM1 patients and healthy matched controls.

Section 4 presents the findings of this thesis, which are placed in a broader perspective in the General Discussion (**Chapter 8**). Moreover, we elaborate on the scientific impact of the conducted research and describe how this can be translated into clinical practice. Finally, we summarize this thesis's contents.

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Section 2

Clinical Genetics

Chapter 2

Myotonic dystrophy type 1

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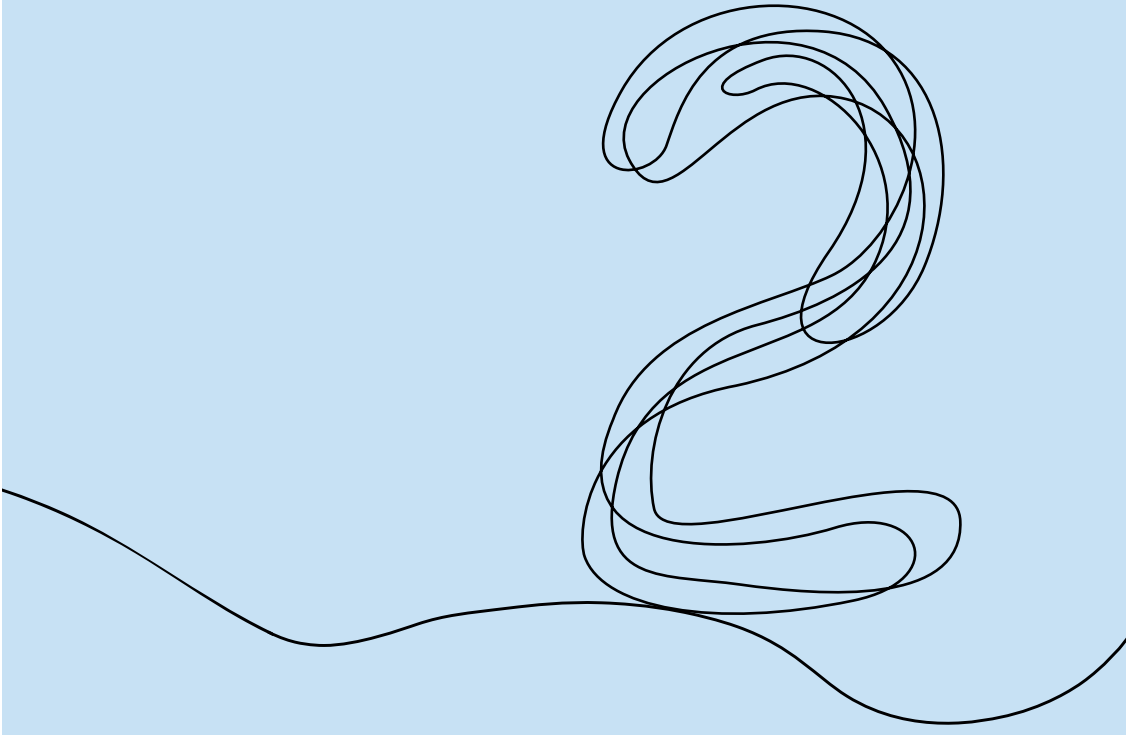

Summary

Myotonic dystrophy type 1 is an autosomal dominant multisystem disease caused by a trinucleotide repeat expansion in the DMPK gene at chromosome 19. Named after its neuromuscular involvement, muscle weakness and myotonia are often key characteristics of the disease. Other organ systems that may be affected include the heart, eyes, brain, gastro-intestinal, reproductive and endocrine systems. Despite progress in the unravelling of pathophysiological mechanisms, a curative treatment has not yet been found. Present management consists of annual health supervision and genetic counseling, which can be challenging due to variable disease manifestation and complex genetics.

Introduction

Main characteristics of myotonic dystrophy type 1 (DM1; also known as Steinert's disease) [MIM #160900] comprise of progressive myotonia and muscular weakness, in combination with multisystem involvement. The disorder was first described in 1909 by Steinert, while the corresponding gene defect was discovered in 1992.[1] In DM1, muscle weakness is most prominent in facial and neck musculature and distal limbs. Although myotonia is a relevant distinguishing feature, individuals with DM1 often do not complain about this symptom. In 1994, a separate disorder with myotonia and more proximal weakness was identified, later acknowledged as myotonic dystrophy type 2 (DM2).[2] This chapter focusses on DM1, while DM2 will briefly be discussed (see **Differential Diagnosis**).

Incidence

DM1 is the most common inherited muscular dystrophy in adults. Before the identification of specific genetic mutations, the combined prevalence of DM1 and DM2 was estimated at 1/8000 (12.5/100.000). Thereafter, several population-based studies on DM1 have shown that prevalence greatly varies with the population under study (**Table 2.1**). High prevalence, such as found in the Saguenay region of Canada, is probably the result of founder effect and population isolation. Low prevalence is reported in sub-Saharan Africa and Asian regions, with DM1 being found in only 0.46/100.000 in Taiwan.[3,4]

Table 2.1 Data on prevalence of myotonic dystrophy type 1 (DM1).

Authors	Country	Prevalence[a]
Mathieu et al. (1990)[5]	Canada	189
MacMillan (1991)[6]	Wales	7.1
Burcet et al. (1992)[7]	Spain	11
Lopez de Munain et al. (1993)[8]	Spain	26.5
Hughes et al. (1996)[9]	Northern Ireland	8.4
Medica et al. (1997)[10]	Croatia	18.4
Siciliano et al. (2001)[11]	Italy	9.3
Mladenovic et al. (2006)[12]	Belgrade	5.3
Suominen et al. (2011)[13]	Finland	54.6
Lindberg et al. (2017)[14]	Sweden	17.8
Lefter et al. (2017)[15]	Republic of Ireland	6.75

[a] per 100.000

Diagnostic criteria

The diagnosis is based on clinical features, family history and ultimately genetic testing (see **Diagnostic Testing**).

Disease subtypes

Because of the extreme phenotypic variability of DM1 (probably the most variable disease around), attempts have been made to stratify patients into groups with similar clinical characteristics. A frequently used approach is classification into groups based on age of onset (see **Table 2.2**).[16] Although there is substantial overlap, classification into different subgroups allows for some organization of clinical variability. It should be noted, however, that subtypes are not absolute and many different classifications have been used in scientific studies.
In general, symptoms of disease seem to be more severe in males than in females, with greater morbidity and mortality, and more profound socio-economic consequences.[17]

Table 2.2 Myotonic dystrophy type 1 disease subtypes.

Clinical phenotype & age of onset	Early manifestations	Later manifestations	CTG repeat length
congenital <1 year	hypotonia; respiratory deficits; intellectual disability; orthopedic complications	gastro-intestinal disorders; bulbar weakness; adult DM1- like involvement	>1000
childhood 1 year – 10 years	intellectual disability; behavioral problems; gastro-intestinal disorders	adult DM1- like involvement	100 – 1000
juvenile/early-adult >10 – <20 years adult >20 – 40 years	muscular weakness; myotonia; gastro-intestinal disorders	severe muscular weakness; apathy; excessive daytime sleepiness; fatigue	100-1000
late-onset >40 years	cataract	myotonia; mild muscular weakness	50 - 150
protomutation	mostly asymptomatic, but can be symptomatic especially later in life	risk of transmitting expanded allele to offspring	51-80
premutation	mostly asymptomatic	risk of transmitting expanded allele to offspring	38-50

Congenital myotonic dystrophy type 1

Congenital DM1 is the most severe subtype of DM1 and can become apparent even before birth with symptoms of polyhydramnios, reduced fetal movements or contractures such as clubfeet. After delivery, the neonate shows signs of hypotonia with only few spontaneous movements and facial diplegia. A typical dysmorphic appearance with a tented upper lip and open mouth might be apparent (see **Figure 2.1**).[18] Usually bulbar weakness leads to impaired sucking and dysphagia. Pulmonary hypoplasia and weakness of respiratory muscles, including the diaphragm, may cause respiratory insufficiency (see **Table 2.3**). In combination with aspiration, respiratory difficulties can lead to lethal complications. Most infants survive the critical neonatal period with intensive support. Still, overall mortality rates range from approximately 15-20%, reaching up to 40% in severely affected cases.[19]

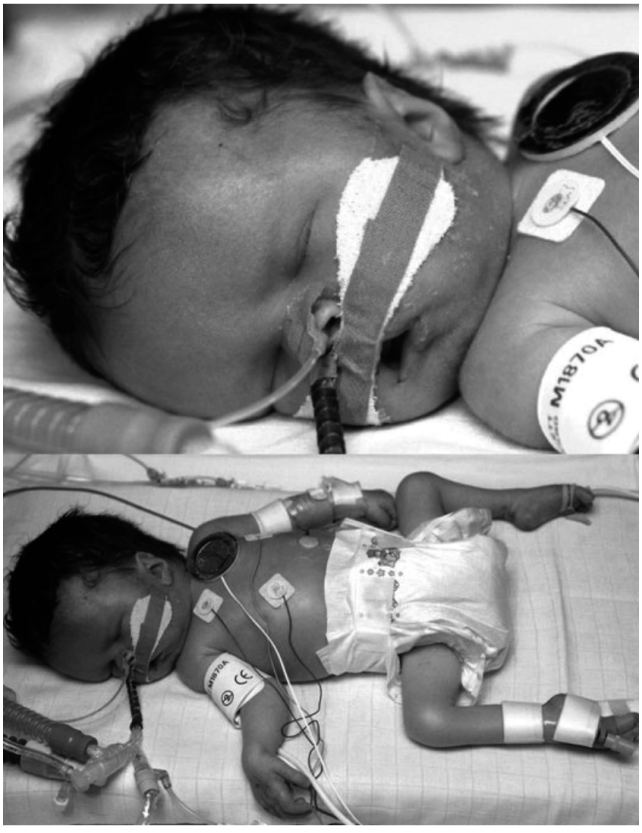

Figure 2.1 A child affected by congenital myotonic dystrophy type 1 with generalized hypotonia and dysmorphic features such as a tented upper lip and open mouth.

After the neonatal period, gradual improvement of motor function is to be expected. Although cognitive and motor milestones are delayed, almost all children will be able to walk.[18] Progressive muscle weakness will start becoming apparent after the first decade. Similarly, myotonia is absent at first and usually develops after the age of 10. Neuromuscular involvement may progress more rapidly than in other DM1 subtypes. Cardiorespiratory problems, including cardiac rhythm disturbances, have been described in children. Abdominal pain with constipation or diarrhea is a frequent complaint.

Apart from somatic expressions of disease, mental deficiency is present with full scale IQ ranging from 40 to 69 (median 53.6).[18] Despite cognitive challenges, most children will learn to speak and eventually learn to take care of themselves through special education. Still, congenital DM1 is associated with a poor prospect on physical and intellectual independence, and a significantly shortened lifespan.

Table 2.3 Manifestations of congenital myotonic dystrophy type 1.

Brain	Delay in mental development
	Intellectual impairment (IQ between 40-69 (median 53.6))
Skeletal muscle	Floppy at birth with possible facial paralysis
	Congenital contractures
	Motor development delayed
	Slowly progressive weakness from about 10 years
	Occasional moderate kyphoscoliosis
	Myotonia starting in late childhood or adolescence
Lungs and respiration	Pulmonary hypoplasia
	Neonatal respiratory insufficiency
Heart	Arrhythmia occasionally already in childhood
	Cardiac conduction defects later on in life
Oral cavity, pharynx	Narrow high-arched palate
Jaws and teeth	Dysphagia
	Poor sucking force
	Dysarthria
	Malocclusion
	Weakened bite force
Gastrointestinal	Abdominal pain
	Delay in gastric emptying
	Diarrhea, constipation
	Pseudo-obstruction
Natural history	Systemic manifestations as in adult type

Childhood myotonic dystrophy type 1

The childhood type has an onset of DM1-related symptoms between the ages of 1 and 10 years (see **Table 2.2**).[20] Clinically, this specific subtype forms a continuum between

congenital DM1 and the juvenile or early adult-onset form (see **Table 2.4)**. Individuals with childhood DM1 and an early onset of symptoms often demonstrate significant overlap with the congenital DM1 phenotype, as described.

Table 2.4 Manifestations of the childhood type of myotonic dystrophy type 1.

Development	Intellectual impairment
	(IQ in low normal range or mildly impaired)
Skeletal muscles	Facial muscle weakness
	Slowly progressive weakness from about 10 years
	Myotonia from about 10 years
Heart	Conduction abnormalities
	Arrhythmia in a few children
Oral cavity and jaw	Dysarthria
	Dysphagia
Gastrointestinal	Abdominal pain
	Diarrhea
	Constipation
Behavior	Attention deficit/hyperactivity in ≤50% of children
Natural history	Systemic manifestations as in adult type from about 10 years

Interestingly, childhood DM1 usually does not present at first with myopathic signs. On the contrary, the first symptoms of the disease frequently consist of speech and language difficulties or mental delay. A diagnosis is often reached after careful examination of family members or systematic investigation of developmental delay.

As affected children grow older, DM1 adult characteristics such as facial, bulbar and distal muscle weakness, and myotonia evolve. Most patients with childhood subtype will be more severely affected than patients with adult-onset DM1. In some cases, affected individuals even become wheelchair dependent when reaching an age above 40. Also multisystem involvement is often more prominent than in adult DM1. Gastrointestinal complaints are common and serious heart involvement can also exist.[18]

As can be expected from initial mental delay and language difficulties, intelligence is usually below average and ranges from borderline impaired (full scale IQ 70-85) to moderately mentally retarded (full scale IQ <55). Studies have shown a negative correlation between CTG repeat length and intelligence quotient.[21] Nevertheless, normal IQ is also possible.

As in congenital DM1, learning and communicative difficulties are often of greatest impact.[22] They may be accompanied by social and behavioral problems such as attention-deficit hyperactivity disorder.

Adult onset myotonic dystrophy type 1

The most characteristic features of adult DM1 are of muscular origin (see **Table 2.5**). They exhibit distal muscle weakness and atrophy in the extremities, with the possibility of developing proximal muscle weakness over time (see **Table 2.6**). Ptosis and temporal muscle wasting usually become apparent at an early stage. In addition, neck flexor and facial weakness are prominent, giving patients a characteristic myopathic appearance (see **Figure 2.2)**. Bulbar muscle weakness can give rise to disabling dysarthria and dysphagia.

Table 2.5 Systemic manifestations of adult type myotonic dystrophy type 1.

Skeletal Muscles	Slowly progressive distal muscle weakness, may evolve to proximal weakness
	Myotonia
Brain	Apathy
	Increased need for sleep
	Fatigue
	Cognitive impairment
	Behavioral disorders
Oral cavity and pharynx	Dysarthria and dysphagia
Jaws and teeth	Structural craniofacial abnormalities
	Decreased oral hygiene (caries, gingivitis and plaque)
	Malocclusion
Gastrointestinal	Dysphagia
	Gastroesophageal reflux
	Abdominal pain
	Obstipation
	Fecal incontinence
Heart	Conduction defects
	Arrhythmia
	Dilated cardiomyopathy
Lungs and respiration	Difficulty in coughing
	Aspiration
	Pneumonia
	Insufficient respiratory drive
	Central sleep apnea or obstructive sleep apnea syndrome
	Respiratory insufficiency
Eyes and ears	Cataract
	Decrease of high tone perception
Endocrine system	Testicular atrophy
	Decreased fertility in early-onset type (in males)
	Hypotestosteronism
	Insulin resistance, sometimes mild type-2 diabetes
Urogenital	Difficulty with micturition
Pregnancy and delivery	Polyhydramnios when fetus is affected
	Increased risk of premature labor
	Prolonged labor
	Abnormal presentation of the fetus
	Neonatal distress
Skin	Baldness (early alopecia androgenetica)
	Pilomatrixomata

Table 2.6 Muscular impairment rating scale (MIRS).

Grade I	No muscular impairment.
Grade II	Minimal signs, without distal weakness. Minimal signs may include digit flexor weakness, ptosis, temporal muscle wasting, neck flexor weakness, myotonia or nasal speech.
Grade III	Distal muscle weakness.
Grade IV	Distal muscle weakness in combination with slight to moderate proximal weakness.
Grade V	Severe proximal weakness.

Source: [26]

Figure 2.2 A 36-year-old woman with typical facial features of adult-onset myotonic dystrophy type 1: long face, temporal muscle atrophy, open mouth and mild ptosis.

A second key feature of adult onset DM1 consists of myotonia, which is expressed as an elongated hand-grip relaxation time and percussion myotonia on neurological examination. Still, this characteristic symptom of disease is not particularly troublesome for most individuals. As a result, they may not bring up these complaints spontaneously.

Myotonia may also be present in bulbar muscles, causing difficulties in chewing or swallowing.

Apart from muscular symptoms, individuals with adult DM1 often demonstrate marked multisystem involvement. In particular, early-onset cataracts are a hallmark of the disease. Severe fatigue and daytime sleepiness are also highly prevalent and result in great disease burden.

Due to muscular weakness and decreased respiratory drive, which is associated with central nervous system (CNS) involvement, nocturnal hypoventilation is frequently present. Dysfunction of the CNS can also affect cognitive domains in variable combinations, e.g., visuospatial and executive functions.[23] Together with behavioral disorders, individuals with DM1 mostly show signs of apathy and personality traits such as avoidance and rigidness. Both cognitive deficits and behavioral disturbances are important determinants of quality of life and participation.

Moreover, a substantial component of DM1 as a multisystemic disorder consists of gastrointestinal dysfunction. Many find gastrointestinal complaints to be the most burdensome manifestation of disease. Complaints include constipation and/or diarrhea, dysphagia, gastro-esophageal reflux and overweight/obesity. Furthermore, numerous patients are diagnosed with cardiac abnormalities, which significantly contribute to classical DM1 morbidity and mortality. Survival studies have shown that most affected individuals only reach an age between 45 and 65 years. Main causes of death consist of cardiac conduction disorders and pneumonia.[24]

Late-onset myotonic dystrophy type 1

Late-onset DM1 presents with clinical symptoms at the age of 40 years or older. As a rule, these individuals have a relatively small CTG repeat expansion. In typical cases, visual loss caused by cataract is the first symptom. In the course of disease, mild or subclinical myotonia can develop and mild muscular weakness appears. Excessive sleepiness is only rarely present.[25] For these patients, a life expectancy within normal range is foreseeable.

Etiology, pathogenesis, and genetics

DM1 is caused by a CTG repeat expansion in the 3' untranslated region of the myotonic dystrophy protein kinase (DMPK) gene, located at chromosome 19q13.32. The number of repeats tends to increase from generation to generation, accounting for genetic

anticipation, which is typical for DM1. As repeat length increases in later generations, more severe symptoms will develop at an earlier age. As can be seen in **Table 2.2**, the vast phenotypical variability of the disease can not solely be accounted for by the variation in CTG repeat expansion size, as there is overlap between subtype repeat sizes.

In healthy individuals, CTG repeat lengths range from 5 to 37. Repeat lengths of 38-50 are considered premutation alleles, whereas 51-80 repeats are called protomutations alleles.[27,28] In general, clinically affected individuals have repeat sizes ranging from 50 up to 4.000, but many pre- and protomutation allele carriers are asymptomatic or only mildly affected. Nonetheless, classification of asymptomatic or mildly affected pre- and protomutation individuals is of importance, since they are at risk of transmitting a further expanded allele to their offspring.

Furthermore, some individuals with DM1 carry so-called “variant repeats” at the DM1 locus, comprised of CTG repeats mixed with other DNA sequences. These variant repeats may be associated with milder or additional symptoms, and seem to have a stabilizing effect on genetic anticipation.[29] Variant repeats could be of great clinical importance, especially when informing patients on their prognosis and risk to future generations. Nevertheless, diagnostic testing in DM1 does not yet include variant repeat information.

Although CTG repeat expansion is measured in blood for diagnostic purposes, it is important to note that repeat mutations are dynamic and instable with variation in different types of tissues and cells. This causes so-called somatic mosaicism with muscle cell repeat length being noticeably larger than in other cell types.[30]

Despite DM1 being a monogenetic disorder, the mechanism by which the CTG repeat expansion causes multisystem manifestations is incompletely understood. Various hypotheses have been proposed in medical literature, none of which are mutually exclusive. Much support has been reported for the toxic RNA gain-of-function hypothesis: mutant DMPK transcripts interact with multiple proteins involved in the cell’s protein synthesis machinery, leading to heterogeneous and widespread downstream effects. Details of this model, as well as other hypotheses, are presented in excellent reviews elsewhere.[31,32]

Diagnostic testing

Since DM1 manifestations are diverse, patients might initially present with several different symptoms such as myotonia, muscle weakness, cataract, cardiac conduction disorders, hypersomnia or even developmental problems in children. If the clinical phenotype of an individual with DM1 is typical, trained neurologists or pediatric neurologists will be able to recognize the disease on the basis of its main features (see Diagnostic Criteria). In such cases, targeted genetic analysis will rapidly lead to confirmation of diagnosis. If genetic analysis confirms clinical suspicion of the disease, further clinical work-up and genetic counseling are indicated (see Manifestations and Management).

Differential diagnosis

If typical symptoms are present, the clinical phenotype of DM1 can be easily recognized by a trained eye. However, due to the broad heterogeneity of DM1 and diversity in age of onset, the diagnosis is not always readily established. In such cases, differential diagnosis is dependent upon the patient's age and presenting symptoms and signs. In neonatal cases, the diagnostic work-up is that of a "floppy infant". In childhood cases, DM1 should be in the differential diagnosis of developmental delay, intellectual deficits and behavioral disturbances. In adults, neuromuscular features of DM1 each have a differential diagnosis. An extensive discussion is beyond the scope of this chapter, and overviews of the differential diagnosis of distal muscle weakness, myotonia, and ptosis can be found elsewhere (for example: www.neuromuscular.wustl.edu).

Some of the clinical characteristics of DM1 can also be found in myotonic dystrophy type 2 (DM2). DM2, with various prevalence among countries, is a different multi-systemic disorder that features myotonia, muscle weakness and cataract.[2] Since muscle weakness is located more proximally than in DM1, the disease is also known as proximal myotonic myopathy (PROMM) or proximal myotonic dystrophy (PDM). DM2 is caused by a CCTG tetranucleotide repeat expansion in the cellular nucleic acid-binding protein (CNBP) gene.[33] Features differentiating DM2 from DM1 consist of absent facial and bulbar weakness, prominent tremors, absence of a congenital form, predominant muscle pain, and proximal muscle weakness as the most incapacitating symptom. Genetically, DM2 is dominantly inherited but lacks anticipation. More information on DM2 is available online (for example: https://www.ncbi.nlm.nih.gov/ books/NBK1466/).

Manifestations and management

By its nature, DM1 can lead to severe physical impairment, restricted social participation, and premature death. At present, no curative or disease-modifying treatment is available. Disease management is based on health supervision focusing on preservation of function, screening for multi-organ involvement and treatment of specific symptoms. This proactive managing approach is likely to reduce morbidity and mortality, especially through early diagnosis of cardiac and pulmonary complications.

As neuromuscular specialists with knowledge of DM1 might be scarce, effective management of individuals with DM1 is sometimes difficult. Management can get even more challenging as several specialists get involved because of the multi-systemic nature of disease. Thus, patient management requires a multidisciplinary integrative approach and is often best performed in the setting of a specialized neuromuscular center. It is advisable that care is coordinated by a specialized (pediatric) neurologist or (pediatric) rehabilitation specialist. This “coordinating doctor” should keep an overview of disease extent, social consequences and involved caregivers. Patients are seen by the coordinating physician at least once a year. During this annual visit, a systematic medical evaluation concerning all possibly affected domains should be conducted. If screening identifies problems in one or more areas, further diagnostics and therapy are initiated. Below, the different domains that may be involved are discussed in more detail. If necessary, complex cases of DM1 may in some countries be referred to a tertiary referral center.

It is important to realize, that as a part of the behavioral phenotype, individuals with DM1 can impede adequate disease management. An avoiding attitude towards care can be the result of lack of initiative, apathy and sleepiness (see **Development and Behavior**). Since patients typically don’t bring up complaints, a proactive approach is required. As a health care provider, it could also help to direct closed-ended questions at the patient and actively involve the partner or caregiver into the consult. Furthermore, sufficient time should be planned for each consultation. Education of the affected patients and relatives might be of help in maintaining consistent medical care. Since family members are commonly affected by the same disease, counseling and support of relatives should be addressed. In addition, attention should be given to the caregiver, who frequently suffers even more from the consequences of DM1 than the individual being provided care.

Individuals with DM1 and their caregivers have to be made well aware of the progressive nature of the disorder and its potentially lethal complications. In particular, they should be instructed to notify any health care provider about having DM1.

Genetic counseling

At the outset of genetic testing, its purpose should be well defined. Testing can be (1) predictive, (2) prenatal or (3) diagnostic, and the person requesting genetic analysis should be counseled accordingly. As knowledge on DM1 is rapidly evolving, health professionals are encouraged to consult the latest (local) guidelines. In general, we advise on early and low-threshold involvement of a clinical geneticist.

DM1 is inherited in an autosomal dominant manner. Nearly all affected individuals have inherited the expanded CTG allele from a parent with an abnormal CTG repeat expansion (see **Etiology, Pathogenesis, and Genetics**). Only rarely do expanded alleles originate from a previously normal allele.

Strikingly, many individuals with a mild form of the disease are unaware of the fact that they have DM1. It is not uncommon to find out about the genetic etiology after a mildly affected patient has a child who is more seriously affected, as a result of genetic anticipation. Particularly, this is seen in cases of unexpected congenital DM1 of maternal origin. If both parents of a proband with a proven DM1 allele are found to have normal CTG repeat sizes, alternate causes may be non-paternity, non-maternity or undisclosed adoption.

Predictive testing

Predictive testing is performed when family members of a DM1-affected individual have the desire to find out whether they have inherited a similar DM1 mutation. Pre-test counseling is of high importance, as test results may have legal, ethical, financial and social consequences.

Also, health care professionals and individuals with DM1 should be aware of the fact that a negative test result can exclude DM1 with great certainty, while a positive test result may raise even more questions given the complex genotype-phenotype relationship (see **Etiology, Pathogenesis and Genetics).**

Usually, predictive testing should only be pursued in adults, as there are significant ethical issues with predictive genetic testing in children. However, recognition of

cardiac risks associated with genetic mutations has raised the issue whether predictive testing should, in some cases, be provided for at-risk children.[34]

Prenatal testing

If patients are knowingly affected by DM1 and have the desire to have children, preconception consultation by a clinical geneticist/genetic counselor is advisable. In this consult, the risk of having an affected child and the options to prevent this should be carefully discussed. Currently, there are two possibilities for prenatal testing. The first option consists of prenatal diagnosis through chorionic villi or cells obtained by amniocentesis. Because this material comprises fetal DNA, CTG repeat size can subsequently be determined. A disadvantage might be that it is quite hard to correlate DM1 genotype to predicted clinical phenotype. In general, it is known that greater CTG repeat lengths are associated with more severe symptomatology. Still, the extent of disease and DM1 subtype cannot be accurately predicted. There is an increased risk for congenital DM1 if CTG repeat size is 730-1000 or higher.[35] In such circumstances, the expecting couple may decide to abort pregnancy.

A second option is preimplantation genetic diagnosis (PGD). In this case, fertilization is performed in vitro. Afterwards, one or two cells are biopsied from the eight-cell stage embryos. If the embryo turns out to have a normal CTG repeat length, it can be placed in utero. Per PGD treatment cycle, pregnancy success rate is about 20%. PGD can be experienced as an emotional and physical challenge for woman. In Europe and the US, PGD is available in specific centers only.

Diagnostic testing

Commercial DNA testing for DM1, using polymerase chain reacting (PCR) and Southern Blot, in individuals with an expanded CTG repeat allele is virtually always diagnostic (see **Diagnostic Testing)**. In case of a positive diagnostic test result, adequate counseling with regard to implications for the proband, as well as family members is essential.

It should be noted that at this time, DM1 trinucleotide repeat expansions are not covered in next generation sequencing (whole exome sequencing/whole genome sequencing approaches). Thus, if the clinical phenotype of DM1 is not recognized, the gene mutation may be missed if not specifically tested for.

Growth and feeding

In babies with a congenital subtype of DM1, sucking and swallowing may be impeded as a result of muscular weakness. Feeding through nasogastric tube might be necessary for a prolonged period of time. Also gastroparesis could lead to stasis of food.

In adolescents and adults, feeding can be difficult as a result of several disease-related factors. Firstly, tongue myotonia and bulbar muscle weakness might hinder normal chewing. Thereafter, swallowing of food can be impaired as a consequence of dysphagia. Dysphagia in DM1 is caused by oropharyngeal weakness and possibly also by localized myotonia. As food gets stuck in the pharynx, patients commonly experience coughing during meals and might need to drink sufficient fluids to help the bolus pass. In severe cases, aspiration can occur and cause (recurrent) pneumonia.

Evaluation

- Referral to an ear, nose and throat (ENT) specialist or speech therapist is necessary when extensive dysphagia is present or multiple bouts of aspiration pneumonia have occurred.
- In severe cases, dysphagia can cause insufficient intake and/or weight loss. It is best to refer to a gastroenterologist to evaluate therapeutic options.

Management

- A specialized speech therapist can give practical feeding advice in case of dysphagia. For example, eating has to take place in a calm environment, food should be cut into small pieces and patients should drink enough fluids during and after meals. Also, tongue myotonia gets better after warming up of the muscles through repeated movement.
- A gastroenterologist should evaluate if a percutaneous gastrostomy might be necessary to retain adequate feeding state in underweight patients.
- If breast or bottle feeding is impossible, feeding through a nasogastric feeding tube could be needed for congenital DM1.

Development and behavior

In congenital and childhood DM1, central nervous system involvement is often more prominent than neuromuscular involvement. Moderate-to-severe intellectual impairment occurs in a majority of individuals with early-onset DM1. Problems at school caused by speech and language delay are common, and are often a reason for special education. Intellectual dysfunction is usually global, but more specifically

affected cognitive domains with relative sparing of global cognition may occur.[20] In addition to cognitive problems, behavioral disorders occur in a majority of patients. The most common are attention deficit/hyperactivity disorder (ADHD), antisocial, aggressive or oppositional behavior. Disorders in the autistic spectrum occur frequently, as well as anxiety and depression. Behavioral disturbances contribute to educational problems, which may also be aggravated by fatigue and excessive daytime sleepiness (see **Central Nervous System Involvement**).[36]

Evaluation

- Neuropsychological and neuropsychiatric evaluation by specialized pediatric psychologists and/or psychiatrists is indicated.

Management

- Special education and training as appropriate.
- Modafinil can be considered if excessive daytime sleepiness and fatigue impede educational performance or quality of life.
- Attention deficit/hyperactivity disorder (ADHD), depression and anxiety may be treated with similar interventions as unaffected individuals.

Neuromuscular involvement

Neuromuscular weakness, progressing in a symmetrical distal-to-proximal fashion and myotonia in the extremities are key manifestations of DM1. Myotonia can be described as the inability to relax muscles following contraction, giving rise to a cramping sensation or stiffness. Patients might report to experience difficulties releasing grip or difficulties with chewing or speech, as myotonia commonly affects the hands and tongue. Myotonia may demonstrate a warm-up phenomenon, that is, become less prominent with repeated performance. Usually, myotonia gradually fades with the progression of muscle weakness.

Bulbar weakness with temporal muscle weakness leads to a specific facial appearance (see **Figure 2.2**), dysarthria and dysphagia. Individuals with DM1 may seem less interested or emotionless due to decreased facial expression. Ptosis can become severe and compensatory tilting of the head might be necessary. Also, weakness of the sternocleidomastoid and neck flexor muscles is specific for DM1, and patients can have trouble lifting their head. Importantly, muscular weakness may lead to falling and fear of falling. Falls are very common in natural DM1 history and require special attention.

Evaluation

- In each annual visit, explicitly ask for progression of muscle weakness and myotonia, and their impact on function. Perform physical and neurological examination to assess muscular weakness, atrophy and myotonia.
- Specific sites that show muscle weakness at an early stage, such as neck flexors, finger flexors and stretchers, and foot musculature, should be evaluated. Strength can be tested formally, but also functionally (lifting head when lying down, walking distance, walking on toes and heels, knee bending).
- Check for action and percussion myotonia. Action myotonia can be induced by asking the patient to make a strong fist and suddenly release. Percussion myotonia can be evoked by percussion of the thenar eminence, consequently the thumb might show myotonia induced flexion.
- Evaluate the occurrence, frequency, and causes of falls.
- Evaluate swallowing and speech for dysarthria and dysphagia.

Management

- Refer individuals with muscular weakness interfering with activities of daily living (ADL) to a rehabilitation specialist for orthoses and physical activity guidance.
- Aids and appliances can be helpful when muscular weakness limits the patient in daily life, such as named orthoses or walking aids. Wheelchairs can be considered if muscular weakness is severe.
- Refer to physiotherapist or rehabilitation specialist for fall prevention, if appropriate.
- Myotonia usually does not interfere with ADL and does not require therapy. If severe, mexiletine can be considered.[37]
- Patients should be advised to stay active. If preferred, a physiotherapist can oversee exercise activities and give home training instructions.
- Refer a patient with significant dysarthria and/or dysphagia to a speech therapist (see **gastrointestinal involvement**).

Central nervous system involvement

Central nervous system (CNS) manifestations of DM1 occur in all subtypes. Particularly in children, CNS features have more impact on daily functioning than neuromuscular symptoms (see **Development and Behavior**). However, also in adult-onset DM1 widespread and heterogeneous involvement of the CNS is an important determinant of health status. Cognitive deficits may occur with variable severity and affecting variable combinations of cognitive domains.[23] Behavioral disturbances include apathy and executive functioning disorders. Common personality traits include rigidness and

avoidance, and these may interfere with interpersonal relations. Subjectively, fatigue is one of the most common and most debilitating symptoms in DM1. Its etiology is likely multi-factorial. Excessive daytime sleepiness occurs frequently and may be attributable to sleeping problems, sleep-related breathing disorders, and involvement of the brain. Neuroimaging in individuals with DM1 may demonstrate a wide spectrum of both structural and functional anomalies, whereas pathological studies report various findings compatible with a neurodegenerative disorder.[38]

Evaluation

- Neuropsychological evaluation may be considered if the patient exhibits clinical symptoms and signs of CNS involvement.
- If fatigue and daytime sleepiness are present, one should be aware of the possibility of underlying nocturnal breathing disorders.
- Fatigue and daytime sleepiness may be evaluated using the Rasch-built Fatigue and Daytime Sleepiness Scale (FDSS)[39] or the subscale "fatigue" of the Checklist Individual Strength (CIS-fatigue).
- The Beck Depression Inventory – fast screen (BDI-FS) may be used to screen for depression.
- Neuroimaging is not routinely indicated, but can be considered if there are signs of CNS involvement that may be attributed to other causes than DM1.

Management

- If cognitive problems interfere with demands of a job, encourage the patient to seek advice from an occupational health care provider.
- Consider cognitive behavioral therapy (CBT) and/or modafinil for the treatment of fatigue and excessive daytime sleepiness, only after other causes such as affective disorders or nocturnal respiratory problems have been ruled out.
- Consider low-threshold referral to a medical psychologist or social worker if there are problems with acceptance of disease or if a patient and/or partner consider their mutual communication as a problem.

Dental involvement

Studies have shown that individuals with DM1 have more caries, gingivitis and plaque compared to healthy individuals.[40] This higher frequency of dental complications is assumed to be an effect of slower oral clearance, impaired muscular coordination and diminished self-care ability. Oral hygiene is expected to worsen as muscular involvement becomes more prominent. Furthermore, dental malocclusion and

structural craniofacial abnormalities were found in the temporomandibular joint and masticatory muscles.[41] Facial myotonia and muscle weakness, in combination with dental complications and structural abnormalities, may cause extra difficulties in food ingestion.

Evaluation

- Regular dental check-ups should take place at least every six months.
- In case of malocclusion or impeding craniofacial abnormalities, individuals with DM1 should be referred to an orthodontist or maxillofacial surgeon.

Management

- Professional prophylactic cleaning of the teeth should take place at least once every six months.
- Individuals with DM1 should be provided with oral health education concerning brushing of teeth and flossing. If possible, an electric toothbrush should be used.
- Orthodontic correction of abnormal teeth position should take place in the prepubertal growth phase.
- In case of craniofacial abnormalities, surgery might be necessary. As for all surgeries in individuals with DM1, the benefits and risks should be weighted carefully (see **Anesthesia**).

Gastrointestinal involvement

According to individuals with DM1, complaints of the gastrointestinal system are regularly considered the most disabling consequence of disease.[42,43] As a result, these complaints have a big impact of quality of life, and they deserve sufficient attention during consultation. Involvement of the gastrointestinal tract may occur from pharynx to anal sphincter and is thought to be the effect of gastrointestinal muscular impairment. Symptoms are likely to arise in the congenital and childhood subtypes, but are also a regular feature of adult-onset DM1. In over 25%, gastrointestinal problems were present before the diagnosis was established.[42] Complaints may consist of general abdominal pain, but can also be more specific.

Individuals with DM1 commonly experience dysphagia, worsening over time as muscle weakness progresses. Dysphagia is a serious complication that may lead to weigh loss and malnutrition, as well as aspiration and pulmonary complications (see **Neuromuscular and Respiratory**). Upper gastro-intestinal problems further include gastroesophageal reflux, stasis, bloating, and emesis. Cholelithiasis is more common

than in the general population, studies have shown that cholecystectomy was necessary in 16.5% of individuals with DM1.[44] Intestinal involvement can give rise to several complaints of which episodic diarrhea is considered the most disabling, especially when anal incontinence is also present.[42] It is known that bacterial overgrowth can be a cause of diarrhea in individuals with DM1, which can be treated with antibiotics.[45] On the other side of the spectrum, constipation is common, possibly leading to discomfort and pain, and even pseudo-obstruction.[46] Finally, overweight and obesity occurs in 40-50% of individuals with DM1, and may detrimentally affect physical and respiratory functioning.

Evaluation

- Perform annual history taking and physical examination for the presence of gastro-intestinal symptoms and signs.
- In case dysphagia causes insufficient intake and/or weight loss or if patients experience prolonged abdominal pain, persistent obstipation, frequent defecation or disabling fecal incontinence, they should be referred to a gastroenterologist.
- See **Growth and Feeding** for additional information on dysphagia.

Management

- Proton pump inhibitors can be prescribed if gastroesophageal reflux is present.
- If dysphagia becomes of severe, a percutaneous gastrostomy might be needed to retain an adequate feeding state.
- In case of symptomatic cholelithiasis or complicated cholelithiasis (causing cholecystitis, choledocholithiasis, cholangitis or acute pancreatitis), laparoscopic cholecystectomy is recommended. The benefits and risks of surgery should be weighted carefully (see **Anesthesia**).
- Diarrhea caused by intestinal bacterial overgrowth can be treated with antibiotics.
- Obstipation in DM1 is treated as any other form of obstipation, using laxatives and/or enemas.
- Referral to a dietician may be considered in case of overweight/obesity.

Respiratory involvement

Pulmonary involvement in DM1 can be detected even in those with minimal muscular disability, and has a multi-factorial etiology. Impaired coughing and dysphagia can give rise to aspiration of food, saliva or gastric contents (see **Gastrointestinal Involvement**), with consequent chronic pulmonary inflammation or pneumonia. Pneumonia was found to be the cause of death in about one third of individuals with DM1.[24]

Neuromuscular weakness may lead to both expiratory and inspiratory muscle weakness and consequently to decreased ventilation. With time, inspiratory capacity declines. In addition, studies have shown upper airway alterations, reduced chest wall compliance and centrally decreased CO_2 responsivity in individuals with DM1. Furthermore, being overweight negatively affects lung volumes. Together, these factors may lead to alveolar hypoventilation and hypercapnia (CO_2 retention), which was shown to be highly prevalent in individuals with DM1.[47] Often the effects of alveolar hypoventilation are more profound during the night, when respiratory drive is reduced and the supine position abrogates the aid of gravity to the diaphragm during inspiration.

In addition to (nocturnal) alveolar hypoventilation, other sleep-related breathing disorders may result from structural airway changes and muscular weakness. Obstructive sleep apnea syndrome (OSAS) and central sleep apnea syndrome (CSAS) were found to be more prevalent in individuals with DM1 than in the general population and can lead to abnormal sleeping patterns.[48] In case of OSAS, recurrent airway collapse will cause cessation of airflow, apneas and possible hypercapnia. Consequently, recurrent arousal might occur and cause daytime sleepiness. Sleep-related breathing disorders may have a negative effect on survival due to cardiovascular and metabolic changes.

Evaluation

- Possible respiratory involvement should be evaluated annually (see **Manifestations and Management**).
- Irrespective of respiratory symptoms, yearly pulmonary function testing (PFT) is recommended.
- If (recurrent) dysphagia-related aspiration is suspected, refer to ENT specialist or speech therapist (see **Gastrointestinal Involvement**).
- Refer to a specialized physiotherapist for cough techniques if coughing is impaired.
- Refer to a pulmonologist if there a signs of alveolar hypoventilation, sleep-related breathing disorders, recurrent airway infections or aspiration, increased breathing effort, abnormal blood gas results or abnormal PFT results.
- Avoid medication that could possibly depress respiratory drive, such as benzodiazepine and opiates (see **Anesthesia**).

Management

- Vaccination for influenza and pneumococcal infections is advisable, as Pneumococcal pneumonia and influenza infections might have serious complications in individuals with DM1.

- If aspiration pneumonia is suspected, individuals should be treated with antibiotic drugs according to local protocol.
- Alveolar hypoventilation may be a reason for non-invasive ventilation at home.
- Consider treatment for sleep-related breathing disorders. If OSAS without hypoventilation is present, continuous positive airway pressure (CPAP) therapy is an option. If there is overlap between OSAS, CSAS and hypoventilation, there may be an indication for non-invasive ventilation.
- CPAP or home ventilation should be explained carefully. It is advisable to regularly check motivation and compliance of therapy.

Cardiovascular involvement

Cardiac manifestations in DM1 are common and may have serious consequences. Importantly, cardiac involvement is frequent even in asymptomatic patients. Conduction disorders mainly consist of atrioventricular (AV) block and bundle branch block (QRS>120ms), which are possibly secondary to degeneration of the cardiac conduction system. Arrhythmia's and conduction disorders occur in approximately 4-28% of individuals with DM1 and are independent of disease severity.[49] Both arrhythmias and conduction disorders may lead to sudden cardiac death, a major cause of mortality in DM1.[24]

As noted, DM1 cardiac involvement may go without any clinical symptoms. The absence of symptoms may relate to relatively mild involvement, to physical inactivity of patients and consequent low cardiac demands, or could be the result of underreporting by patients. It is important to realize that pacemaker implantation does not protect against sudden death due to tachyarrhythmias, and individuals at risk for tachyarrhythmias consequently may need implantation of an cardioverter defibrillator (ICD).[50,51]

Recommendations for cardiac investigation in adult DM1 were summarized in an international workshop.[52] For children, no consensus has been reached, despite the fact that cardiac involvement may have been underestimated.

Evaluation

- Annual follow-up by the coordinating doctor should consist of taking cardiac and family history (see below), physical examination and electrocardiogram (ECG). Alternatively, annual cardiac follow-up may be performed by a cardiologist. Special attention should be paid to symptoms and signs of arrhythmias, conduction disorders and heart failure.

- Cardiac evaluation should include possible cardiovascular complaints (dizziness, syncope, palpitations, angina and orthopnea) and family history for sudden death, ventricular fibrillation, sustained ventricular tachycardia or pacemaker implantation.
- If cardiac involvement is suspected, referral to a cardiologist is indicated.
- Holter monitoring should be performed in case of cardiac symptoms or ECG abnormalities. Holter monitoring is indicated every two to five years in asymptomatic patients.
- Echocardiography should be performed at the time of diagnosis and in the presence of manifestations of heart failure or ECG changes. In asymptomatic patients, routine echocardiogram should be performed every three years. Cardiac MRI can be considered in some cases.
- The exact role of electrophysiological (EF) studies is not established; these may primarily be used to evaluate the conduction system in symptomatic individuals.

Management

- Atrial arrhythmias, such as atrial fibrillation or flutter, are common and antiarrhythmic treatment might be necessary. Important to note is that preexisting tendency to ventricular tachyarrhythmias or bradycardia might worsen by antiarrhythmic medication.[52]
- Pacemaker implantation should be considered in each degree of atrioventricular block. In case of a second or third degree AV block or HV interval >70 ms on EF study, pacemaker implantation is necessary.
- An ICD is indicated in case of: (1) a history of ventricular fibrillation or sustained ventricular tachycardia (VT) with hemodynamic instability, (2) sustained VT in combination with structural heart damage, (3) syncope in combination with inducible sustained VT with hemodynamic instability, syncope in combination with a left ventricular ejection fraction <35% or syncope in combination with heart failure NYHA II-III.
- An ICD can be considered in case of: (1) unexplained syncope, (2) significant dysfunction of the left ventricle, (3) sustained VT in combination with normal left ventricular function and (4) familial cardiomyopathy associated with sudden death, in combination with a left ventricular ejection fraction <35% and heart failure NYHA class I.

Opthalmologic involvement

Cataract is a distinguishing and common feature in DM1. In case of late-onset DM1, visual loss due to opaqueness will often be the first symptom of disease. In the remaining subtypes, early onset cataract is also frequent, although it is rarely seen in

young children. Slit-lamp evaluation of the lens can show posterior subcapsular iridescent opacities or cataract, which is often of polychromatic nature.[53] Due to the highly reflective multicolored corneal crystals in polychromatic cataract, it is also known as “Christmas tree” cataract.

Besides cataract, hypermetropia and strabismus are common in individuals with DM1, especially in children.[54] Vision can further be affected by ptosis, and weakness of the orbicularis oculus muscle may lead to insufficient closure of the eyes. The retina can demonstrate abnormalities of the macula or the retinal periphery.

Evaluation

- In case of glare or blurred vision, individuals should be referred to an ophthalmologist. If lens opacities or cataract are found, annual monitoring is recommended.
- Children with DM1 should receive regular ophthalmic examination, in which special notice should be paid to possible hypermetropia and strabismus.

Management

- If cataract interferes with visual acuity or interferes with daily life, intraocular lens implantation (under local anesthesia) is recommended.[53]
- Corrective treatment of strabismus and hypermetropia, when present, is not different from the general population.
- If ptosis interferes with vision, surgery may be considered. Nonetheless, surgical treatment should be postponed as long as possible since muscle weakness progresses, and ptosis will recur.
- No treatment is available for DM1 retinopathy.

Dermatologic involvement

Considering the multi-systemic expression of DM1, skin involvement could be expected; however, few studies into dermatological features of DM1 have been conducted. Skin manifestations of DM1 include focal hyperhidrosis, pedunculus fibromas, early androgenic alopecia and other adnexal abnormalities.[55] Also, there is an association between DM1 and pilomatrixomata, a benign tumor of the hair matrix.[56] The relationship between DM1 and (pre)neoplastic cutaneous lesions still remains unclear.

Evaluation

- Referral to a dermatologist is only necessary if individuals are bothered by dermatological features, such as pilomatrixomata.

Management

- Pilomatrixomata can be surgically removed by a dermatologist or (plastic) surgeon.
- There is no treatment for early androgenic alopecia.

Ears and hearing

Although there are few studies of DM1 and ears and hearing, excessive sensorineural high-tone hearing loss is more frequent in DM1 compared to healthy individuals of the same age.[57,58]

Evaluation

- Individuals should be referred to an audiologist for evaluation if hearing loss is suspected.
- Since hearing loss might lead to extra difficulties for children with developmental delay or cognitive impairment, threshold for evaluation should be low.

Management

- Treatment consists of a personalized hearing aid, provided by a certified audiologist.

Musculoskeletal involvement

Orthopedic involvement is most prominent in the congenital and the childhood subtypes of DM1. Commonly, impairments consist of foot and spinal deformities, and contractures.[59] Congenital contractures probably develop as a result of reduced fetal movements, with clubfeet being the most frequent, but contractures of the hips or shoulders might also arise. Muscle weakness and hypotonia of the trunk make it difficult to maintain an upright position of the spine, which could cause kyphoscoliosis.

Evaluation

- If severe and/or interfering with function, deformities and contractures should be examined by an orthopedic surgeon to explore therapeutic possibilities.

Management

- Contractures are treated conservatively at first, if possible. If there is not enough response to conservative treatment, surgery might be necessary.
- In case of clubfeet, the conservative treatment should start within three days after birth. Passive stretching through physiotherapy might help to improve the position of the feet. Fixation in plaster or a splint should help maintain the improved position. After six months, the orthopedic surgeon has to evaluate the effect of conservative treatment and decide whether surgery is needed. Important to note is that surgical correction should always take place before the child attempts to walk. The child should be followed-up by an orthopedic surgeon and orthopedic shoemaker until full-grown.
- Recommendations on the treatment of spinal deformities differ, as they can either be treated conservatively or surgically. It is best to have an orthopedic surgeon evaluate each specific case.

Endocrine involvement

Various endocrine disturbances may occur in DM1. Disturbances in the hormonal axes associated with reproduction are the most common. In DM1 affected men, testicular atrophy occurs in 60-80% of patients. Male fertility is reduced, especially in early adult-onset DM1, and more than a third of men have androgen insufficiency.[60] In women, there is a high rate of reproductive loss both early and late in pregnancy. While late loss of pregnancy is likely the result of problems caused by congenitally affected fetuses, early pregnancy loss may be the result of endocrine disturbances.

Moreover, DM1 is often characterized by insulin resistance. Less frequently, patients may be affected by type 2 diabetes mellitus. Other possible endocrine disorders are (para)thyroid dysfunction and disturbances of the adrenal gland.[60]

Evaluation

- Couples should be referred to a gynecologist or reproductive endocrinologist in case of fertility problems. Investigations into the cause of reduced fertility should follow standard procedures. Genetic counseling is also indicated (see **Genetic Counseling**).
- DM1-affected women that want to undergo in vitro fertilization, eventually combined with preimplantation genetic diagnosis, should be cautioned about a possible increased risk for anesthetic complications and rhythm disturbances caused by medication used during treatment. Risks and benefits should be discussed carefully (see **Genetic Counseling**).

- Screening for endocrine dysfunction (PTH, TSH and glucose) is advisable at first presentation and during follow-up.[60]

Management

- If pregnancy is desired, severe oligozoospermia is an indication for in vitro fertilization with intracytoplasmic sperm injection.
- Diabetes Mellitus type 2 and (para)thyroid dysfunction should be treated according to standard guidelines.

Pregnancy and delivery

In contrast to the well-known male infertility described in DM1 (see **Endocrine Involvement**), the issue of female fertility remains controversial.[61]

Nevertheless it is known that DM1 can have several adverse effects on the course of pregnancy and delivery.[61,62] Therefore, counseling women with DM1 that are contemplating pregnancy is imperative. Counseling involves giving information on the risk of having affected offspring (see **Genetic Counseling**) and involves discussing the risks of pregnancy for the patient itself.

As fallopian tube mobility and uterine function might be affected due to smooth muscle involvement, a higher rate of ectopic pregnancy is suspected, and placenta previa is significantly more frequent. Moreover, there is a markedly increased incidence of pre-term labor with only half of pregnancies reaching full term. It seems that the increased risk for early delivery is related to woman carrying affected offspring, as such was the case in most of the observed incidents. Next to these serious complications, maternal urinary tract infections are more common, possibly caused by subtle pelvic floor weakness.[61] While some studies indicate miscarriages being more frequent in DM1 affected women, this is still debatable.[61,62]

During labor, abnormalities can occur in all three stages as an effect of uterine dysfunction and lack of voluntary assistance. Therefore, vaginal delivery interventions and cesarean sections are more common. Fetal distress is a frequent complication, perinatal mortality was found to be 16% in a British Cohort of DM1 women.[63] The higher risk of perinatal death and several other complications, such as polyhydramnios and clubfeet, are mainly due to fetuses being affected by congenital DM1.[61]

Evaluation

- Preconception planning should include obstetric and general history and an assessment of current disease status. Cardiac and respiratory evaluation deserves extra attention.
- Pregnancies should be monitored closely in a high-risk pregnancy clinic by a physician familiar with DM1. Extra attention should be paid to possible complications, as mentioned above.
- DNA testing by means of amniocentesis or chorionic villus sampling (CVS) can be considered (see **Genetic Counseling**).
- A multidisciplinary approach of pregnancy and delivery is advised. Make a plan for delivery that includes mode, location, anesthesia and fetal presentation.[64]
- Third stage of delivery should be actively managed to prevent postpartum hemorrhage caused by uterine inertia or atony.

Management

- Cesarean or assisted vaginal delivery might be necessary when there are signs of maternal exhaustion or fetal distress.
- Uterine inertia can cause blood loss and usually responds to oxytocin.[64] If blood loss is extent, blood transfusion and manual placenta evacuation can be required.

Anesthesia

Studies have shown an increased prevalence of perioperative complications in DM1.[65] Most of the time, complications consist of pulmonary difficulties or cardiac events. Cardiac complications may include rhythm disturbances or even acute death. Pulmonary complications mainly consist of respiratory insufficiency due to hypoventilation, which may lead to impossibility to wean patients from the ventilator. Late pulmonary complications include atelectasis, pneumonia and retained bronchial secretions. Importantly, apathy and behavioral characteristics can cause patients to omit their disease status at pre-operative screening. Due to high prevalence of peri-operative complications, inestimable reactions to succinylcholine (possible hyperthermia) and prolonged and increased sensitivity to analgesics and sedatives, it is absolutely necessary for an anesthesiologist to be aware of the potential operative complications of DM1. Unfortunately, in some patients the diagnosis may not have been established prior to operation and complications cannot be anticipated.

Evaluation

- Recommendations for anesthetic management in patients with DM1 were summarized by The Myotonic Dystrophy Foundation (available at www.myotonic.org).
- Anesthesiologists and surgeons should always be aware of the fact that the patient has DM1 before performing surgery. Ideally, pre-operative planning is started early.
- In addition to neurological progression, cardiac, pulmonary and gastrointestinal involvement should be evaluated prior to surgery. If necessary, other medical specialties should be consulted.
- A preoperative ECG is always indicated.
- Evaluate whether general anesthesia can be avoided by opting for locoregional anesthesia.
- Prepare the patient for possible prolonged post-anesthesia mechanical ventilation or prolonged ventilatory assistance.

Management

- Try to avoid pre-operative sedatives (such as benzodiazepines) and opioids as much as possible.
- Avoid depolarizing neuromuscular blocking agents and anticholinesterases.
- Reduce the usage of opioid as much as possible, and avoid opioids with long half-life.
- Continuously monitor SpO2 and electrical activity of the heart (ECG) for at least 24 hours after surgery or until the patient has fully regained pre-operative status. If analgesics or sedatives are still being used, continue monitoring. A minimum of 48 hours of monitoring may be considered after abdominal surgery or in severely affected patients.Beware of late post-operative pulmonary complications such as pneumonia, and treat according to local protocol.

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Chapter 3

Parental repeat length instability in myotonic dystrophy type 1 pre- and protomutations

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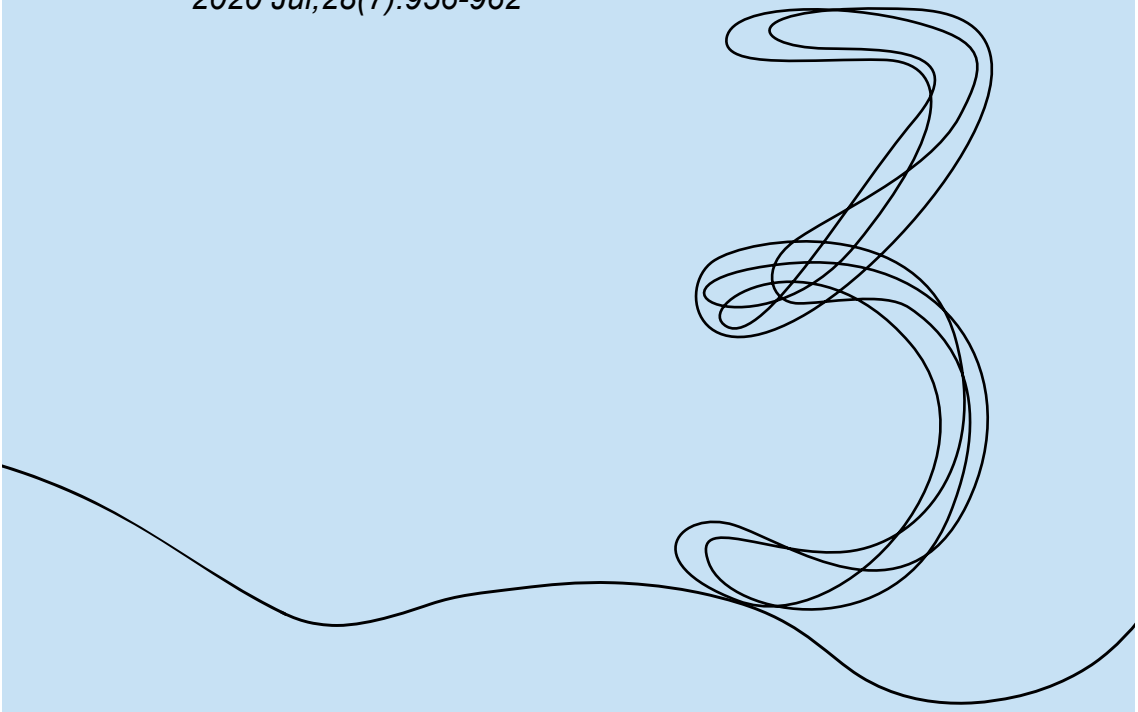

Abstract

Myotonic dystrophy type 1 (DM1) is caused by a CTG trinucleotide repeat expansion on chromosome 19q13.3. While DM1 premutation (36-50 repeats) and protomutation (51-80 repeats) allele carriers are mostly asymptomatic, offspring is at risk of inheriting expanded, symptom-associated, (CTG)n repeats of n>80. In this study we aimed to evaluate the intergenerational instability of DM1 pre- and protomutation alleles, focussing on the influence of parental gender. 146 parent-child pairs (34 parental premutations, 112 protomutations) were retrospectively selected from the DM1 patient cohort of the Maastricht University Medical Center+. CTG repeat size of parents and children were determined by (triplet-primed) PCR followed by fragment length analysis and Southern blot analysis. 58 out of 81 (71.6%) paternal transmissions led to a (CTG)n repeat of n>80 in offspring, compared to 15 out of 65 (23.1%) maternal transmissions (p<.001). Repeat length instability occurred for paternal (CTG)n repeats of n≥45, while maternal instability did not occur until (CTG)n repeats reached a length of n≥71. Transmission of premutations caused (CTG)n repeats of n>80 in offspring only when paternally transmitted (2 cases), while protomutations caused (CTG)n repeats of n>80 in offspring in 71 cases, of which 56 (78.9%) were paternally transmitted. In conclusion, our data shows that paternally transmitted pre- and protomutations were more unstable than maternally transmitted pre- and protomutations. For genetic counseling this implies that males with a small DMPK mutation have a higher risk of symptomatic offspring compared to females. Consequently, we suggest addressing sex-dependent factors in genetic counseling of small-sized CTG repeat carriers.

Introduction

Myotonic dystrophy type 1 (DM1; OMIM #160900) is an autosomal dominant neuromuscular disorder, caused by a cytosine-thymine-guanine (CTG) repeat expansion on chromosome 19q13.3.[1] The CTG expansion, located at the 3'untranslated region of the dystrophia myotonica protein kinase (DMPK) gene, seems to alternate RNA-binding protein activity through the production of mutant DMPK transcripts.[2] This pathophysiological process is presumed to give rise to DM1's clinical features, which vary in age of onset, symptomatology and severity depending on the DM1 subtype.

From a clinical perspective, DM1 can be divided into four categories, ranging from late-onset to congenital DM1. Late-onset DM1 is associated with repeat lengths <100, congenital DM1 is often associated with repeat lengths >1000, and intermediate phenotypes have repeat lengths in between.[3,4] While late-onset DM1 may cause early onset cataract and muscle weakness at older age, congenital DM1 leads to hypotonia and severe respiratory distress at birth.[3,4] Main features of the remaining two subtypes, known as juvenile and adult-onset DM1, consist of muscular weakness and myotonia in combination with organ involvement such as cardiac conduction defects or nocturnal hypoventilation.[3,4] In juvenile and congenital DM1, developmental delay may also be present.

In stable non-pathogenic DMPK alleles, the number of CTG repeats ranges from 5 to 35 per allele.[5-9] Repeat expansions of 36-50 are not associated with symptoms, but are designated DM1 premutations.[10,11] In case of CTG repeat expansions of 51-150, the diagnosis of DM1 is confirmed if accompanying symptoms are evident.[11] When symptoms of DM1 are absent (asymptomatic family member or foetus), individuals are at risk of developing DM1.[11] Still, individuals carrying a CTG repeat of 51-80 frequently remain asymptomatic.[11-13] These small-sized CTG repeat expansions, that may be transmitted in relatively stable manner for several generations, were designated DM1 protomutations.[12] Repeat expansions >80, that often cause a strong amplification upon transmission, were designated full-sized DM1 mutations.[12,13]

Genetic anticipation (due to further lengthening of the CTG repeat) is known to cause more severe symptoms, and a decrease in age of onset of DM1 in successive generations.[3] Consequently, it is of great importance to identify CTG repeat expansion carriers, even if these individuals might not be clinically symptomatic. In case of DM1 pre- and protomutation carriers, offspring might develop symptomatic adult-onset, juvenile or even congenital DM1 due to repeat length instability.

Several factors are presumed to play a role in DM1 repeat length stability. While the presence of CTG repeat tract interruptions might work as a stabilizing factor, studies have shown that parental gender can evoke repeat length instability.[14-18] In mothers diagnosed with adult-onset DM1, the CTG repeat seems prone to extreme expansion when transmitted to offspring, resulting in congenital DM1.[17,18] For pre- and protomutations however, a reversed gender effect was suggested. In patients carrying relatively small CTG repeat expansions, paternal transmission caused larger CTG repeat lengths in offspring than maternal transmission.[12,13,19-21]

Still, knowledge of the inheritance of small-sized CTG repeat expansions is scarce, causing uncertainty in genetic counseling. Current guidelines on DNA testing in DM1 describe that small-sized CTG repeats may be unstable and that relatives of carriers are at risk of developing DM1.[11] However, the effect of parental gender is not addressed.

In this retrospective study, we aim to provide more precise data on gender-dependent intergenerational instability of DM1 pre- and protomutations, in order to improve genetic counseling for DM1 pre- or protomutation allele carriers.

Materials and methods

Study population

In order to identify individuals with a pre- or protomutation of de DM1 allele, the DM1 patient cohort database of the Clinical Genetics laboratory of the Maastricht University Medical Center+ was checked for individuals tested between 1993 and 2017. Detection of DM1 pre- or protomutations are mostly the result of family investigation, following the DM1 diagnosis of a symptomatic proband. Family trees were reviewed, to select parent-child pairs in which a pre- or protomutation was transmitted to a successive generation. If a pre- or protomutation carrying parent had multiple children, all children were included as separate parent-child pair. Expanded CTG lengths were categorized based on the mean CTG repeat length (as results are usually given in a range), which was (CTG)n, n=36-50 in case of a premutation, (CTG)n, n=51-80 in case of a protomutation, and (CTG)n, n>80 in case of a full mutation. CTG repeat length instability was defined as an expansion of the pre- of protomutation CTG repeat into (CTG)n, n>80 in offspring. All CTG repeats used in the study were analysed as part of regular patient care. Since the determination of DM1 subtypes is based on clinical features, which can become apparent at an older age in case of juvenile, adult- or late-onset DM1, only the occurrence of congenital DM1 in offspring was recorded.

Characterisation of CTG repeat lengths

Genomic DNA was extracted from whole blood using NucleoSpin ®8 Blood Isolation kit (Macherey-Nagel, Düren, Germany) according to manufacturer's instructions. CTG repeat length analysis was performed by CTG-PCR, followed by Southern blot hybridization, and triplet-primed PCR (TP-PCR). For the CTG-PCR, 200 ng genomic DNA was used with 20 pmol Fw-P1 primer 5'-AGAAAGAAATGGTCTGTGATCCC-3', 20 pmol 6-FAM labelled Rv-P2 primer 5'-GAAGGGTCCTTGTAGCCGGGAA-3' and 10% DMSO. TP-PCR was performed on both strands of the CTG repeat according to Warner *et al.* (1996) [22]. After PCR amplification, the fragments were analysed on ABI 3730 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Subsequently, Southern blot analysis was performed to confirm the CTG-PCR and TP-PCR results. Therefore, PCR products obtained using Fw-P1 and Rv-P2 were separated on a 1.5% agarose gel and blotted onto a Nylon membrane (Roche Diagnostics GMbH, Mannheim, Germany). The membrane was hybridized with a 5'digoxygenine labelled $(CTG)_{10}$ oligo probe. After stringency washes, the digoxygenine label was visualized using anti-digoxigenin-AP-conjugate Roche Diagnostics GMbH, Mannheim, Germany and CDP-Star (Roche Diagnostics GMbH, Mannheim, Germany).

CTG repeat interruptions were determined by modification of the TP-PCR. The Rv-P2 primer was replaced by the Fw-P1 primer, and P4CAG primer (tacgcatcccagtttgagacgCAGCAGCAGCAGCAG) by a GGC or CCG specific primer (tacgcatcccagtttgagacgTGCCGCTGCCGCTGCC or tacgcatcccagtttgagacgTGGGCCTGGGCCTGGGC, respectively). After PCR amplification, the fragments were analysed on ABI 3730 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). CTG tract interruptions in DM1 pre- and protomutations were confirmed by DNA sequencing. All collected repeat sequences were submitted to ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/, accession numbers SCV001156422 to SCV001156483)

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics software version 24 (SPSS Inc, Chicago, IL, USA). The distribution of continuous variables was assessed for normality by visual inspection of histograms and standardized normal probability plots. Continuous variables are expressed as mean±standard deviation (SD) when normally distributed. Categorical variables are expressed as counts with corresponding percentages. Qualitative data was compared using the chi-squared (χ^2) test or Fisher's exact test, quantitative data was compared using the unpaired Student's t-test. $P<0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 146 parent-child pairs with a known parental pre- ((CTG)n, n=36-50) or protomutation ((CTG)n, n=51-80) of the DM1 locus were included. 34 (23.3%) parents carried a premutation and 112 (76.7%) carried a protomutation (**Figure 3.1**). A total of 35 parents with multiple children were included. Of the transmitting parents, 81 were male and 65 were female. Baseline characteristics of included parents are further summarized in **Table 3.1**.

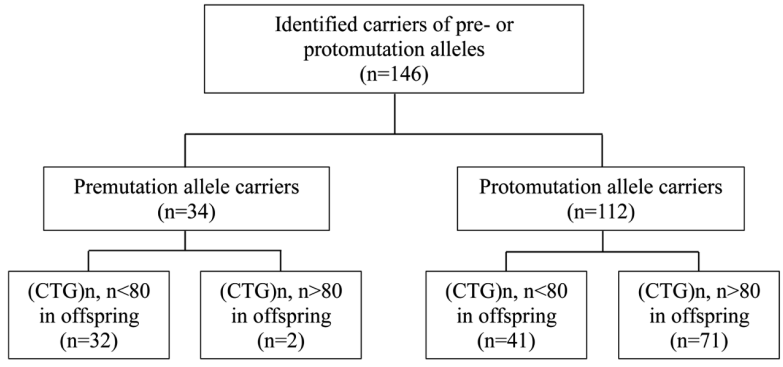

Figure 3.1 Included premutation ((CTG)n, n=36-50) and protomutation ((CTG)n, n=51-80) allele carrying parents, selected from the myotonic dystrophy type 1 (DM1) patient cohort database of the Clinical Genetics laboratory of the Maastricht University Medical Center+ between 1993 and 2017. Intergenerational instability of the CTG repeat length is displayed for both groups separately. Out of 146 pre- and protomutation transmissions, 97 transmissions regard first-born offspring.

Table 3.1 Baseline characteristics and intergenerational instability of CTG repeats.

	Total n=146	**Paternal transmissions n=81**	**Maternal transmissions n=65**
Parental age at birth offspring, years ± SD	30 ± 5	30 ± 5	29 ± 5
Type of mutation			
Premutation ((CTG)n, n=36-50)	34	18 (22,2%)	16 (24,6%)
Protomutation ((CTG)n, n=51-80)	112	63 (77,8%)	49 (75,4%)
Mean CTG repeat ± SD	59 ± 11	58 ± 11	59 ± 12
Intergenerational instability			
(CTG)n in offspring, n≤80	73	23 (28,4%)	50 (76,9%)
(CTG)n in offspring, n>80	73	58 (71,6%)	15 (23,1%) *

± values indicate means ± standard deviation (SD). * Indicates statistical significant difference between paternal and maternal transmission, p<0.001.

Intergenerational instability

Upon transmission in the premutation group, 2 out of 34 alleles (5.9%) expanded into (CTG)n of n>80 in offspring. In the protomutation group, 71 out of 112 alleles (63.4%) expanded into (CTG)n of n>80 in offspring (**Figure 3.1**). Chi-square analysis indicated a significant association between the type of mutation (pre- or protomutation) and expansion of the CTG repeat into (CTG)n, n>80 ($p<0.001$). None of the children that inherited a (CTG)n of n>80 were affected by the congenital subtype of DM1. CTG tract interruptions were observed in two DM1 premutation carrying parents and their offspring.

Intergenerational instability in relation to parental gender

The combined results of both pre- and protomutation transmissions, show that 58 out of 81 (71.6%) paternal transmissions lead to a (CTG)n repeat of n>80 in offspring, in comparison to 15 out of 65 (23.1%) maternal transmissions ($p<0.001$) (**Table 3.1**). Repeat length instability occurred for the entire range of paternal (CTG)n repeats of n≥45, while maternal instability was not observed until (CTG)n repeats reached a length of n≥71 (**Figure 3.2**). Apart from the observed CTG thresholds in our study population ((CTG)n, n=45 for paternal transmission and (CTG)n, n=71 for maternal transmission), paternal transmission of DM1 pre- and protomutations seemed to be more frequently unstable than maternal transmission, even if the (CTG)n repeat in offspring did not reach lengths over n>80 (**Figure 3.3**).

When restricting the analysis to first-born offspring (n=97), paternal transmission of pre- and protomutations lead to (CTG)n of n>80 in offspring in 41 out of 57 cases (71.9%). For maternal inheritance, transmission of pre- and protomutations lead to (CTG)n of n>80 in offspring in 10 out of 40 cases (25%). Chi-square analysis indicated a significant association between parental gender and expansion of the CTG repeat into (CTG)n, n>80 in case of first-born offspring ($p<0.001$). The observed sex-dependent CTG threshold of (CTG)n, n≥45 for males and (CTG)n, n≥71 for females remained the same.

Transmission of premutations (n=34) caused (CTG)n repeats of n>80 in offspring in two cases, of which both were paternally transmitted. Transmission of protomutations (n=112) caused (CTG)n repeats of n>80 in offspring in 71 cases, of which 56 (78.9%) were paternally transmitted.

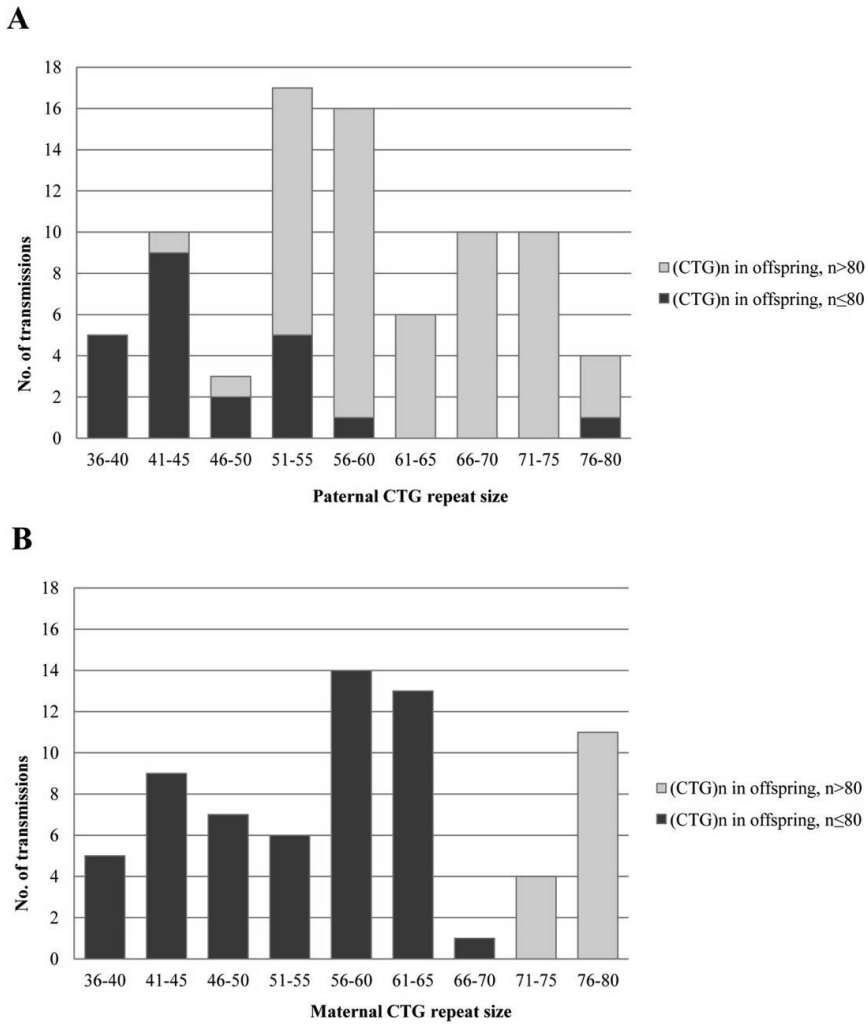

Figure 3.2 Relationship between parental CTG repeat length and myotonic dystrophy type 1 (DM1) status in offspring, for DM1 premutation ((CTG)n, n=36-50) and protomutation ((CTG)n, n=51-80) inheritance. DM1 status in offspring is based on a cut-off value of (CTG)n, n>80. (A) Paternal transmission. (B) Maternal transmission.

Inheritance pattern in case of multiple children

For 35 DM1 pre- or protomutation allele carrying parents, we had information about the CTG repeat size in more than one child. In 31 of these families, all tested children were in the same CTG category (either all tested children had a (CTG)n of n>80, or all tested children carried a pre- or protomutation). In four of the investigated families,

some of the tested children inherited a (CTG)n repeat of n>80, while others inherited a relatively stable form of the pre- or protomutation. In two of these families, only the second child inherited a (CTG)n of n>80 (one out of two children, 50%). In a family of three children, the second and third child had a (CTG)n of n>80 (66.7%). In another family of five children, only the third child (20%) was affected by DM1 with (CTG)n, n>80. In these four families, all transmitting parents were of male gender.

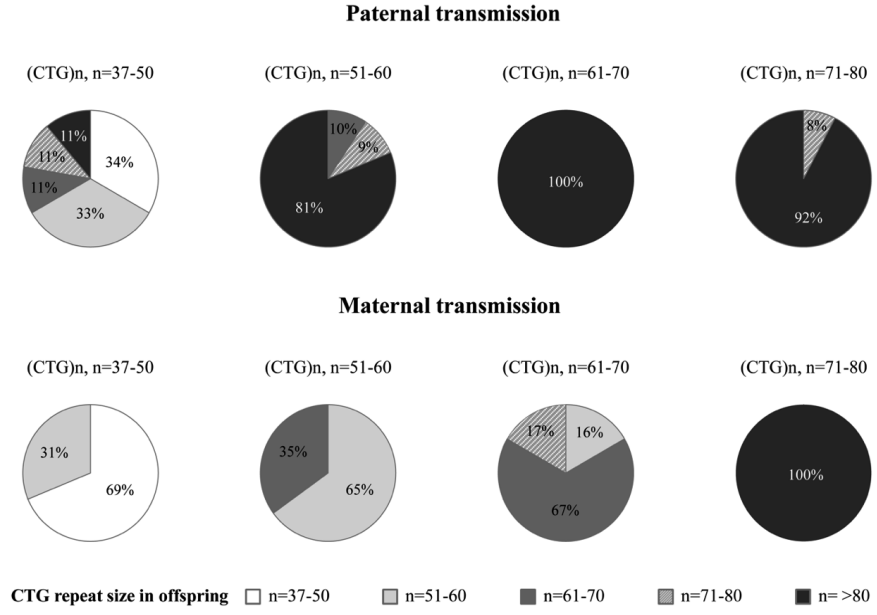

Figure 3.3 Relationship between parental CTG repeat length and CTG repeat length in offspring, categorized by parental gender. DM1 status in offspring is based on a cut-off value of (CTG)n, n>80. The values above each pie chart represent parental CTG repeat length.

Discussion

In this study we retrospectively evaluated the intergenerational instability of DM1 pre- and protomutation alleles, focussing on the influence of parental gender. Our results show that paternal transmission of both pre- and protomutations is relatively unstable, causing (CTG)n repeats of n>80 in offspring in 71.6% of cases. For maternal transmission, only 23.1% of offspring inherited a (CTG)n repeat of n>80. Moreover, the (CTG)n threshold for DM1 pre- and protomutation instability in our study population

was n≥45 for fathers, in comparison to (CTG)n, n≥71 for mothers. In general, DM1 protomutations were far less stable than DM1 premutations.

Some studies have previously reported on the influence of parental gender on DM1 pre- and protomutation transmission.[12,13,17] These studies support that paternal transmission is more likely to cause repeat length instability than maternal transmission.[12,13,17] In these studies however, the proportions of paternal unstable transmission were even higher than the 71.6% found in our study.[12,17] Possibly, this was caused by an overestimation due to smaller sample sizes and broader inclusion ranges (parental (CTG)n repeats up to n=100).

We also report on gender-dependent CTG thresholds for the inheritance of small-sized repeat expansions (**Figure 3.2**). Paternal repeat length instability started from (CTG)n repeats as low as n=45. Although the CTG threshold for female inheritance is based on only 15 cases, the higher threshold value further validates the role of parental sex. Moreover, paternal transmission was found to be of a more unstable nature, even if CTG repeats in offspring did not exceed (CTG)n, n=80 (**Figure 3.3**).

None of the children in our study population were affected by the congenital subtype of DM1. The congenital subtype is typically the result of maternal inheritance of adult DM1 with (CTG)n repeats of n>150.[11,17,18,23] Thus, it may seem as if maternally transmitted large CTG repeat expansions are more unstable than paternally transmitted repeat expansions. This apparent reversed relationship between parental gender and CTG repeat size in offspring might be explained by negative selection of large DM1 alleles at spermatogenesis.[17,24,25] Consequently, paternally transmitted small-sized CTG repeats would demonstrate substantial lengthening of the repeat in offspring, as observed in our study, while paternally transmitted congenital DM1 would be rare due to natural selection. This proposed mechanism is strengthened by the limited number of case reports on paternally inherited congenital DM1, in which paternal repeat lengths were mostly on the lower end of the scale ((CTG)n between n=65 and n=200).[25-29] In our study population however, large repeat expansions in offspring and congenital DM1 were not observed, which could be considered a limitation that possibly attenuates the aforementioned hypothesis.

In other trinucleotide repeat disorders, such as Huntington Disease (HD), parental gender differences in transmission have also been observed.[30-33] For HD, large CAG expansions in offspring occur almost exclusively through paternal transmission, while maternal transmission was found to be relatively stable.[32] HD intermediate alleles,

which resemble DM1 pre- and protomutations since they rarely cause clinical symptoms but are prone to intergenerational instability, show a similar effect of paternal sex.[31]

Still, parental gender does not seem to be the only factor contributing to DM1 pre- or protomutation instability. As our results show, different children of the same transmitting parent can inherit either (CTG)n repeats of n>80, or a relatively stable form of the pre- or protomutation. This phenomenon was observed in four families, in which the transmitting parent was the father. The length of the parental repeat expansions itself seems to be of influence on allele instability (**Figure 3.3**), but literature suggests that other factors such as parental age, genetic modifiers, and DNA repair mechanisms might also play a role.[12,25,33,34] Since first-born offspring in these four families did not inherit (CTG)n repeat lengths of n>80, paternal somatic instability of the repeat might have also had an effect.

Apart from this, it is known that repeat stability can be influenced by DMPK allele methylation and by the presence of interruptions in the DMPK CTG repeat tract.[35-38] DMPK allele methylation was not assessed in this observational study, since determination of the methylation profile is not part of routine DMPK repeat length analysis. While the exact role of CTG repeat interruptions has not been clarified, they seem to be present in <5% of DM1 patients and can possibly cause stability or even contraction of the CTG repeat.[35,36,39] In our study population, CTG tract interruptions were demonstrated in only two DM1 premutation carrying parents and their offspring. Thus, the effect of CTG tract interruptions in this study seems limited.

For the interpretations of our results, it is important to consider the role of DM1 tissue heterogeneity. Previous research has shown that somatic variation of CTG repeat expansions can contribute to observed intergenerational differences of CTG repeat lengths.[19,40] Moreover, for larger repeats, the size of the determined CTG repeat expansion appears to be age-dependent and test results could therefore differ after several years.[40,41] However, somatic variation seems to be less prominent and independent of age for small-sized DM1 alleles, presumably minimizing its effect.[13,19]

In the current study, several parent-child pairs with the same transmitting parent were included. In order to determine the potential influence of multiple transmissions, we repeated our analysis while restricting it to first-born offspring. This analysis determined that the percentages of DM1 affected offspring in first-born children were comparable to the results for the entire group of 146 DM1 parent-child pairs.

There are however some limitations to this study. First of all, data was collected in a retrospective manner and it should be noted that new mechanistic assays were not performed. Moreover, pre- or protomutation carriers were identified through clinically affected probands. Families in which the pre- or protomutation has been transmitted in a relatively stable manner over several generations, without the presence of a clear clinical picture, are therefore missed in the study. This could have resulted in an overestimation of intergenerational instability. Collecting prospective data on pre- and protomutation transmissions in families of the general population, without knowledge of an affected proband, seems unachievable however. Yet, the current study describes the largest cohort of parent-child pairs in which a small sized CTG repeat was transmitted to the next generation. In addition, the results of both pre- and protomutation transmissions were combined in a single study, describing possible sex-dependent CTG thresholds for the first time.

In clinical practice, the results of this study can be of significant value when counseling small-sized CTG repeat allele carriers. Guidelines for molecular testing in DM1 describe that small-sized CTG repeats ((CTG)n, n=36-50) may be unstable, but are non-specific and ignore the role of parental gender.[11] We recommended to counsel pre- or protomutation allele carriers in a specific manner, addressing the influence of parental gender. In case of a male small-sized repeat carrier, the risk of having a symptomatically affected child is considerably large, as paternal instability was observed to start for (CTG)n, n=45. For female allele carriers, the risk is lower, but increases as the maternal CTG repeat lengthens. Based on these risk figures, the choice of future parents to opt for natural pregnancy with or without prenatal testing, or pre-implantation genetic testing (PGT) may be individualised.

In conclusion, we found that paternal transmission of DM1 pre- and protomutations is far more unstable compared to maternal transmission of small-sized CTG repeats. We also found a lower CTG thresholds for the instability of paternal DM1 pre- and protomutation alleles. Ultimately, we recommend a sex-dependent genetic counseling advice for DM1 small-sized repeat carriers.

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Section 3

Multisystem Involvement

Chapter 4

Electrocardiographic predictors of infrahissian conduction disturbances in myotonic dystrophy type 1

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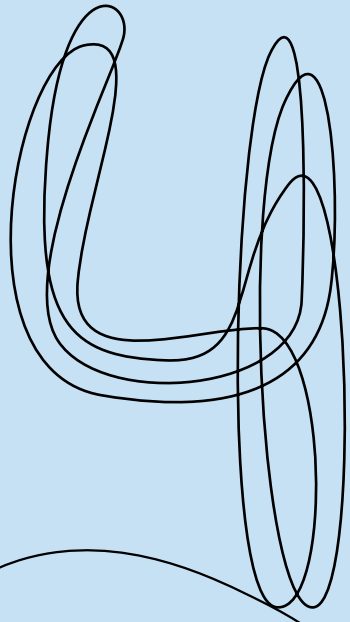

Abstract

Aims

To determine electrocardiographic (ECG) criteria predicting abnormal infrahissian conduction in patients with myotonic dystrophy type 1 (DM1), as these criteria could be used to identify the need for an electrophysiological study (EPS).

Methods

A retrospective multicenter study was conducted including DM1 affected individuals who underwent EPS between 2007 and 2018. For each individual, EPS indication, His-ventricle (HV) interval, resting ECG parameters prior to EPS, left ventricular ejection fraction (LVEF), neurological status, and DM1 DNA analysis results were collected. ECG parameters of patients with a normal HV interval were compared to ECG parameters of patients with a prolonged HV interval. Logistic regression was performed to determine predictors for a prolonged HV interval of ≥70ms on EPS and diagnostic accuracy of ECG parameters was ascertained.

Results

Among 100 DM1 affected individuals undergoing EPS, 47 had a prolonged HV interval. The sole presence of a PR interval >200ms (OR 8.45, CI 2.64-27.04), or a QRS interval >120ms (OR 9.91, CI 3.53-27.80) on ECG were independent predictors of a prolonged HV interval. The combination of both parameters had a positive predictive value of 78% for delayed infrahissian conduction on EPS. HV interval was independent of DM1 genetic mutation size, neuromuscular status and LVEF.

Conclusions

The combination of a prolonged PR interval and widened QRS complex on ECG accurately predicts abnormal infrahissian conduction on EPS in patients with DM1. These ECG parameters could be used as a screening tool to determine the need for referral to a specialized multidisciplinary neuromuscular team with EPS capacity.

Introduction

Myotonic dystrophy type 1 (DM1; also known as Steinert disease) is an autosomal dominantly inherited neuromuscular disease affecting patients of all ages. The genetic basis of DM1 lies in a cytosine-thymine-guanine (CTG) repeat expansion on chromosome 19, with the number of repeats being correlated to disease severity.[1] While the main characteristics of DM1 consist of muscle weakness and myotonia (inability to relax muscles), most of the affected individuals die as a result of systemic complications.[2] Cardiac involvement is, after pneumonia, the second most frequent cause of mortality.[2]

Cardiac involvement in DM1 is thought to be the result of myocardial fibrosis and fatty infiltration, leading to conduction disturbances, arrhythmias and cardiomyopathy.[3] On 12 lead electrocardiography (ECG), frequently observed conduction disorders are first degree atrioventricular (AV) blocks (PR interval >200ms), ventricular conduction delay (QRS intervals >120ms), and prolonged QTc intervals.[4] While conduction disorders in DM1 are generally slowly progressive, faster deterioration has been observed as well.[5] In case of progression into higher degree AV block or development of ventricular arrhythmias, these manifestations could lead to sudden cardiac death.

Since conduction disturbances in DM1 are frequently asymptomatic, follow-up of DM1 patients should include regular screening. Despite the need for screening protocols, evidence-based consensus guidelines for the timing, extent and frequency of DM1 cardiac follow-up are lacking. Currently, most centers perform regular ECGs, 24 hours rhythm monitoring (Holter) and echocardiographic evaluations. In case of progressive conduction disorders on ECG, or clinical symptomatology such as palpitations, dizziness or (pre)syncope, an invasive electrophysiological study (EPS) can be considered.

During EPS, His-ventricle (HV) intervals of 70ms or greater are considered an indication for prophylactic pacemaker (PM) implantation in DM1 patients, in order to protect against bradycardia (class of recommendation I, level of evidence B-NR).[6-8] While an EPS is the diagnostic test of choice for additional assessment of the cardiac conduction system in DM1, strict indications for performing EPS in DM1 remain unclear.[6,7,9] Moreover, as cardiac follow-up in DM1 is frequently carried out in hospitals without DM1 expertise, or even by a neurologist through the performance of annual ECGs, the establishment of clear cardiac management guidelines would be of great value in the daily care of patients with DM1.

In this study, we therefore aim to determine ECG criteria predicting abnormal infrahissian conduction (HV ≥70ms) in patients with DM1, in order to identify criteria for performing EPS.

Methods

Study population

A retrospective multicenter study was conducted at the Maastricht University Medical Center+ (MUMC+), Maastricht, The Netherlands and Radboud University Medical Center (Radboudumc), Nijmegen, The Netherlands. The MUMC+ and Radboud UMC together form the national Myotonic Dystrophy Expertise Center in The Netherlands. The Dutch DM1 patient registry (MYODRAFT study) was used to identify DM1 affected individuals who underwent EPS between 2007 and 2018 at one of both centers. For each individual, the following data was collected: reason for EPS, HV interval, resting ECG parameters prior to EPS, possible PM implantation reason and date, neurological assessment consisting of muscular impairment rating scale (MIRS) score, and DM1 DNA analysis results consisting of the CTG repeat size. Data was compared between patients with a normal HV interval (HV <70ms) on EPS, and patients with a prolonged HV interval (HV ≥70ms) on EPS.

Data was collected as part of the Dutch DM1 patient registry (MYODRAFT study) for which written informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki, and the research protocol was approved by the institutional Medical Ethics Committee (METC 16-4-001, approved on 18-03-2016). All clinical measurements were carried out as part of routine clinical care.

Cardiac assessment

At each yearly visit of DM1 patients, history taking, physical examination, and resting ECG were performed. The presence of cardiac symptoms (palpitations, dyspnea, dizziness, syncope) was assessed. Echocardiogram was performed every 3 years, and the last known left ventricular ejection fraction (LVEF) was collected. Holter registration was performed every other year. In case of (progressive) conduction disorders on resting ECG, conduction disorders on Holter monitoring, or clinical symptomatology (palpitations, dizziness or (pre)syncope), an EPS was performed. The decision whether to perform an EPS was always left to the discretion of the electrophysiologist, and was performed independent of inclusion in the DM1 observational registry.

Electrophysiological study

EPS was performed under local anesthesia via the right femoral vein. A bolus of 2500 IE of Heparin was administered as thrombo-embolic prophylaxis. Next, a quadripolar electrophysiological catheter was used to map the His-bundle region. The HV-interval was measured with the catheter in a proximal His-position. The HV-interval was defined as the time interval between onset of the His-potential to the onset of the QRS-complex on the surface ECG. A HV-interval of 70ms or more was considered abnormal and considered an indication for PM implantation according to recommendations for DM1 patients.[6,8]

Electrocardiogram

The last recorded baseline 12-lead ECG, performed at annual cardiac screening in DM1 or at interval check-up due to cardiac complaints, prior to EPS, was collected. All ECGs were evaluated by a qualified electrophysiologist for the following parameters: cardiac rhythm, heart rate in beats per minute, heart axis, PR interval in ms, categorical assessment of AV conduction (normal PR interval (PR≤200ms) or prolonged PR interval (PR>200ms), and further categorized into 1st degree -, 2nd degree Wenckebach -, 2nd degree Mobitz II -, 3rd degree AV block. A PR interval of more than 240ms was considered a separate category as this has been linked to sudden cardiac death in DM1 (10). Furthermore, QRS duration was assessed in ms, and a categorical assessment of QRS duration and morphology was made (narrow in case of QRS ≤120ms or widened in case of QRS>120ms). If the QRS complex was widened it was further classified into left anterior hemi block (LAHB), right bundle branch block (RBBB), left bundle branch block (LBBB) or intra-ventricular conduction delay (IVCD). QTc time was evaluated in ms, and categorically assessed as normal, or abnormal in case of QTc ≥450ms in men or ≥460ms in women.

Neurological assessment

As standard of care, DM1-affected individuals visit the neurology outpatient clinic each year to determine disease progression and muscle status. In order to define neuromuscular progression at the time of EPS, MIRS scores of the same year were collected. The MIRS score is a disease-specific ordinal five-point rating scale, based on manual muscle testing of 11 muscle groups.[11] DM1-affected individuals with a MIRS score of 1-3, indicating distal muscle weakness, were categorized as having a low MIRS score. Patients with a MIRS score of 4 or 5, indicating proximal muscle weakness, were categorized as having a high MIRS score.

DNA analysis

DNA analysis took place at DM1 diagnosis. All CTG-repeat lengths were determined by analyzing DNA extracted from peripheral blood samples through polymerase chain reaction (PCR), followed by fragment length analysis and Southern blot analysis.

Data analysis

Statistical analysis was performed using IBM SPSS statistics software version 24 (SPSS Inc, Chicago, IL). The distribution of continuous variables was assessed for normality using Shapiro-Wilk test or Kolmogorov-Smirnov when appropriate, and was visually evaluated by inspection of histograms and standardized normal probability plots. Continuous variables are expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR) in case of skewness. Categorical variables are expressed as counts (percentages). Differences between groups were compared using the chi-squared (χ^2) test or Fisher's exact test (categorical data), and the unpaired Student's t-test or the Mann-Whitney U test (continuous variables).

Univariable binary logistic regression using predefined variables was performed to identify predictors for the presence of a prolonged HV interval of ≥70ms on EPS. Selected variables consisted of age, gender, PR interval >200ms on ECG, QRS interval >120ms on ECG, and having a high MIRS score (MIRS 4-5). Selection of these variables was based on literature and clinical experience of a qualified electrophysiologist with DM1 expertise.[5,12] Variables with $p<0.20$ on univariable analysis were considered important and were included in the multivariable logistic regression analysis for identification of independent predictors, presented as odds ratios (OR) with confidence intervals (CI). Diagnostic accuracy was determined by calculation of sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and by drawing receiver operating characteristic (ROC) curves. Area under the curve (AUC) is presented with corresponding CI. P values of <0.05 were considered statistically significant.

Results

Study population

A total of 100 patients underwent EPS between 2007 and 2018, of which 90 underwent EPS in the Maastricht University Medical Center+, Maastricht, The Netherlands and 10 underwent EPS in Radboud University Medical Center, Nijmegen, The Netherlands.

Reasons for performing EPS, which were most frequently conduction disturbances on the 12 lead ECG, are displayed in **Table 4.1**. Median age of the study population was 49 years old [41-56]. Other baseline characteristics of patients are presented in **Table 4.2**.

Table 4.1 Reasons for performing EPS.

	Total (n=100)
PR interval >200ms and QRS interval >120ms on resting ECG	46
PR interval ≥200ms on resting ECG	26
QRS interval >120ms on resting ECG	10
Conduction delay on Holter monitoring (with normal ECG)	6
Conduction delay on Holter monitoring (with abnormal ECG)	3
Other ECG abnormalities on resting ECG	5
PR interval >200ms on resting ECG and cardiac complaints	2
Recurrent cardiac complaints with normal resting ECG	2

EPS, electrophysiological study; ECG, electrocardiogram.

Table 4.2 Baseline characteristics.

	Total (n=100)	**Normal HV time <70ms group (n=53)**	**Prolonged HV time ≥70ms group (n=47)**	**P value**
Age (years), median [IQR]	49 [41-56]	49 [40-57]	50 [42-56]	0.931
Male, n (%)	56 (56%)	32 (60%)	24 (51%)	0.350
CTG repeat size, median [IQR]	200 [150-200]	190 [126-200]	200 [150-200]	0.209
Cardiac symptoms, n (%)	20 (20%)	12 (23%)	8 (17%)	0.480
palpitations	*5 (5%)*	*4 (8%)*	*1 (2%)*	
(near) syncope	*9 (9%)*	*4 (8%)*	*5 (11%)*	
dizziness	*5 (5%)*	*4 (8%)*	*1 (2%)*	
other	*1 (1%)*	*0 (0%)*	*1 (2%)*	
High MIRS score (4-5), n (%)	38 (38%)	17 (32%)	21 (45%)	0.231
Normal ECG, n (%)	8 (8%)	8 (15%)	0 (0%)	0.006
PR interval >200ms, n (%)	72 (72%)	31 (58%)	41 (87%)	0.001
PR interval >240ms, n (%)	24 (24%)	10 (19%)	14 (30%)	0.202
QRS >120ms, n (%)	59 (59%)	21 (40%)	38 (81%)	0.000
LBBB	*22*	*4*	*18*	
RBBB	*11*	*5*	*6*	
LAHB	*4*	*2*	*2*	
IVCD	*31*	*15*	*16*	
PR >200ms and QRS>120 ms, n (%)	41 (41%)	9 (17%)	32 (68%)	0.000
PR >200ms and LBBB, n (%)	18 (18%)	4 (8%)	14 (30%)	0.004
Prolonged QTc, n (%)	24 (24%)	10 (19%)	14 (30%)	0.202
LVEF, % (SD)	56% (8)	56% (8)	57% (8)	0.643

HV, his-purkinje; MIRS, muscular impairment rating scale with high MIRS scores (4-5) indicating extensive muscle weakness; LBBB, left bundle branch block; RBBB, right bundle branch block; LAHB, left anterior hemi block; IVCD, intraventricular conduction delay; LVEF, left ventricular ejection fraction.

Of the 100 DM1 affected individuals undergoing EPS, 47 (47%) had a prolonged HV interval of ≥70ms. In the group of DM1 affected individuals with a prolonged HV time, there was a higher frequency of prolonged PR intervals (87% vs. 58%, p=0.001, **Table 4.2**) and a higher frequency of prolonged QRS duration (81% vs. 40%, p<0.001, **Table 4.2**) on 12-lead ECG. In our cohort, prolonged PR intervals of >240ms were uncommon in patients with a prolonged HV interval (30%). Yet, the combination of a prolonged PR and widened QRS complex was more frequently observed in the group of individuals with a prolonged HV interval at EPS (68% vs. 17%, p<0.001, **Table 4.2**). Specifically, the combination of a prolonged PR interval and the presence of LBBB was more common in individuals with a prolonged HV interval (30% vs. 8%, p=0.004, **Table 4.2**).

All 47 patients with HV intervals of ≥70ms, were referred for direct PM implantation after EPS. In the group of patients with normal HV intervals (<70ms), 10 out of 53 patients required PM implantation during follow-up. Reasons for PM implantation during follow-up consisted of deterioration of conduction delay on ECG, or recurrent syncope symptoms. EPS was not repeated in these cases.

Eight patients undergoing EPS had a normal resting ECG and underwent the procedure due to cardiac complaints or conduction abnormalities on Holter registration. All of these eight patients had a normal HV interval (**Table 4.2**).

There was no statistical difference in age (49 vs. 50 years, p=0.931), CTG repeat size (190 vs. 200 repeats, p=0.209), and frequency of high MIRS scores (32% vs. 45%, p=0.231) between individuals with a normal or prolonged HV time (**Table 4.2**). Moreover, there was no relationship between LVEF and HV time, as LVEF was comparable between both groups (56% vs. 57%, p=0.643).

Prolonged HV interval on EPS

Logistic regression analysis was performed to assess the impact of pre-defined resting ECG predictors on having a prolonged HV interval of ≥70ms on EPS (**Table 4.3**). The multiple logistic regression model contained two independent variables (PR interval >200ms and QRS interval >120ms on ECG). As shown in **Table 4.3**, both independent variables made a statistically significant contribution to the model (PR interval >200ms (OR 8.45, CI 2.64-27.04) and QRS interval >120ms (OR 9.91, CI 3.53-27.80) on resting ECG).

Table 4.3 Binary logistic regression analysis for occurrence of prolonged HV interval on EPS.

	Univariate			Multivariate		
	OR	**CI**	**P value**	**OR**	**CI**	**P value**
Age	1.01	0.97-1.05	0.59			
Gender	0.69	0.31-1.52	0.35			
PR interval >200ms	4.85	1.76-13.40	0.002	8.45	2.64-27.04	0.000
QRS interval >120ms	6.43	2.59-16.01	0.000	9.91	3.53-27.80	0.000
High MIRS score (4-5)	1.67	0.72-3.85	0.23			

HV, His-ventricle; EPS, electrophysiological study; OR, odds ratio; CI, confidence interval; MIRS, muscular impairment rating scale with high MIRS scores (4-5) indicating extensive muscle weakness. A prolonged HV interval was defined as ≥70ms on electrophysiological study.

Diagnostic accuracy

The diagnostic accuracy of three variables predicting a prolonged HV interval on EPS were determined: PR interval >200ms on resting ECG, QRS interval of >120ms on resting ECG, and the combination of both (**Figure 4.1**). For a prolonged PR interval (>200ms), the PPV and NPV were 56.9% and 78.6%, respectively. For a widened QRS complex (>120ms), the PPV and NPV were 64.4% and 78.0%, respectively. The combination of both ECG criteria (PR interval >200ms and QRS complex >120ms) had a sensitivity of 68.1% and a specificity of 83.1%, with corresponding PPV and NPV values of 78.0% and 74.6%, respectively. ROC curve analysis of the combination of ECG criteria (PR interval >200ms and QRS complex >120ms) demonstrated an AUC of 0.79 (CI 0.70-0.88).

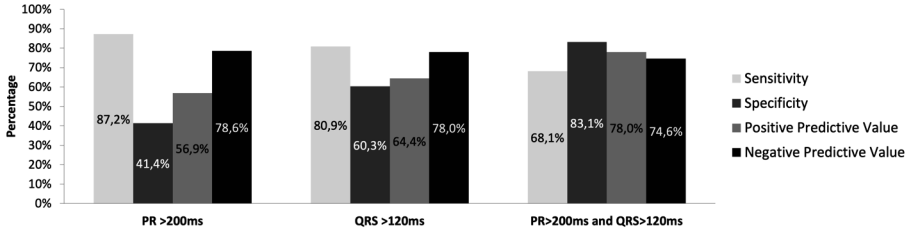

Figure 4.1 Diagnostic Accuracy of ECG parameters. The grouped bar chart gives an overview of diagnostic accuracy of specific ECG abnormalities in patients with myotonic dystrophy type 1, for the prediction of abnormal infrahissian conduction (≥70ms) on electrophysiological study.

Discussion

In a population of 100 individuals with genetically confirmed DM1, we demonstrated that either the presence of a PR interval >200ms, or the presence of a QRS complex

>120ms on ECG were independent predictors of having a prolonged HV interval of ≥70ms on EPS. When combined, these ECG parameters have a high PPV for the presence of delayed infrahissian conduction (HV ≥70ms) on EPS.

Prevalence of ECG abnormalities and prolonged HV intervals

ECG abnormalities are a common phenomenon in DM1, as PR prolongation is described in 28-45% of patients, and widened QRS complexes are observed on 17-20% of surface ECGs.[4,10,13] In the current study, ECG abnormalities were even more prevalent and only 8 DM1 patients had a normal ECG prior to EPS. This corresponds with the fact that ECG abnormalities were the main reasons for performing EPS in our cohort.
When comparing patients with a normal HV interval to patients with a prolonged HV interval, we observed LBBB to be more frequently present (combined with first degree AV block) in DM1 patients with a HV interval ≥70ms. This observation seems to be in accordance with the 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients with Bradycardia and Cardiac Conduction Delay, describing that the observation of a LBBB on ECG markedly increases the likelihood of distal conduction disturbances and underlying structural heart disease.[8]

In the general DM1 population, HV intervals have been reported to be abnormal in 43-54% of cases.[7,12,14] When looking at DM1 patients with clinical symptoms and/or conduction disturbances on ECG however, percentages up to 94% have been described.[13,15,16] Since the selection criteria for the performance of an EPS differed among studies and was usually influenced by expert opinion, these results might not be representative for the entire DM1 population.[13,15,16]

The role of ECGs as a predictor of prolonged HV intervals

Infrahissian conduction is unstable over time and has the tendency to increase in DM1 patients.[5,17] Simultaneously, the number of ECG abnormalities seems to increase with patients' age, suggesting a time-dependent degenerative process.[18] Still, the rate of cardiac progression seems to be variable among DM1 patients.[5,17] Previously, ECG abnormalities have been found to be indicative of cardiac conduction system disease and have been linked to autopsy findings such as cardiac fibrosis, fatty infiltration and atrophy.[10,12,15] As a result, the usefulness of ECGs as a predictive tool to determine the need and appropriate timing for an invasive measure of the conduction system has been previously researched.[5,12] A study of 39 consecutive DM1 patients demonstrated that the PPV of an abnormal ECG prior to EPS was 65,2% in predicting a prolonged HV interval.[12] In a study evaluating the effect of prophylactic PM implantation in 100 DM1

patients, the PPV of ECG abnormalities prior to EPS was 66%.[7] Although the role of ECG abnormalities were taken into account in other EPS studies in DM1[13,14,16], the current study is the first to describe the diagnostic value of distinct and combined ECG parameters, for the presence of a prolonged HV interval.

PR intervals >240ms have been associated with an increased risk of sudden cardiac death[10] and the same PR interval cut-off value is described in the 2018 ACC/AHA/HRS Guidelines as an indicator for possible prophylactic pacing.[8] Remarkably, we did not observe PR intervals greater than 240ms to be more frequently present in patients with a prolonged HV interval. Based on the data in the current study, a cut-off value of 240ms as an indicator for performance of an EPS may therefore be too high, specifically when other conduction disturbances are already present.

Despite the possible role of ECGs in determining the need for EPS, it has also been reported that DM1 patients with normal ECGs may have infrahissian conduction abnormalities.[14,15] In our study, eight patients had a normal resting ECG and all of these patients had HV intervals <70ms.

Relationship between ECG abnormalities and DM1 severity

Several studies have suggested a relationship between the size of the CTG repeat expansion and the extent of cardiac involvement, and between the degree of neuromuscular and cardiac involvement in DM1.[4] In the current study however, we did not find a difference in MIRS score and mean CTG repeat size between patients with a normal HV interval and patients with a prolonged HV interval. Moreover, it is known that the length of the CTG repeat is instable and may increase over time in the same individual, making it difficult to correlate CTG repeat size to disease severity at a given time point.[19] Importantly, it has also been reported that DM1 patients with small sized CTG repeat expansions are at increased risk of severe cardiac conduction abnormalities, making cardiac follow-up essential for DM1 patients across the entire range of DM1 related CTG repeat lengths.[20]

Clinical implications

While the 2018 ACC/AHA/HRS Guidelines recommend PM implantation in case of HV intervals of 70ms or greater in neuromuscular patients[8], the 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy merely describe that PM implantation might be considered in case of a prolonged HV interval.[9] In neither guideline, recommendations for the timing of EPS are addressed, making it difficult to

determine when EPS is necessary in clinical practice. Even though specialized neuromuscular centers are available, practical limitations such as disabling muscle weakness, travel distance, and lack of motivation in DM1 patients make local cardiac management a necessity. Hence, the utility of ECGs as a fast and accessible screening tool is of great value, especially if specific ECG parameters can be used to determine the need for referral. As demonstrated by the data in this study, the PR interval and QRS complex could play an important role in the assessment of screening ECGs in DM1. Due to the high PPV of the combined parameters, referral to a hospital with a multidisciplinary DM1 team and EPS capacity should be considered when both ECG abnormalities are present. Most likely, such guiding ECG criteria could significantly increase DM1 quality of care, as early PM implantation can protect against complete atrioventricular block and sudden cardiac death.[6,10]

Since the 2018 ACC/AHA/HRS Guidelines also state that the recommendations for other neuromuscular disorders are similar to recommendations in DM1, these screening ECG parameters may be useful in the management of other neuromuscular diseases.[8] Nevertheless, it is important to note that the absence of the combination of a prolonged PR interval and widened QRS complex, should not indicate that referral to a specialized center is unnecessary, specifically when symptoms or progressive conduction disorders are present.

The results of this study raise the question whether PM implantation could take place without prior performance of EPS in the future. While avoiding an invasive measure in a group of vulnerable patients could be beneficial, a PPV of 78% would also cause overtreatment. Thus in order to consider direct PM implantation based on ECG conduction abnormalities, we believe that the suggested ECG criteria should be validated in a prospective study including patients with normal resting ECGs.

Limitations

The main limitations of this study consist of its retrospective nature and the fact that included DM1 affected individuals had already been selected for EPS by an electrophysiologist, introducing potential selection bias. Consequently, our study may have overestimated the predictive value of ECG parameters, specifically when comparing these results to the general DM1 population without conduction abnormalities on their ECG. Furthermore, there was a difference in the amount of EPS performed at both participating centers. As the decision whether to perform an EPS in DM1 was left to the discretion of an experienced electrophysiologist, this suggests a

difference in local opinions, possibly affecting the outcomes of this study. Yet again, these different managing approaches stress the need for specific guidelines in DM1.

Conclusions

This retrospective study demonstrates the predictive value of specific ECG conduction abnormalities in a group of 100 genetically confirmed DM1 patients. The combination of a prolonged PR interval and widened QRS complex on ECG, accurately predicts abnormal infrahissian conduction on EPS. Therefore, these criteria could be used as a screening tool in clinical practice in order to select patients for referral to a multidisciplinary neuromuscular team with EPS capacity. As the presence of a prolonged HV interval was independent of DM1 genetic mutation size, neuromuscular status and last recorded LVEF, ECG abnormalities should be taken seriously in any DM1 patient. Finally, there is a need for DM1 specific consensus guidelines on the timing, extent and frequency of DM1 cardiac follow-up.

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Chapter 5

An evaluation of 24 h Holter monitoring in patients with myotonic dystrophy type 1

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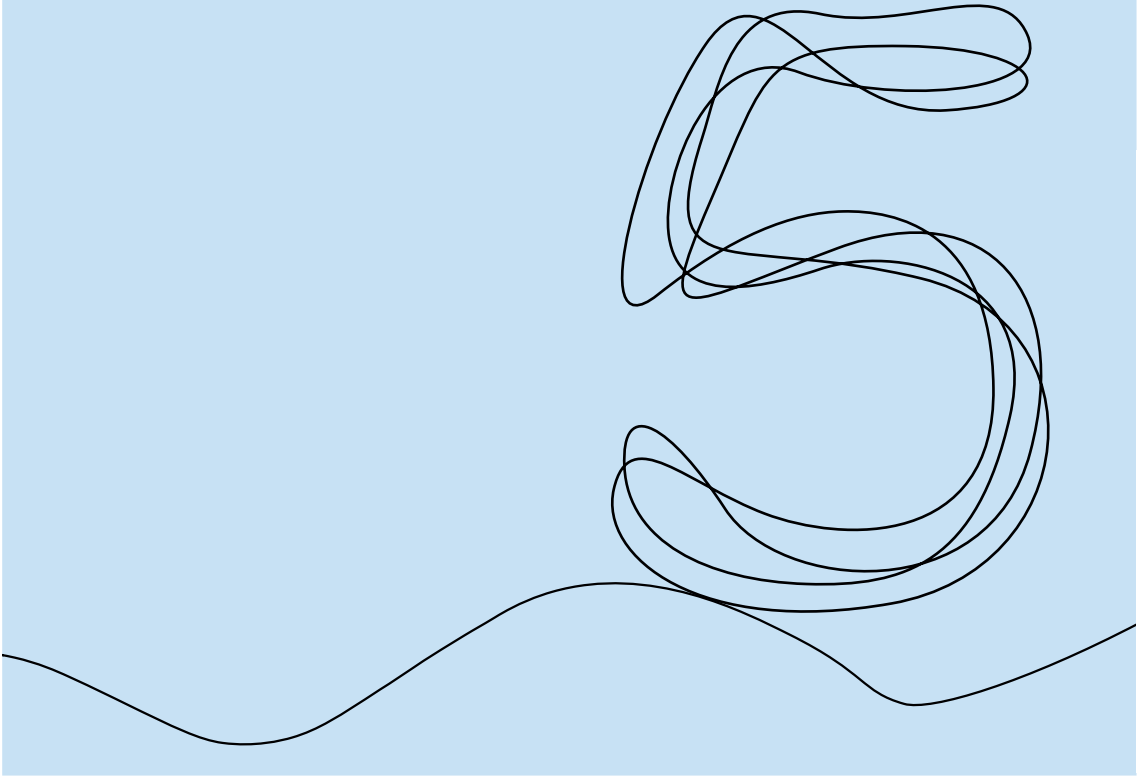

Abstract

Aims

To evaluate the clinical effectiveness of routine 24 h Holter monitoring to screen for conduction disturbances and arrhythmias in patients with myotonic dystrophy type 1 (DM1).

Methods

A retrospective two-centre study was conducted including DM1-affected individuals undergoing routine cardiac screening with at least one 24 h Holter monitoring between January 2010 and December 2020. For each individual, the following data were collected: Holter results, results of electrocardiograms (ECG) performed at the same year as Holter monitoring, presence of cardiac complaints, and neuromuscular status. Holter findings were compared to the results of cardiac screening (ECG + history taking) performed at the same year. Cardiac conduction abnormalities and/or arrhythmias that would have remained undiagnosed based on history taking and ECG alone, were considered de novo findings.

Results

235 genetically confirmed DM1 patients were included. Abnormal Holter results were discovered in 126 (54%) patients after a mean follow-up of 64±28 months in which an average of 3±1 Holter recordings per patient was performed. Abnormalities upon Holter mainly consisted of conduction disorders (70%) such as atrioventricular (AV) block. Out of 126 patients with abnormal Holter findings, 74 (59%) patients had de novo Holter findings including second-degree AV block, atrial fibrillation/flutter and non-sustained ventricular tachycardia. Patient characteristics were unable to predict the occurrence of de novo Holter findings. In 39 out of 133 (29%) patients with normal ECGs upon yearly cardiac screening, abnormalities were found on Holter monitoring during follow-up.

Conclusions

24 h Holter monitoring is of added value to routine cardiac screening for all DM1 patients.

Introduction

Myotonic dystrophy type 1 (DM1, also known as Steinert disease) is a highly variable neuromuscular disease with frequent cardiac involvement.[1] DM1 is caused by a CTG-repeat expansion on chromosome 19 and symptom severity has been demonstrated to correlate with increasing repeat lengths.[2,3] At present, curative or disease modifying treatment options are still unavailable, and disease management focuses on early detection of organ complications and improving quality of life.

Since as many as 50% of DM1 patients may experience cardiac involvement, and arrythmias are among the most frequent causes of death in the DM1 population, cardiac screening is a significant part of disease management.[1,4] Even though strict guidelines on the cardiac management of DM1 are still lacking, consensus-based care recommendations describe the necessity of annual screening through history taking and electrocardiogram (ECG).[5,6] Apart from ECG, routine cardiac imaging and 24 h Holter monitoring are commonly carried out, even though the exact role of Holter monitoring has not yet been validated.[6]

While ECG abnormalities such as prolonged PR interval, widened QRS complex and prolonged QTc interval are known to be common in DM1 patients, ambient conduction abnormalities and arrhythmias such as advanced (nocturnal) atrioventricular block and non-sustained ventricular arrhythmias could remain unnoticed on ECG.[1,7,8] Therefore, 24 h Holter monitoring may be of added value, even more so since conduction disorders tend to remain asymptomatic in most patients (8). In case of (progressive) conduction disorders or arrhythmias on Holter monitoring or ECG, a diagnostic electrophysiological study (EPS) and subsequent cardiac device implantation can be considered.[9,10]

The current study aims to evaluate the clinical effectiveness of routine 24 h Holter monitoring to screen for conduction disturbances and arrhythmias in DM1 patients.

Methods

Study population

A retrospective two-centre study was conducted at the Maastricht University Medical Centre+ (MUMC+) and Radboud University Medical Centre (Radboudumc). The MUMC+ and Radboudumc form the Myotonic Dystrophy Expertise Centre in The Netherlands.

The Dutch DM1 patient registry (MYODRAFT study) was used to identify adult DM1 affected individuals who underwent routine cardiac screening including at least one 24 h Holter monitoring at one of both centres between January 2010 and December 2020. For each individual, the following data were collected: 24 h Holter monitoring results, results of 12-lead ECGs performed at the same year as the Holter monitoring, the presence of cardiac complaints, the occurrence of cardiac treatment consequences during follow-up, baseline left ventricular ejection fraction (LVEF), neurological assessment consisting of muscular impairment rating scale (MIRS) score, DM1 DNA analysis results consisting of the CTG-repeat size, and the presence of an indication for nightly non-invasive ventilation (NIV). Follow-up time was based on the number of months between the first 24 h Holter monitoring and December 2020.

Data was collected as part of the Dutch DM1 patient registry (MYODRAFT study) for which written informed consent was obtained. The study was conducted in accordance with the Declaration of Helsinki, and the research protocol was approved by the institutional Medical Ethics Committee (METC 16-4-001, approved on 18-03-2016). All clinical measurements were carried out as part of routine clinical care. The data underlying this article will be shared on reasonable request to the corresponding author.

Cardiac assessment

At each yearly visit of DM1 patients, history taking, physical examination, and resting 12-lead ECG were performed. The presence of cardiac related symptoms was assessed. 24 h Holter monitoring was performed every other year. Echocardiography was conducted with a three-year interval.

In case of (progressive) conduction disorders on resting ECG, conduction disorders or arrythmias on Holter monitoring, or clinical symptomatology (palpitations, dizziness or (pre)syncope), an EPS was considered. The decision whether to perform an EPS was always left to the discretion of a cardiac electrophysiologist with DM1 expertise, and was performed independent of inclusion in the DM1 observational registry.

Twenty-four hour Holter monitoring

Holter monitoring data was evaluated by a qualified cardiac electrophysiologist and the first Holter evaluation was considered the baseline measurement. The following parameters were considered clinically relevant in DM1 follow-up: first-, second- or third-degree AV block, bundle branch block, atrial fibrillation/flutter (episodes lasting

>30 seconds**)**, supraventricular tachycardia other than atrial fibrillation/flutter (episodes lasting >30 seconds**)**, non-sustained ventricular tachycardia (≥3 consecutive ventricular beats at ≥120 beats/min lasting <30 seconds) and sustained ventricular tachycardia, symptomatic sinus bradycardia <40 beats per minute, frequent ventricular extrasystoles (>5% of total number of heartbeats), and sinus arrest >3 seconds.

Holter findings were compared to the results of DM1 screening (history taking, physical examination, and resting 12-lead ECG) performed at the same year. Cardiac conduction abnormalities and/or arrhythmias upon Holter monitoring that would have remained undiagnosed based on history taking and ECG alone, were considered as de novo findings.

Electrocardiogram

Standard 12-lead ECG results, performed at the same year as each 24 h Holter monitoring evaluation, were collected. All ECGs were evaluated by a qualified cardiac electrophysiologist for the following parameters: cardiac rhythm, heart rate in beats per minute, heart axis, PR interval, categorical assessment of AV conduction (normal PR interval (PR≤200ms) or prolonged PR interval (PR>200ms), and further categorized into first-degree, second-degree Wenckebach, second-degree Mobitz, third-degree AV block), QRS duration, categorical assessment of QRS complex (narrow in case of QRS ≤120ms or widened in case of QRS>120ms), QTc time, and categorical assessment of QTc time (normal, or abnormal in case of QTc ≥450ms in men or ≥460ms in women).

Neurological assessment

As standard of care, DM1-affected individuals visit the neurology outpatient clinic annually to determine disease progression and muscle status. In order to define neuromuscular progression at the time of 24 h Holter monitoring, MIRS scores determined at the same year were collected. The MIRS score is a disease-specific ordinal five-point rating scale, based on manual muscle testing of 11 muscle groups.[11] DM1-affected individuals with a MIRS score of 1-3, indicating distal muscle weakness, were categorized as having a low MIRS score. DM1-affected individuals with a MIRS score of 4 or 5, indicating proximal muscle weakness, were categorized as having a high MIRS score.

Respiratory follow-up

Respiratory involvement was assessed through history taking by the coordinating neuromuscular neurologist upon yearly visits. In case of (suspected) respiratory

involvement, patients were referred to the pulmonologist for detailed screening consisting of pulmonary function testing, polysomnography (PSG) and blood gas analysis. Data on non-invasive home mechanical ventilation (NIV) indications were collected as part of the MYODRAFT registry. The indication for NIV was based on the 207th European Neuromuscular Centre Workshop (21-07-2014).

DNA analysis

DNA analysis took place at DM1 diagnosis. All CTG-repeat lengths were determined by analysing DNA extracted from peripheral blood samples through polymerase chain reaction (PCR), followed by fragment length analysis and Southern blot analysis.

Data analysis

Statistical analysis was performed using IBM SPSS statistics software version 25 (SPSS Inc, Chicago, IL). The distribution of continuous variables was assessed for normality using Shapiro-Wilk test or Kolmogorov-Smirnov when appropriate, and was visually evaluated by inspection of histograms and standardized normal probability plots. Continuous variables are expressed as mean±standard deviation (SD) or as median with interquartile range (IQR) in case of skewness. Categorical variables are expressed as counts (percentages). Differences between groups were compared using the chi-squared (χ^2) test or Fisher's exact test (categorical data), and the unpaired Student's t-test or the Mann-Whitney U test (continuous variables).

Univariable binary logistic regression using predefined variables was performed to identify predictors for the presence of de novo findings upon 24 h Holter monitoring. Selection of variables was based on literature and clinical experience of a qualified electrophysiologist with DM1 expertise.[1,12] Variables with $p<0.20$ on univariable analysis were considered important and were included in the multivariable logistic regression analysis for identification of independent predictors, presented as odds ratios (OR) with confidence intervals (CI). P values of <0.05 were considered statistically significant.

Results

Study population

The MYODRAFT registry consisted of 293 patients undergoing routine cardiac evaluation in the Myotonic Dystrophy Expertise Centre (*Figure 5.1*). Fifty-eight patients

were excluded due to reasons listed in *Figure 1*. Mean age of the study population was 46±14 years old. Patients were followed-up for a mean timeframe of 64±28 months, in which an average of 3±1 Holters was performed per patient. The total number of Holters per patients can be found in **Supplementary Table S5.1**. Other baseline characteristics are presented in **Table 5.1**.

Rhythm or conduction abnormalities had been discovered in 126 out of 235 (54%) included patients by the end of follow-up. Patients in whom rhythm or conduction abnormalities were found on 24 h Holter monitoring, were significantly older than patients without abnormalities on Holter monitoring (50 vs. 41 years old, p<0.001, **Table 5.1**).

ECG abnormalities (described in **Table 5.1**) were more frequently present in the group of patients with abnormalities upon 24 h Holter monitoring compared to patients without abnormalities upon Holter monitoring (69% vs. 14%, p<0.001, **Table 5.1**). Moreover, high MIRS score upon neurological evaluation (27% vs. 12%, p=0.006, **Table 5.1**) and NIV indications (48% vs. 28%, p=0.002, **Table 5.1**) were more common in DM1 patients with abnormalities upon Holter monitoring. There was no significant difference in sex (53% vs. 49% male, p=0.572, **Table 5.1**), median CTG repeat size (150 vs. 150, p=0.570, **Table 5.1**) or LVEF (59% vs. 60%, p=0.277, **Table 5.1**). Mean follow-up time was longer in the group of patients with rhythm or conduction abnormalities upon Holter monitoring (68 vs. 59 months, p=0.024, **Table 5.1**), with a higher mean number of Holters per patient (3 vs. 2, p=0.001, **Table 5.1**).

Table 5.1 Baseline characteristics.

	Total (*n*=235)	**Patients with abnormalities upon Holter screening (*n*=126)**	**Patients without abnormalities upon Holter screening (*n*=109)**	***P*-Value**
Age (years), mean ± SD	46 ± 14	50 ± 14	41 ± 13	<0.001
Male, *n* (%)	120 (51%)	67 (53%)	53 (49%)	0.572
ECG abnormalities, n (%)	102 (43%)	87 (69%)	15 (14%)	<0.001
First-degree AV block	*53*	*44*	*9*	
Second-degree AV block	*1*	*1*	*0*	
Bundle branch block	*10*	*6*	*4*	
Bundle branch block + first-degree AV block	*34*	*32*	*2*	
Atriumfibrillation/flutter	*4*	*4*	*0*	
CTG repeat size, median [IQR]	150 [120-200]	150 [120-200]	150 [100-200]	0.570
High MIRS score (4-5), *n* (%)	47 (20%)	34 (27%)	13 (12%)	0.006
NIV indication	90 (38%)	60 (48%)	30 (28%)	0.002
Follow up time in months, mean ± SD	64 ± 28	68 ± 26	59 ± 30	0.024
Mean no. of Holters, mean ± SD	3 ± 1	3 ± 1	2 ± 1	0.001
LVEF, mean % ± SD	59% ± 6	59% ± 7	60% ± 5	0.277

Holter monitoring abnormalities

The incidence of abnormalities upon Holter monitoring increased over time (**Figure 5.2-A**). Holter abnormalities mainly consisted of conduction disorders (70%) such as intermittent first-degree AV block and bundle branch block (**Table 5.2**). A combination of intermittent first-degree AV block + bundle branch block had been discovered in 10 patients by the end of follow-up. Moreover, a second-degree AV block was observed in 14 patients.

Arrhythmias such as atrial fibrillation/flutter were present in 8 patients and non-sustained ventricular tachycardia (NSVT) had been observed in 5 patients by the end of follow-up (**Table 5.2***).* Holter monitoring revealed other abnormalities such as frequent ventricular extrasystoles, symptomatic bradycardia <40 bpm and sinus arrest (>3 seconds) in 12 patients (9%, **Table 5.2**).

Out of 126 patients with discovered abnormalities upon 24 h Holter monitoring during follow-up, 74 (59%) patients were classified as having de novo findings that would have remained undiagnosed by ECG and history taking alone (**Figure 5.1**). The remaining 41% of patients had abnormal findings on Holter monitoring that had already been ascertained through ECG and/or history taking. Cardiac complaints were present in 9 out of 126 (7%) patients with de novo findings upon Holter screening.

A total of 133 out of the 235 included patients had normal ECGs upon yearly screening during follow-up. In 39 out of 133 (29%) patients, abnormal Holter findings had been discovered by the end of follow-up, while ECG remained normal. The incidence of de novo Holter findings in patients without ECG abnormalities, increased over time (**Figure 5.2-B**). De novo findings included 4 patients with a (intermittent) second-degree AV block, 2 patients with NSVT, 1 patient with atrial fibrillation and 1 patient with a combination of first-degree AV block + bundle branch block.

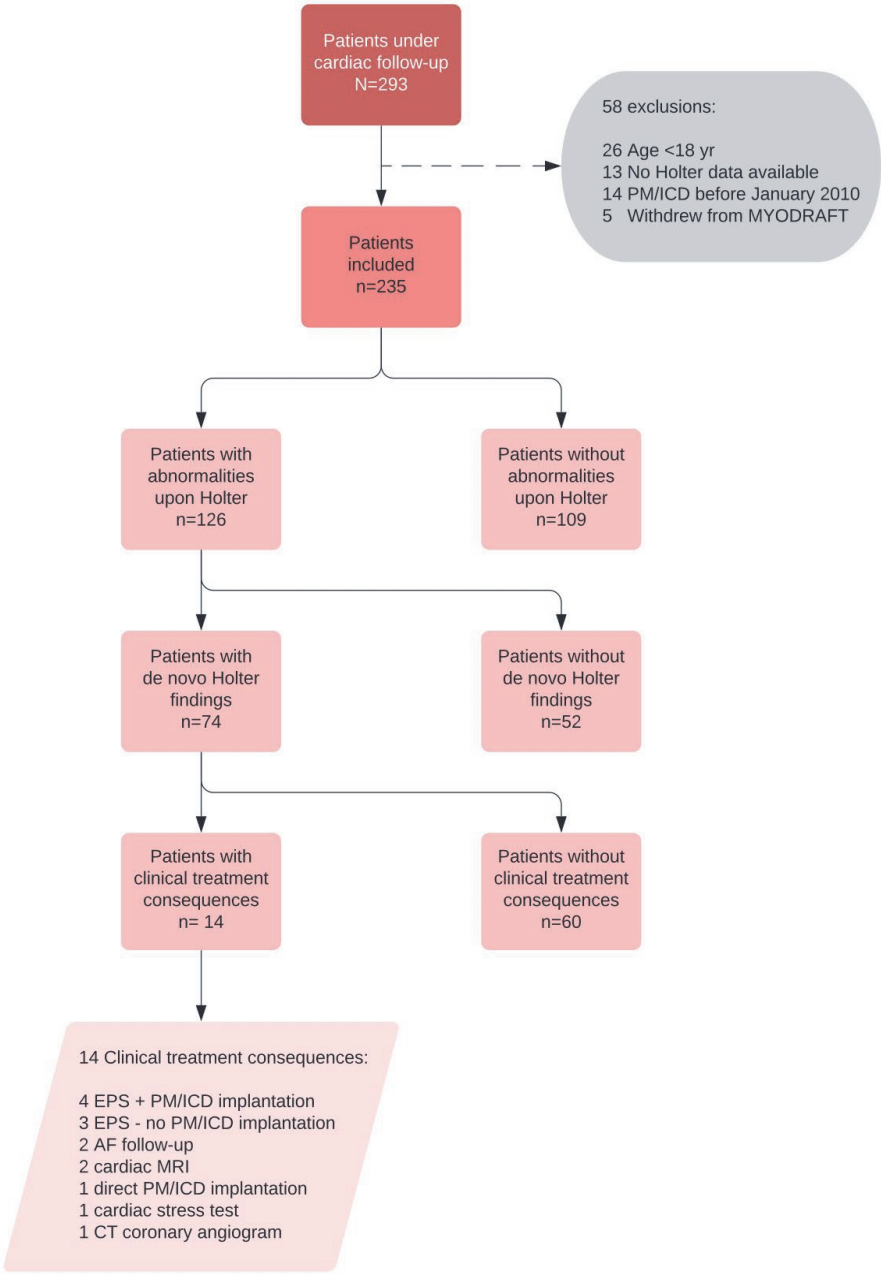

Figure 5.1 Flowchart of included myotonic dystrophy type 1 patients.
AF; atrial fibrillation, CT; computed tomography, EPS; electrophysiologic study, ICD; implantable cardioverter defibrillator, MRI; magnetic resonance imaging, PM; pacemaker

Table 5.2 Abnormalities on 24 h Holter monitoring.

	Total number of patients (n=126)	Patients with de novo Holter findings (n=74)	Patients without de novo Holter findings (n=52)
Conduction disorders, n (%)	88 (70%)	42 (57%)	46 (88%)
First-degree AV block	*43*	*18*	*25*
Second-degree Wenckebach block	*13*	*13*	*0*
Second-degree Mobitz block	*1*	*1*	*0*
Bundle branch block	*21*	*8*	*13*
First-degree AV block + bundle branch block	*10*	*2*	*8*
Arrhythmias, n (%)	26 (21%)	21 (28%)	5 (10%)
Supraventricular tachycardia	*13*	*13*	*0*
Atrial fibrillation/flutter	*8*	*3*	*5*
Non-sustained ventricular tachycardia	*5*	*5*	*0*
Other, n (%)	12 (9%)	11 (15%)	1 (2%)
Symptomatic bradycardia <40 bpm	*2*	*1*	*1*
Frequent ventricular extrasystoles	*9*	*9*	*0*
Sinus arrest/RR > 3 seconds	*1*	*1*	*0*

AV; atrioventricular, BPM; beats per minute

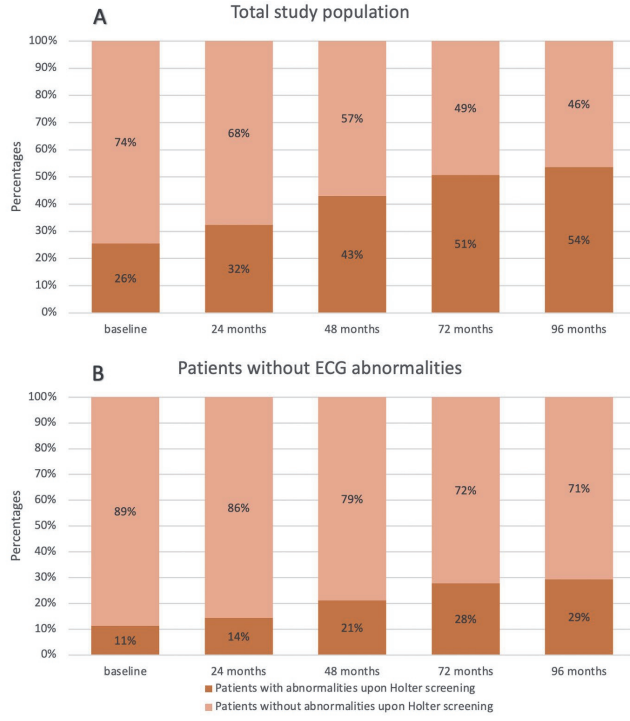

Figure 5.2 Percentages of DM1 patients with Holter abnormalities during follow-up.
A) Total study population, B) Patients without ECG abnormalities. DM1; myotonic dystrophy type 1, ECG; electrocardiogram.

Predictors of Holter findings

Logistic regression analysis was performed to assess the impact of pre-defined predictors on having de novo findings upon 24 h Holter monitoring (**Table 5.3**). The multiple logistic regression model contained two independent variables (age and high MIRS score). As displayed in **Table 5.3**, neither independent variable made a statistically significant contribution to the model (age (OR 1.017, CI 0.997-1.038) and high MIRS score (OR 1.447, CI 0.738-2.835)). Binary logistic regression analysis was repeated to assess the impact of pre-defined predictors on having abnormal findings upon 24 h Holter monitoring in general (see **Supplementary Table S5.2**). Age (OR 1.037, CI 1.012-1.062) and the presence of ECG abnormalities (OR 11.225, CI 5.600-22.502) made a statistically significant contribution to the multiple regression model.

Table 5.3 Binary logistic regression analysis for the presence of de novo Holter findings.

	Univariate			Multivariate		
	OR	**CI**	**P value**	**OR**	**CI**	**P value**
Age	1.017	0.998-1.037	0.087	1.017	0.997-1.038	0.095
Gender	1.101	0.634-1.910	0.733			
CTG repeat length	1.000	0.999-1.002	0.520			
ECG abnormalities	1.364	0.784-2.372	0.272			
Cardiac complaints	1.441	0.344-6.045	0.617			
High MIRS score (4-5)	1.571	0.808-3.052	0.183	1.447	0.738-2.835	1.447
NIV indication	1.148	0.653-2.016	0.632			

ECG; electrocardiographic, MIRS; muscular impairment rating scale, NIV; non-invasive ventilation.

Clinical treatment consequences

In our study population, de novo findings upon Holter monitoring had clinical treatment consequences in 14 out of 74 (19%) patients (**Figure 5.1**). Treatment consequences were not solely based on the presence of cardiac conduction abnormalities and/or observed arrythmias specific for DM1, but could also be based on other abnormalities such as frequent ventricular extrasystoles, described in **Table 5.2**. The decision whether to take clinical treatment consequences was always left to the discretion of a cardiac electrophysiologist with DM1 expertise.

Discussion

In a population of 235 patients with genetically confirmed DM1, abnormalities upon 24 h Holter monitoring had been discovered in 54% of patients after a mean follow-up of approximately 5 years. In 59% of cases, abnormal findings were classified as de novo findings, meaning they would have remained undiagnosed through ECG and history

taking alone. Abnormalities upon 24 h Holter screening were not only present in patients with previously ascertained ECG abnormalities, but also in 29% of patients without ECG abnormalities upon yearly cardiac screening during follow-up. Even though the exact role of 24 h Holter monitoring has remained unclear in DM1 cardiac care recommendations due to lack of evidence, the current results demonstrate the added value of routine 24 h Holter monitoring.

Prevalence of cardiac abnormalities and the role of 24 h Holter monitoring in DM1

Conduction abnormalities such as AV blocks and bundle branch blocks are observed in 17-45% of patients, while atrial fibrillation/flutter and ventricular arrhythmias are described to be present in respectively 5-13% and 1-4% of the DM1 population.[1,13,14] In the current study, ECG abnormalities were present in 43% of patients, with conduction disorders being the most prevalent. In the group of patients with abnormalities upon Holter monitoring, ECG abnormalities were even more common, which is a logical consequence of most ECG abnormalities also being present upon ambulatory monitoring.

Outcomes of Holter screening in DM1 have been evaluated in a small number of studies so far. A retrospective study of 47 DM1 patients reported that ambulatory monitoring was unable to predict sudden cardiac death or other cardiovascular events, and therefore did not consider Holter monitoring to be useful.[15] However, data of a second Holter was only available for 32 patients after a 5-year follow-up period. In several other small studies, Holter screening did appear to have an additional value by establishing de novo conduction delay or arrhythmias in approximately 30% of patients with normal baseline ECGs.[7,16,17] De novo abnormalities included findings such as second-degree AV block, AF and NSVT warranting treatment consequences such as cardiac device implantation.[7,16,17] Even though the results of these studies are in line with the current data, we are the first to describe 24 h Holter monitoring data in a large DM1 cohort with multiple measurements during follow-up in a multicentre setting.

Patient characteristics as predictors of cardiac abnormalities

Even though there seems to be a correlation between CTG repeat size and the degree of clinical symptomatology in DM1 in general, the relationship between cardiac involvement and repeat expansion size has remained ambiguous.[1,8] Increasing age and male gender however, do seem to influence the risk of developing cardiac abnormalities over time.[18] In our study population, median age was higher in the group

of patients with abnormalities on Holter screening and an increased risk based on age could be verified for having Holter abnormalities in general (**Supplementary Table S5.2**). Age did not increase the risk of having de novo abnormalities (**Table 5.3**). While more severely affected DM1 patients with proximal muscle weakness and NIV indications presented with abnormalities upon Holter more often (**Table 5.1**), the presence of an NIV indication and high MIRS score did not make a significant contribution to the regression analysis either.

Treatment consequences

De novo findings upon Holter screening had clinical treatment consequences in 14 out of 74 patients (19%, **Figure 5.1**) during follow-up. Nevertheless, it is of importance to point out that the current study was merely of a retrospective observational nature. As a result, our data gives an overview of treatment consequences taken in clinical practice before 2020 based on expert opinion, since guidelines and/or clinical care recommendations were unavailable at that time. Based on current knowledge however, the actual percentage of patients having an indication for treatment consequences may be higher than described in the current study. The most recently published ESC guidelines on cardiac pacing recommend direct pacemaker implantation in DM1 patients with any second- or third-degree AV block or abnormal EPS result.[9] As second-degree AV block was a de novo finding in 14 patients on Holter screening (**Table 5.2**), pacemaker implantation would have been warranted. Also for patients with a de novo finding of a combined AV block and bundle branch block, EPS and possible device implantation could have been advisable.[8]

Clinical implications

While specific guidelines for the cardiac follow-up of DM1 are still lacking, an overview of clinical care recommendations for cardiologists treating adults with myotonic dystrophy were published in 2020.[6] Even though the publication of these expert consensus based recommendations are a step forward in DM1 care, the role of Holter monitoring has remained uncertain. Ambulatory monitoring is described to possibly be helpful in detecting ambient or asymptomatic arrhythmias, while it is advised only to perform this type of monitoring in case of ECG abnormalities or in patients with symptoms suggestive of arrhythmias.[6] Based on the data presented in the current study, in which abnormalities on Holter were ascertained in 54% of the screened DM1 population and even in 29% of patients with normal baseline ECGs, we believe that Holter monitoring should be considered an important factor in DM1 cardiac care. In addition, de novo Holter findings were of such nature that they are considered clinically

relevant and influence treatment. Another retrospective study has suggested that cardiac conduction abnormalities and arrhythmias detected through Holter monitoring seem to be predictive of future cardiac events and death in DM1 patients as well.[19] Since only 7% of patients with de novo Holter findings experienced cardiac symptoms and specific patient characteristics such as muscle weakness, NIV indication or age did not seem to influence the risk of having de novo findings either, ambulatory monitoring should be part of DM1 screening in all patients. Due to the slowly progressive nature of disease and lack of prospective studies on the value of Holter screening however, it remains difficult to determine an optimal interval for this screening modality at the current time. Also, future studies should provide more data on the prognostic value of Holter monitoring abnormalities.

Limitations

The main limitations of this study consist of its retrospective nature and the relatively short period of follow-up for a slowly progressive disorder. Moreover, patients with abnormalities upon Holter screening had a longer mean follow-up time with more frequent Holter examinations (**Table 5.1**). As a result, chances of abnormalities being present in this group were higher to begin with. Holter monitoring data was not compared to PSG data, while previous reports have described that arrhythmias may sometimes be precipitated by functional triggers.[20] Due to the fact that this study only used data of patients under cardiac follow-up in the Dutch DM1 expertise centre, a possible bias could have resulted from the fact that more severely affected patients are more likely to be under follow-up in a DM1 specific care centre.

Conclusion

This retrospective study evaluated the clinical effectiveness of routine 24 h Holter monitoring in a large cohort of 235 DM1 patients. Abnormalities upon Holter screening were present in 54% of patients after a mean follow-up of approximately 5 years. In 59% of patients with discovered abnormalities on Holter, the ascertained conduction abnormalities and/or arrhythmias would have remained undiagnosed through cardiac screening with ECG and history taking alone. De novo findings were common not only in patients with ECG abnormalities but also in patients with normal ECGs upon yearly cardiac screening. Moreover, specific patient characteristics were unable to predict the occurrence of de novo Holter findings. Consequently, we believe that 24 h Holter monitoring is of additional value to routine cardiac screening in all DM1 patients, even though an optimal screening interval is to be investigated in a prospective trial. Yet

again, we would like to stress the need for clear DM1-specific cardiac guidelines, to improve cardiac care for this vulnerable patient population.

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Supplementary table

Table S5.1 Number of Holters per patient.

	Total (*n*=235)	**Patients with abnormalities upon Holter screening (*n*=126)**	**Patients without abnormalities upon Holter screening (*n*=109)**
Number of Holters per patient			
One	56	21	35
Two	68	33	35
Three	44	28	16
Four	67	44	23

Chapter 6

Myotonic dystrophy type 1: a comparison between the adult- and late-onset subtype

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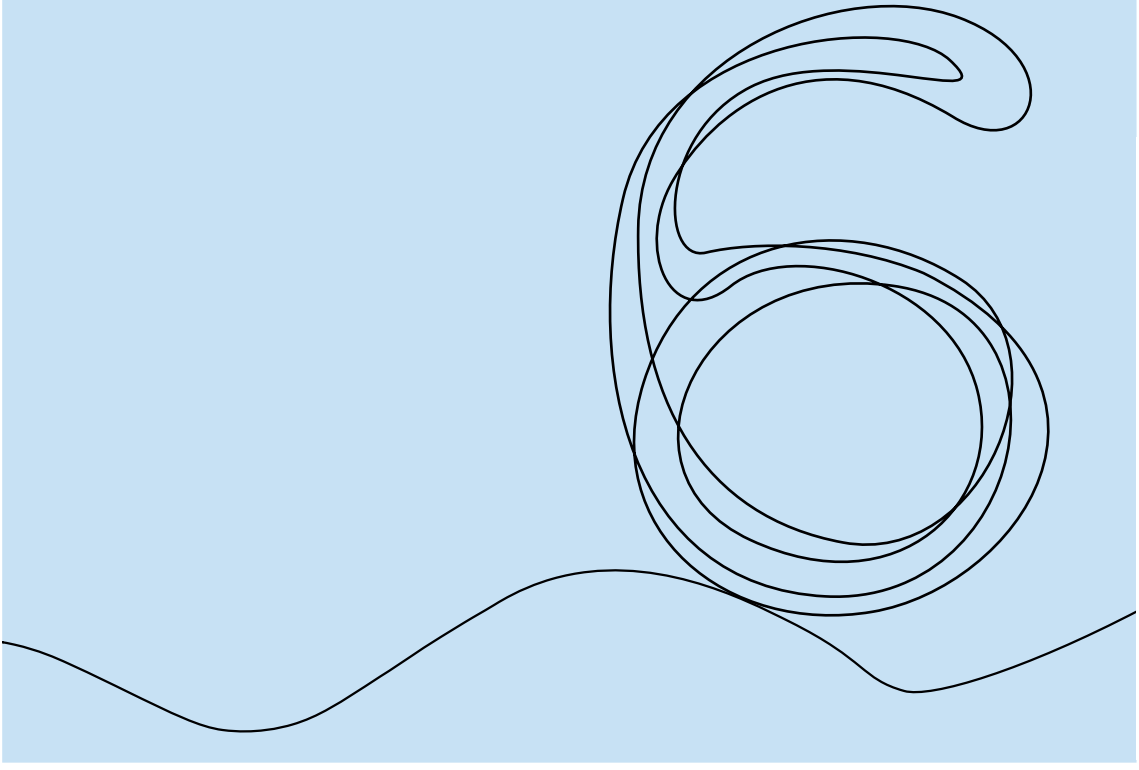

Abstract

Introduction/aims

While the extent of muscle weakness and organ complications has not been well-studied in patients with late-onset myotonic dystrophy type 1 (DM1), adult-onset DM1 is associated with severe muscle involvement and possible life threatening cardiac and respiratory complications. This study aimed to compare the clinical phenotype of adult-onset versus late-onset DM1, focusing on the prevalence of cardiac, respiratory and muscular involvement.

Methods

Data was prospectively collected in the Dutch DM1 registry.

Results

275 adult-onset and 66 late-onset DM1 patients were included. Conduction delay on electrocardiogram was present in 123 out of 275 (45%) adult-onset patients, compared to 24 out of 66 (36%) late-onset patients (p=0.218). DM1 subtype did not predict presence of conduction delay (OR 0.706, CI 0.405-1.230, p=0.219). Subtype did predict indication for non-invasive ventilation (NIV) (late-onset vs. adult-onset, OR 0.254, CI 0.104-0.617, p=0.002) and 17% of late-onset patients required NIV compared to 40% of adult-onset patients. Muscular impairment rating scale (MIRS) scores were significantly different between subtypes (MIRS 1-3 in 66% of adult-onset vs. 100% of late-onset (p<0.001)), as were DM1-Activ^{C} scores (67±21 in adult-onset vs. 87±15 in late-onset, p<0.001).

Discussion

Although muscular phenotype was milder in late-onset compared to adult-onset DM1, the prevalence of conduction delay was comparable. Moreover, subtype was unable to predict the presence of cardiac conduction delay. Even though adult-onset patients had an increased risk of having an NIV indication, 17% of late-onset patients required NIV. Despite different muscular phenotypes, screening for multi-organ involvement should be equally thorough in late-onset as in adult-onset DM1.

Introduction

Myotonic dystrophy type 1 (DM1) is a muscle disease caused by a CTG repeat expansion on chromosome 19 in the myotonic dystrophy protein kinase (*DMPK*) gene.[1] The number of CTG repeats in healthy individuals ranges up to 35, whereas repeat expansions larger than 50 are associated with DM1.[2] While the main symptoms of DM1 consist of muscle weakness and myotonia, multisystemic involvement is a relevant feature, including cardiac, respiratory, and gastro-intestinal dysfunction with a highly variable clinical phenotype.

Based on age of onset and length of the CTG repeat expansion, DM1 is often divided into four subtypes.[3-5] The classical/adult, childhood/juvenile, and congenital subtypes are associated with repeat expansions larger than 100 ranging up to several thousand, with CTG repeat size overlap between different phenotypes.[3,4] Clinically, these subtypes have been linked to profound muscle weakness and systemic involvement, which can have life threatening complications.[3,4,6]

The late-onset subtype gives rise to symptoms after the age of 40 years and has been associated with CTG repeat expansions of 50-150.[3-5,7,8] Clinical findings consist of early onset cataracts and mild muscular involvement, while the prevalence of other organ complications in this subtype remains unclear.[5,8] Moreover, insufficient data is available on the life expectancy of patients with late-onset DM1, whereas patients affected by the adult subtype have been demonstrated to have a markedly reduced survival.[9]
Since a reduced life span in DM1 is most frequently the result of cardiac or respiratory complications, disease management focuses on early detection of organ involvement.[9] Yearly follow-up by a coordinating physician (neuromuscular neurologist) is advised, including an annual electrocardiogram (ECG) to detect possible cardiac conduction delay.[10,11] In case of conduction disorders or cardiac symptoms, referral to a cardiologist is indicated.[10,11] Regular pulmonary function testing (PFT) is also recommended and referral to a pulmonologist is advised in patients with respiratory symptoms.[11]

Due to large differences in DM1 phenotypes, subtype treatment stratification has been suggested.[7,12] Even though the prevalence of organ complications has not been well-studied in late-onset DM1, some studies have suggested that cardiac and respiratory involvement might be as frequently present as in adult-onset DM1.[7,13] While not all multisystemic abnormalities may have treatment consequences, it would be of added value to further specify the frequency and severity of organ involvement in the late-

onset subtype. Therefore, the aim of the current study was to compare the clinical phenotype of adult-onset and late-onset DM1, focusing on the prevalence of cardiac, respiratory and muscular involvement.

Methods

Participants

Data was prospectively collected as part of the observational Myotonic Dystrophy type 1: Dutch Registry and Follow-up Study (MYODRAFT study) at the Maastricht University Medical Centre+ (MUMC+) and Radboud UMC Nijmegen. The MUMC+ and Radboudumc form the national Myotonic Dystrophy Expertise Centre in the Netherlands. Data collection for the MYODRAFT study started in March 2017. All participants are 18 years or older and have a genetically confirmed diagnosis of DM1. For the current study, all consecutive patients diagnosed with adult-onset or late-onset DM1 that joined the MYODRAFT up until March 2021 were included.

The research protocol was approved by the institutional Medical Ethics Committee (METC 16-4-001). Written informed consent was obtained from all included participants. For legally incapacitated patients, written informed consent was signed by a legal guardian.

MYODRAFT protocol and subtype classification

As standard of care, DM1-affected individuals visit the neurology outpatient clinic annually to determine disease progression. MYODRAFT data was collected during these standard follow-up visits. Upon inclusion (baseline), data on the diagnosis, age of first symptoms, age of diagnosis, CTG repeat size and DM1 subtype were collected. DM1 subtype classification was performed by a trained neuromuscular specialist and was based on age of onset and CTG repeat size.[3,4] The late-onset subtype was defined as an age of onset >40 years with a CTG repeat expansion between 50-150.[3,4] The adult-onset subtype was defined as an age of onset between 10-40 years with a CTG repeat expansion between 100-1000.[3,4] Patients in which the DM1 subtype remained unclear, as is sometimes the case for asymptomatic genetically confirmed patients under the age of 40 years in whom symptoms may still arise, were not included (n=1).

In order to define neuromuscular progression, the muscular impairment rating scale (MIRS) score was determined for each patient annually. The MIRS score is a disease-

specific rating scale, based on manual muscle testing.[14] MIRS scores between 1-3, indicating no or distal muscle weakness, were categorized as a low MIRS score. MIRS scores of 4-5, indicating both distal and proximal muscle weakness, were categorized a high MIRS score. The most recently determined MIRS score for each participant was used for analysis. Moreover, clinical data on the presence of myotonia was collected. Patients also completed the DM1-Activ^{C} questionnaire at baseline and during annual follow-up. This disease-specific patient-reported outcome measure determines activity and social participation in patients with DM1.[15] DM1-Activ^{C} raw scores were translated into centrile metric scores ranging from 0 (most severe limitations in activity and social participation) to 100 (no activity and social limitations).[15] Centrile metric scores >70 indicated few limitations, and ≤30 indicated severe limitations in activities of daily living.[16] The most recently determined DM1-Activ^{C} score for each participant was used.

DNA analysis

DNA analysis took place at DM1 diagnosis as part of standard care. All CTG repeat lengths were determined by analyzing DNA extracted from peripheral blood samples through polymerase chain reaction (PCR), followed by fragment length analysis and Southern blot analysis.[2] In case of a CTG repeat length expressed as CTG > X, value X was used for statistical analysis. In case of a CTG repeat length expressed as a range, mean CTG repeat length was used for statistical analysis.

Cardiac follow-up

During annual visits, patients were evaluated by a DM1-experienced cardiologist as standard of care. History taking and resting 12-lead ECG were performed. The presence of cardiac symptoms (palpitations, dyspnea, light-headedness, dizziness, syncope) was assessed.

Cardiac conduction delay was defined as a PR interval >200ms, widened QRS complex >120ms, and/or prolonged QTc time of ≥450ms in men or ≥460ms in women, on at least one of the ECGs during follow-up. In case of atrioventricular (AV) conduction delay, this was further classified into 1st degree -, 2nd degree Wenckebach -, 2nd degree Mobitz -, or 3rd degree AV block. Baseline left ventricular ejection fraction (LVEF) and data on the presence of a pacemaker (PM) or implantable cardioverter defibrillator (ICD) was collected. LVEF was considered abnormal if <50%.[17]

Respiratory follow-up

Respiratory involvement was assessed through history taking by the coordinating neuromuscular neurologist upon yearly visits. In case of (suspected) respiratory involvement, patients were referred to the pulmonologist for detailed screening consisting of PFT, polysomnography and blood gas analysis. PFT was considered abnormal in case of a forced vital capacity (FVC) <80% of predicted on at least one PFT during follow-up.[18]

Data on non-invasive home mechanical ventilation (NIV) indications were collected. The indication for NIV was based on the 207th European Neuromuscular Centre Workshop (21-07-2014)[18,19], comprising the presence of at least one or more daytime or night time symptoms suggestive of chronic respiratory insufficiency in combination with (1) daytime hypercapnia, (2) FVC <50% of predicted, or (3) evidence of nocturnal hypoventilation on polysomnography.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 25 (IBM, Armonk, NY). The distribution of continuous variables was assessed for normality, by visual inspection of histograms and standardized normal probability plots. Continuous variables are expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR) in case of skewness. Categorical variables are expressed as counts (percentages). Differences between groups were compared using the chi-squared (χ^2) test or Fisher's exact test (categorical data), and the unpaired Student's t-test or the Mann-Whitney U test (continuous variables). Univariable binary logistic regression using predefined variables was performed to identify predictors for the presence of conduction disorders on ECG and for the presence of an NIV indication. Selected variables were age, gender, DM1 subtype (adult or late-onset DM1), CTG repeat size and having a high MIRS score (MIRS 4–5). Variables with P<0.20 on univariable analysis were considered important and were included in the multivariable logistic regression analysis for identification of independent predictors, presented as odds ratios (ORs) with confidence intervals (CIs). Missing data was not imputed. P values of <0.05 were considered statistically significant.

Results

Study population

The MYODRAFT population consisted of 481 DM1 patients, of which all consecutive 341 participants diagnosed with adult- or late-onset DM1 were selected for the current study. 275 (81%) patients had been diagnosed with the adult-onset subtype and are presented in **Table 6.1**.

Table 6.1 Clinical characteristics.

	Total (n=341)	Adult onset DM1 (n=275)	Late-onset DM1 (n=66)	P value
Age at inclusion (years), mean ± SD	48 ± 13	46 ± 13	57 ± 13	<0.001
Male, count (%)	172 (50%)	125 (45%)	47 (71%)	<0.001
CTG repeat size, median [IQR]	150 [96-200]	150 [120-200]	72 [61-97]	<0.001
Follow-up time (years), mean ± SD	3 ± 1	3 ± 1	2 ± 1	0.006
Age of onset (years), median [IQR]	27 [16-38]	25 [16-34]	50 [42-52]	<0.001
Age at diagnosis (years), median [IQR]	33 [25-43]	30 [24-39]	51 [43-59]	<0.001
Symptom duration (years), median [IQR]	18 [10-27]	20 [11-28]	12 [6-14]	<0.001

DM1, myotonic dystrophy type 1; IQR, interquartile range; SD, standard deviation.

Age of onset and clinical symptomatology

Adult-onset DM1 patients first noted DM1-related features at a median age of 25 years, which consisted of myotonia (54%), muscle weakness (21%), fatigue (11%), cataracts (4%), or other symptoms such as gastro-intestinal abnormalities, apathy or dysphagia (12%).

Seven late-onset DM1 patients were subjectively asymptomatic and also showed no signs of DM1 upon evaluation. In the other 59 late-onset patients, DM1-related features were reported to start at a median age of 50 years, and consisted of cataracts (31%), fatigue (20%), mild muscle weakness (17%), myotonia (12%), or dysphagia (3%). The remaining 17% of late-onset patients were asymptomatic, but showed multi-organ involvement as a sign of DM1 upon evaluation.

Cardiac involvement

Conduction delay on ECG was present in 123 out of 275 patients with adult-onset DM1, in comparison to 24 out of 66 patients with late-onset DM1 by the end of follow-up (**Figure 6.1**). First degree AV block was the most commonly observed conduction delay on ECG in both subtypes, frequently combined with bundle branch blocks (**Table 6.2**). In

24 out of 147 (16%) patients with conduction delay, ECG had been completely normal upon baseline evaluation.

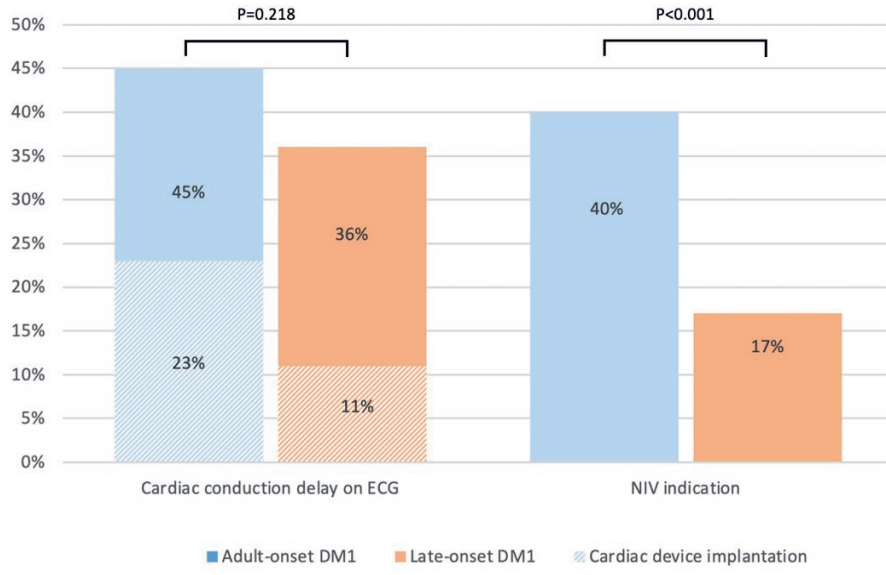

Figure 6.1 Prevalence of cardiac conduction delay and NIV indications in patients diagnosed with adult-onset versus late-onset myotonic dystrophy type 1.
ECG, electrocardiogram; NIV, non-invasive ventilation; DM1, myotonic dystrophy type 1.

Table 6.2 Conduction delay.

	Adult-onset subtype n=123	**Late-onset subtype n=24**
First degree AV block	59 (48%)	13 (54%)
First degree AV block and bundle branch block	37 (30%)	4 (17%)
First degree AV block and prolonged QTc	0	1 (4%)
Second degree AV block	3 (2%)	0 (0%)
Bundle branch block	24 (20%)	6 (25%)

AV, atrioventricular; ECG, electrocardiogram.

As displayed in **Table 6.3**, both age and MIRS category independently predicted the presence of conduction delay. DM1 subtype was not a predictor for conduction delay on ECG.

In the adult-onset subgroup, 62 out of 275 patients had a PM or ICD, in comparison to 7 out of 66 in the late-onset subtype group (**Figure 6.1**). Two of the late-onset subtype

patients with a cardiac device had no subjective symptoms of DM1 upon presentation, making asymptomatic cardiac conduction delay the sole expression of disease upon evaluation.

Cardiac symptoms were present in only 34 out of the total 147 (23%) patients with conduction abnormalities on ECG. These symptoms consisted of recurrent dizziness (47%), palpitations (23%), chest pain (18%), or syncope (12%). LVEF was reduced in 10% of adult-onset patients versus 4% of late-onset patients (p=0.205).

Table 6.3 Binary logistic regression analysis.

	Univariate			Multivariate		
	OR	**CI**	**P value**	**OR**	**CI**	**P value**
For the presence of cardiac conduction delay on ECG						
Age	1.053	1.034-1.072	<0.001	1.049	1.030-1.068	<0.001
Gender (female vs. male)	1.146	0.746-1.760	0.533			
CTG repeat length	1.002	0.999-1.004	0.222			
DM1 subtype (late-onset vs. adult)	0.706	0.405-1.230	0.219			
High MIRS score (4-5)	2.687	1.649-4.379	<0.001	2.251	1.355-3.740	0.002
For the presence of an NIV indication						
Age	1.026	1.009-1.044	0.003	1.051	1.026-1.077	<0.001
Gender (female vs. male)	1.431	0.916-2.236	0.115	0.649	0.376-1.119	0.120
CTG repeat length	1.007	1.003-1.011	0.001	1.007	1.002-1.012	0.002
DM1 subtype (late-onset vs. adult)	0.300	0.150-0.599	0.001	0.254	0.104-0.617	0.002
High MIRS score (4-5)	2.198	1.351-3.576	0.002	1.015	0.540-1.905	0.964

CI, confidence interval; DM1, myotonic dystrophy type 1; ECG, electrocardiogram; MIRS, muscular impartment rating scale; NIV, non-invasive ventilation; OR, odds ratio.

Respiratory involvement

In the adult-onset group, 108 out of 275 (39%) had an FVC <80% of predicted, compared to 3 out of 66 (5%) in the late-onset group (p<0.001). An FVC lower than 50% of predicted was observed in 29 adult-onset patients (11%) and none of the late-onset patients.

NIV indications were present in 110 out of 275 adult-onset patients and in 11 out of 66 late-onset patients (**Figure 6.1**). NIV indication was most frequently based on the presence of sleep-related breathing disorders (SRBD, **Table 6.4**). Only age, CTG repeat length and DM1 subtype independently predicted the presence of an NIV indication (**Table 6.3**).

Table 6.4 NIV indications.

	Adult-onset subtype n=110	Late-onset subtype n=11
Nocturnal hypoventilation	34 (31%)	0 (0%)
Daytime hypercapnia	4 (4%)	1 (9%)
Obstructive sleep apnea	37 (34%)	7 (64%)
Central sleep apnea	26 (23%)	2 (18%)
Mixed sleep apnea	9 (8%)	1 (9%)

NIV, non-invasive ventilation

Muscular involvement and disability

All late-onset DM1 patients had a low MIRS score, compared to 66% of the adult-onset patients (p<0.001, **Figure 6.2**). Mean DM1-Activ^{C} scores were significantly different among subtypes, with a mean score of 67 ± 21 in adult-onset patients compared to 87 ± 15 in late-onset patients (p<0.001). Also, late-onset DM1 patients did not experience severe limitations in activities of daily living (DM1-Activ^{c} <30, **Figure 6.2**). Myotonia was present in 231 out of 275 (84%) adult-onset patients versus 17 out of 66 (26%) late-onset patients (p<0.001).

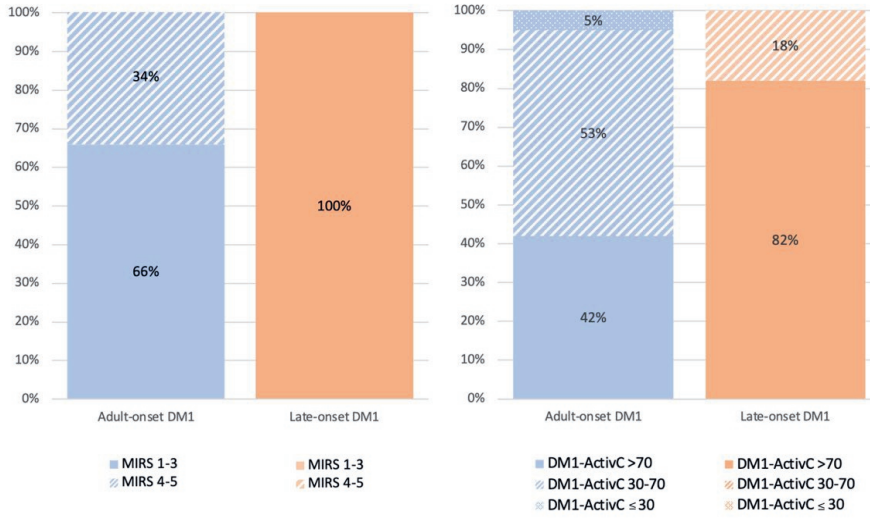

Figure 6.2 MIRS and DM1-Activ^{C} scores in patients diagnosed with adult-onset versus late-onset myotonic dystrophy type 1.
DM1, myotonic dystrophy type 1; MIRS, muscular impairment rating scale.

Discussion

Cardiac and respiratory involvement were common in both adult- and late-onset DM1, despite clear differences in muscular status. The prevalence of conduction delay on ECG was comparable between both groups and the presence of conduction abnormalities was independent of DM1 subtype. Even though patients with adult-onset DM1 were more likely to have an NIV indication, 17% of late-onset patients still required NIV treatment.

Cardiac conduction defects are described to be present on 17-50% of ECGs in the general DM1 population, which is in line with our results.[7,20-22] For late-onset DM1 however, less is known about the frequency of cardiac abnormalities since multi-organ involvement has not been well-studied. A study investigating patients with small CTG repeat expansions found ECG abnormalities in 17-21% of participants, but ECG evaluation criteria were not specified.[13] In the French DM-scope registry, cardiac conduction delay was present in 50.1% of adult-onset and even in 55.8% of late-onset DM1 patients.[7] Yet again, ECG criteria were not provided.

For DM1 cardiac screening, annual ECG follow-up has been accepted as the most important screening tool.[10,23] In our study population, a large proportion of patients with ECG abnormalities was asymptomatic and had a normal ECG at baseline, stressing the need for standard follow-up. Even though percentages of cardiac device implantation were high in both subtypes, guidelines on when to perform an invasive measurement of the cardiac conduction system are still lacking.[23] Consequently, the true number of patients requiring device implantation may be higher. Indications for device implantation were not revised, and ICD implantation may be based on prevention of ventricular arrhythmias instead of conduction delay.

There was a clear distinction between the amount of patients with FVC values <80%. Respiratory insufficiency is described in approximately 30% of the general DM1 population[7,24], while the prevalence of SRBD is highly variable among studies reporting percentages between 16-75%.[24,25] In the DM-scope registry, prevalence was comparable between both groups (32%) possibly resulting from the regular performance of PFTs regardless of symptoms.[7] In the current study, patients were referred only in case of suspected respiratory involvement, possibly inducing screening bias. A specification of respiratory symptoms was not included in the MYODRAFT registry, nor in the DM-scope article. Unfortunately, NIV indications were not included in the DM-scope paper.[7]

It should be noted, that the value of PFT as a screening modality in neuromuscular disorders is under debate, as PFT seems unable to predict the presence of SRBD.[26] Most NIV indications were based on sleep apnea ascertained through polysomnography.

While the degree of multi-organ involvement was more comparable than previously known, a difference between MIRS, DM1-Activ^{C} scores and presence of myotonia between subtypes was expected. None of the late-onset patients had MIRS scores above three, confirming that severe muscle weakness is rare in late-onset DM1.[5,7,13] The current study also demonstrated a difference in functioning and participation between subtypes through DM1-Activ^{C} scores.

Even though CTG repeat length is presumed to play an important role in the severity of DM1 subtypes, other factors are likely to influence phenotype establishment as well. Previous studies have described the phenomenon of disease manifestations arising in a relatively short period of time in late-onset DM1.[7,11] Possibly, this results from RNA toxicity passing a threshold for deregulation of cell function.[5,27] Also tissue-specific sensitivity to RNA foci may be related to variability in organ sensitivity and muscular sensitivity.[6]

While RNA toxicity is likely to increase over patients' lifetimes, the effects of general aging must be taken into account. As patients affected by late-onset DM1 develop symptoms at an age above 40 years, they were consequently older than adult-onset patients. Even though activity and participation are affected by age, this is taken into account in the DM1-Activ^{C} scoring system. In the general Dutch population, the frequency of ECG abnormalities increases above the age of 65.[28] As median age was 57 years in the late-onset group however, first degree AV block and bundle branch block could have been expected on approximately 4% and 1% of ECG's respectively, as is the case in the Dutch population.[28] In the current study, age increased the risk of having ECG abnormalities yet the prevalence of conduction disorders was clearly higher than in healthy Dutch adults.[28] Additionally, respiratory function is known to be influenced by aging, and age increased the risk of having an NIV indication in our study population.[29,30] While age is taken into account in FVC predicted values, the prevalence of SRBD was also higher than in the aging Dutch population.[31] Despite effects of aging, the current study demonstrates a high prevalence of multi-organ involvement among all patients, stressing the need for adequate screening and follow-up despite age or DM1 subtype.

Another limitation is that subtype determination may be challenging in clinical practice. CTG repeats are known to overlap between subtypes, to demonstrate tissue-specific expansions, and to be unstable throughout life.[32,33] Also, many different classifications have been used in the literature. In our study, age of onset was used as the primary feature for subtype differentiation, yet CTG repeat size was taken into account.

Even though the late-onset group was considerably smaller than the adult-onset group, a relatively large amount of patients of both subtypes were included, despite the fact that late-onset DM1 patients can remain unknown to health care providers. Nevertheless, this may have influenced cohort characterization, since more affected patients are more likely to be under follow-up. Additionally, other multisystemic complications such as central nervous system involvement and metabolic abnormalities were not evaluated[34], as well as use of medication and its possible effects on cardiac conduction.

In conclusion, the prevalence of cardiac conduction delay in late-onset DM1 was comparable to the prevalence of conduction delay in adult-onset DM1. Moreover, DM1 subtype was unable to predict the presence of conduction delay on ECG. As most of the patients with cardiac abnormalities remained clinically asymptomatic, yearly screening through ECG is essential. Even though patients diagnosed with the adult-onset subtype were more likely to have an NIV indication, 17% of late-onset DM1 patients still required NIV treatment. As a result, screening for multi-organ involvement in DM1 should be equally thorough and frequent in late-onset as in adult-onset DM1.

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Chapter 7

Energy expenditure, body composition, and skeletal muscle oxidative capacity in patients with myotonic dystrophy type 1

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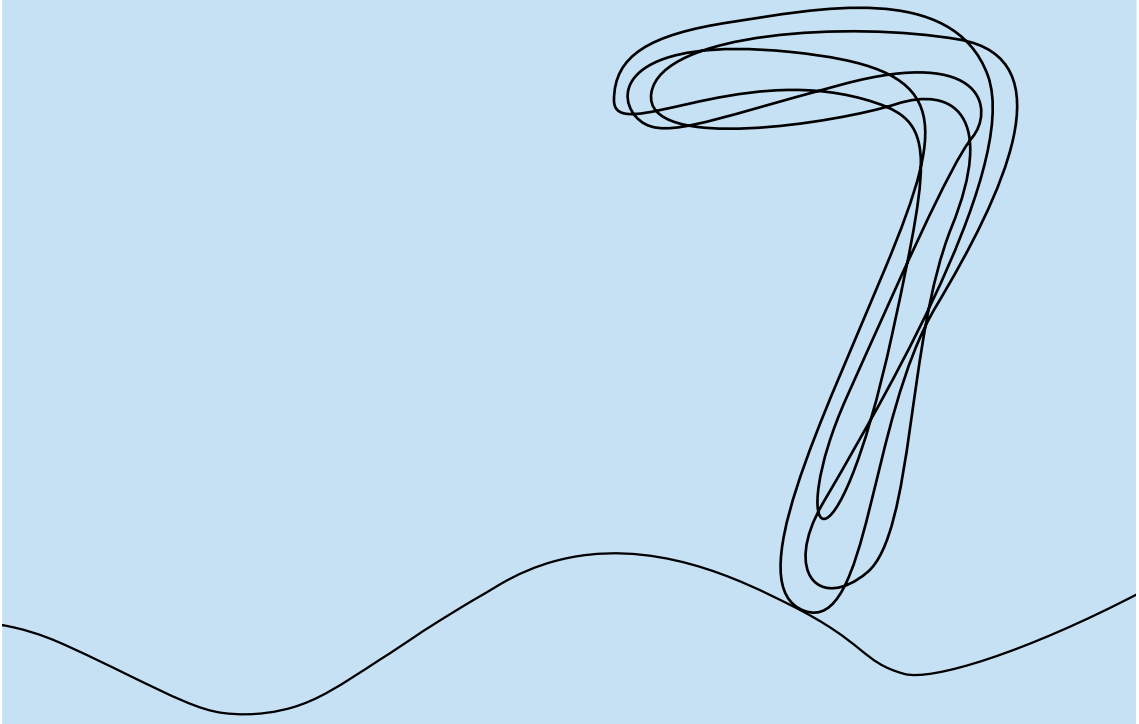

Abstract

Background

Myotonic dystrophy type 1 (DM1) patients are at risk for metabolic abnormalities and commonly experience overweight and obesity. Possibly, weight issues result from lowered resting energy expenditure (EE) and impaired muscle oxidative metabolism.

Objectives

This study aims to assess EE, body composition, and muscle oxidative capacity in patients with DM1 compared to age-, sex- and BMI-matched controls.

Methods

A prospective case control study was conducted including 15 DM1 patients and 15 matched controls. Participants underwent state-of-the-art methodologies including 24h whole room calorimetry, doubly labeled water and accelerometer analysis under 15-days of free-living conditions, muscle biopsy, full body magnetic resonance imaging (MRI), dual-energy x-ray absorptiometry (DEXA), computed tomography (CT) upper leg, and cardiopulmonary exercise testing.

Results

Fat ratio determined by full body MRI was significantly higher in DM1 patients (56 [49-62] %) compared to healthy controls (44 [37-52] %; p=0.027). Resting EE did not differ between groups (1948 [1742-2146] vs. (2001 [1853-2425] kcal/24h, respectively; p=0.466). In contrast, total EE was 23% lower in DM1 patients (2162 [1794-2494] vs. 2814 [2424-3310] kcal/24h; p=0.027). Also, DM1 patients had 63% less steps (3090 [2263-5063] vs. 8283 [6855-11485] steps/24h; p=0.003) and a significantly lower VO_2 peak (22 [17-24] vs. 33 [26-39] mL/min/kg; p=0.003) compared to the healthy controls. Muscle biopsy citrate synthase activity did not differ between groups (15.4 [13.3-20.0] vs. 20.1 [16.6-25.8] µM/g/min, respectively; p=0.449).

Conclusions

Resting EE does not differ between DM1 patients and healthy, matched controls when assessed under standardized circumstances. However, under free living conditions, total EE is substantially reduced in DM1 patients due to a lower physical activity level. The sedentary lifestyle of DM1 patients seems responsible for the undesirable changes in body composition and aerobic capacity.

Introduction

Myotonic dystrophy type 1 (DM1) is an autosomal dominantly inherited disease characterized by its progressive multisystemic nature. While muscle weakness and myotonia (inability to relax muscles) form the basis of the DM1 phenotype, organ involvement can cause possible life-threatening complications during the course of disease. Since curative or disease modifying treatment options are currently unavailable, disease management focusses on early detection of organ involvement and improving quality of life.[1]

The genetic basis of DM1 lies in a CTG repeat expansion located on chromosome 19, with repeat lengths being roughly correlated with disease severity.[2,3] Based on symptomatology, age of onset and CTG repeat length, DM1 is often classified into four clinical subtypes.[2,4] The adult-onset subtype is the most prevalent and has been linked to profound organ involvement.[2]

Apart from organ complications, DM1 is known to have metabolic consequences such as insulin resistance, and increased levels of total cholesterol, low-density lipoprotein and triglycerides imposing possible risk factors for cardiovascular disease.[5] Overweight and obesity are also frequently observed[6-9], with a prevalence of 28 and 22%, respectively, in our own DM1 population of 493 patients (*unpublished data*). Moreover, alterations in body composition in this patient population have been described previously.[6,10]

Overweight, obesity and other adverse changes in body composition in DM1 may result from decreased physical activity due to motor impairments and/or from the lack of motivation due to neuropsychological expression of disease. However, literature also suggests that resting energy expenditure (EE) may be lower in DM1 patients and that muscle oxidative metabolism could be impaired.[11,12] To accurately assess potential derangements in EE in these patients, differences in body composition and habitual physical activity need to be taken into account. In this study we applied various state-of-the-art methodologies to assess EE, body composition, and skeletal muscle oxidative capacity in 15 patients with DM1 as well as 15 healthy age-, sex- and BMI-matched controls.

Materials and methods

Study design and participants

A prospective cross-sectional case control study was conducted including 15 DM1 patients and 15 healthy age-, sex- and BMI-matched controls. Age matching was based on decades (18-29, 30-39, 40-49, 50-59, 60-69 and >70 years). BMI matching was based on the WHO BMI classification[13]: BMI 18.5-24.9, 25-29.9, 30-35 kg/m^2. Each healthy volunteer originated from the same age- and BMI group as the matched DM1 patient, and was of the same sex. In order to be eligible to participate, subjects had to be 18 years or older. DM1 patients had to have a genetically confirmed DM1 diagnosis of the adult-onset subtype, had to be able to walk and cycle, and have a muscular impairment rating scale (MIRS, a DM1 specific scale for muscle weakness) score <5.[14] Exclusion criteria consisted of: use of medication interacting with muscle metabolism (such as steroids and statins), diabetes mellitus, weight loss of more than 3 kg within the last three months, and the use of protein supplements. Healthy volunteers were also excluded in case of a diagnosed neuromuscular disorder, an abnormal neurological examination, or another medical condition possibly interfering with muscle strength or muscle mass. Patients and healthy volunteers were recruited between 2019-2021 from the neurology outpatient clinic of the Maastricht University Medical Centre+ and through the Dutch DM1 expertise centre website (mdexpertisecentrum.nl). As similar studies have not been conducted in this specific or comparable patient populations, we were unable to determine an estimated effect size for standard sample size calculation. Literature suggests that sample sizes for pilot studies must include a minimum of 12 participants per group.[15] When taking possible drop-out rates of 10-20% into account, an amount of 15 participants per group was established.

Standard protocol approvals, registrations, and patient consents

The study was conducted in accordance with the Declaration of Helsinki, and the research protocol was approved by the institutional Medical Ethics Committee (METC 182009, approved on 27-06-2018). Written informed consent was obtained from all included participants.

Study procedures

Eligible participants were invited for screening, to verify in- and exclusion criteria and to confirm adequate matching. At screening, medical history, medication use, and body weight and height were determined. Fasting glucose was assessed by finger-prick glucose test, with a fasting glucose of >7 mmol/L being considered an exclusion

criterion. Neurological examination was performed by a trained neuromuscular neurologist, to determine the degree of muscle weakness and MIRS score in patients, and to confirm normal strength in healthy participants. A trained neuromuscular neurologist evaluated subjects' eligibility based on in- and exclusion criteria and matching criteria. In case of confirmed eligibility, a 2-hour 7-point oral glucose tolerance test (OGTT) was performed on the day of screening. Thereafter, participants completed a 15-day study period (**Figure 7.1**):

- Day 0-1: 24-hour resting EE was determined by whole room calorimetry (see **Respiration Chamber**). Baseline urine samples were collected for doubly labeled water (DLW) analysis of total EE under free living conditions (see **Doubly Labeled Water**). DLW bolus was then administered orally to participants in the controlled environment of the respiration chamber (RC). Another urine sample was collected upon exiting the RC. An activity monitor and corresponding instructions were provided upon leaving the RC after 24-hours, and participants were asked to wear their monitor daily until study day 15 (see **Activity Monitor**).
- Day 1-14: Urine was collected at home on the evening of day 7 and morning of day 8. On day 8, participants visited the hospital to hand in urine samples and undergo muscle biopsy (see **Muscle Biopsy**). After leaving the hospital on day 8, participants returned to free living conditions while still wearing the activity monitor. Another urine sample was collected for DLW analysis on the evening of day 14.
- Day 15: On the morning of day 15, participants collected a urine sample at home and returned to the hospital. In the hospital, subjects handed in urine samples and underwent a full body magnetic resonance imaging (MRI), dual-energy x-ray absorptiometry (DEXA) and single slice computed tomography (CT) scan of the upper leg to assess body composition and muscle mass (see **Full Body MRI, CT upper leg** and **DEXA)**. Exercise testing for determination of maximum oxygen uptake capacity was performed (see **Exercise testing**).

Oral glucose tolerance test

Glucose tolerance was determined by a standardized 7-point OGTT that was performed after an overnight fast, using a 200 mL glucose solution containing 75 grams of glucose. Blood samples were collected at t = 0, 10, 20, 30, 60, 90 and 120 minutes for the measurement of plasma glucose concentrations. OGTT was considered normal in case of a fasting plasma glucose <5.6 mmol/L and a plasma glucose <7.8 mmol/L at t=120 minutes. Impaired fasting glucose was defined as a fasting plasma glucose of 5.6-6.9 mmol/L.[16] Impaired glucose tolerance was defined as a plasma glucose of 7.8-11.0 mmol/L at t=120 minutes.[16]

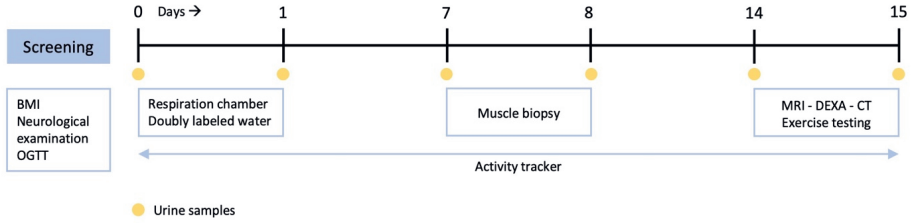

Figure 7.1 Overview of 15-day study period.
BMI, body mass index; CT, computed tomography; DEXA, dual-energy X-ray absorptiometry; MRI, magnetic resonance imaging, OGTT, oral glucose tolerance testing

Respiration chamber

Subjects resided in a RC for whole room calorimetry from 09:00 PM on day 0 until 09:00 PM on day 1. The RCs are located at the Metabolic Research Unit Maastricht (Maastricht University). 24-hour resting EE was determined through continuous monitoring and analysis of O_2 and CO_2 concentrations of incoming and outgoing air. O_2 consumption and CO_2 production rates were expressed in mL per min, measured at 5 min intervals over a 24-hour period. 24-hour resting EE was calculated using mean O_2 consumption and mean CO_2 production rates in mL/min in Weir's formula.[17] Subjects consumed standardized meals (16% protein, 55% carbohydrate, 28% fat) and were instructed to avoid exhaustive physical activity during the 24-hour stay. Participants did not receive instructions on (hours of) sleep, but were served breakfast at a standardized time.

Doubly Labeled Water

DLW bolus consisted of a small volume of water (80-160 mL depending on body weight) containing 5 Atomic percent (At%) ^2H_2O and 10 At% $H_2{}^{18}O$ per os, resulting in an initial excess body water enrichment of 150 ppm for ^2H and 300 ppm for ^{18}O. Urine samples were collected at time points described above and stored in a cooled environment, until final storage within 12 hours after collection in an air-tight screw-capped glass container, in a -30°C freezer. At the end of the study, urine samples were analyzed according to The Maastricht Protocol.[18] Excess disappearance rate of ^{18}O relative to ^2H through urine was converted to an estimate of total EE according to the Maastricht protocol for the measurement of body composition and EE with labeled water.[18-20]

Activity monitor

Participants wore a Philips Actical accelerometer attached to a belt on the left hip during a 14-day period, starting directly after leaving the RC until study day 15. Participants were instructed to wear the accelerometer at all times, except for when sleeping or showering. Accelerations were converted into number of steps per 24 hours and % time sedentary per 24 hours by Actical software. We used data of 12 full measuring days for analysis as participants resided in the hospital on study day 8 and 15 and had to take off the accelerometer during and between measurements.

Muscle biopsy

A muscle biopsy was obtained 15 cm above the patella from the vastus lateralis muscle approximately 2 cm below the fascia, by percutaneous needle biopsy technique as described by Bergström et al.[21]. Skin and muscle fascia were locally anesthetized using 1% xylocaine. Mitochondrial citrate synthase (CS) activity was measured as previously described.[22,23]

Full body MRI

Full body MRI was performed using a 3T MAGNETOM Prisma Fit scanner (Siemens Healthcare, Erlangen, Germany) using the whole-body coil and the body array coil 18 elements (Siemens Healthcare, Erlangen, Germany). A 6-minute dual-echo Dixon Vibe protocol was applied, providing a water and fat separated volumetric data set covering head to ankles. In total 8 slabs were acquired containing all individual images. Common scanning parameters for all included slabs were: flip angle (α)=10°, repetition time (TR)=3.89 milliseconds, echo time (TE)=1.22/2.45 milliseconds, bandwidth=930 Hz/Px and 256x192 matrix. There was no interslice gap (0 mm). Slabs covering the abdomen were acquired during 18-second expiration breath-holds and consisted of 44 slices with a voxel size 2.0x2.0x5.0 mm^3. The slabs covering the legs, consisted of 88 slices with a voxel size of 2.0x2.0x3.0 mm^3. Body composition analysis was performed by using the AMRA Profiler Research (AMRA Medical AB, Linköping, Sweden).[24-26] Scans were analyzed for total lean tissue volume (including thigh muscle volume), total adipose tissue volume (including visceral adipose tissue volume and subcutaneous adipose tissue volume), posterior thigh muscle fat infiltration (expressed in %) and fat ratio (expressed in %). Fat ratio was defined as: (visceral adipose tissue volume + subcutaneous adipose tissue volume) / (visceral adipose tissue volume + subcutaneous adipose tissue volume + thigh muscle volume). Following the automated segmentation and analysis process, an experienced operator reviewed each segmentation for anatomical correctness and technical quality.

CT upper leg

Muscle cross-sectional area (as a proxy for muscle mass) was assessed from a single-slice CT scan (Somatom Definition Flash; Siemens Healthineers, Forchheim, Germany). While subjects were lying supine, with their legs extended and their feet secured, a 2-mm thick axial image was taken 15 cm proximal to the top of the patella. Analysis included manual tracing of the quadriceps muscle using ImageJ software by an experienced and blinded researcher, to determine cross-sectional area (CSA) of the quadriceps, as previously described.[27]

Dual-energy X ray Absorptiometry (DEXA)

A DEXA scan was performed on a commercially available clinical system (Discovery A; Hologic, Bedford, MA, USA) with system's software package (Hologic-Apex software, version 4.5.3, with viewer software Hologic Physician's viewer, version 7.1) to determine total lean mass and fat mass.

Exercise testing

Aerobic capacity was tested with a cardiopulmonary exercise test to exhaustion with continuous electrocardiography and respiratory gas analysis. Tests were performed on a cycle ergometer (Lode Corival, Groningen, the Netherlands). Ventilatory parameters were measured breath-by-breath (Carefusion; San Diego, USA). After 3 min of unloaded cycling, the workload was increased according to an individualized ramp protocol aiming at a total test duration of 8–12 minutes. Subjects were instructed to cycle with a pedaling rate of >60 revolutions·min^{-1}. The test was ended when the subjects stopped cycling or were unable to maintain the required pedaling frequency. Maximal workload (Wmax), peak oxygen uptake (VO_2peak) and peak respiratory exchange ratio (RER_{peak}) were recorded as the final 30 sec averaged value of the test.

DNA analysis

DNA analysis took place at DM1 diagnosis, as standard of care. CTG-repeat lengths were determined by analyzing DNA extracted from peripheral blood samples through polymerase chain reaction (PCR), followed by fragment length analysis and Southern blot analysis.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 25 (SPSS Inc, Chicago, IL). The distribution of continuous variables was assessed for normality, by visual inspection of

histograms and standardized normal probability plots. Continuous variables are expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR) in case of skewness. Categorical variables are expressed as counts (percentages). Differences between groups were compared using the chi-squared (χ^2) test or Fisher's exact test (categorical data), and the unpaired Student's t-test or the Mann-Whitney U test (continuous variables). P values of <0.05 were considered statistically significant.

Results

Study population

Fifteen patients diagnosed with DM1 and 15 healthy matched controls were included in the study (**Table 7.1**). CTG repeat length and MIRS classification of DM1 patients are described in **Table 7.1**. Fasting blood glucose concentrations were normal in all participants, except for 6 DM1 patients who met the criteria for having an impaired glucose tolerance based on abnormal OGTT values. Missing data consisted of one full body MRI in the DM1 group, one CT upper leg in the DM1 group and one muscle biopsy in the healthy control group.

Table 7.1 Baseline characteristics.

	Myotonic dystrophy patients (*n*=15)	**Healthy controls (*n*=15)**	**P value**
Age, median [IQR]	41 [30-50]	42 [30-50]	1.000
Male, n (%)	7 (47%)	7 (47%)	1.000
BMI, median [IQR]	26.5 [21.8-28.6]	26.2 [22.9-29.4]	1.000
BMI category, n (%)			
18.5 - 24.9 kg/m²	6 (40%)	6 (40%)	1.000
25 – 29.9 kg/m²	7 (47%)	7 (47%)	1.000
30 – 35 kg/m²	2 (13%)	2 (13%)	1.000
CTG repeat length, n (%)			
100-150	3 (20%)		
>150	6 (40%)		
>200	4 (27%)		
>350	2 (13%)		
MIRS, n (%)			
1	0 (0%)		
2	2 (13%)		
3	5 (33%)		
4	8 (54%)		
Patients with abnormal fasting glucose, n (%)	0 (0%)	0 (0%)	1.000
Patients with impaired glucose tolerance, n (%)	6 (40%)	0 (0%)	0.006

BMI, body mass index; MIRS, muscular impairment rating scale.

Body composition

Total lean and adipose tissue volumes determined by full-body MRI were not statistically different between groups, with median total lean tissue volume 19.81 [18.81-23.19] L in the DM1 group versus 22.74 [20.54-28.72] L in the control group (p=0.066). Median total adipose tissue volume was 25.11 [19.31-31.33] L in DM1 patients versus 20.82 [16.65-28.25] L in healthy controls (p=0.466). Fat ratio was significantly higher in DM1 affected individuals (median 56 [49-62] %) than in healthy controls (median 44 [37-52] %; p=0.027; **Figure 7.2**). Also, visceral adipose tissue volume was significantly higher in DM1 patients when compared with healthy controls (median 5.06 [2.66-6.06] vs. 2.79 [1.51-4.28] L, p=0.027). A representative image of the adipose tissue assessment for both a DM1 patient and a healthy control is given in **Figure 7.3**. Furthermore, DM1 patients had significantly more posterior thigh muscle fat infiltration than healthy adults (median muscle fat infiltration 12.43 [9.07-13.99] % in DM1 patients versus 9.62 [8.71-11.80] % in healthy adults; p=0.027). Body composition was also assessed by using DEXA scan. Total fat and total lean mass determined by DEXA were not statistically different between groups (see **Supplementary Table S7.1**). In addition, CT assessment of quadriceps CSA tended to be lower in the DM1 patients, with a CSA of 5533 [5287-6431] mm^2 in DM1 patients vs. 7057 [5965-7881] mm^2 in healthy controls (p=0.066).

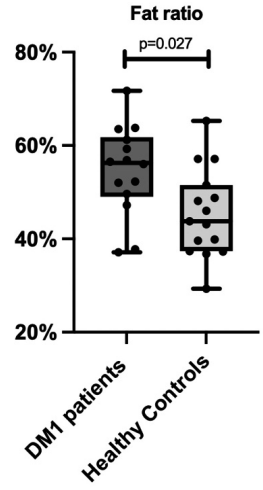

Figure 7.2 Comparison of fat ratio between myotonic dystrophy type 1 (DM1) patients and healthy age-, sex- and BMI-matched controls, based on full-body MRI measurements.

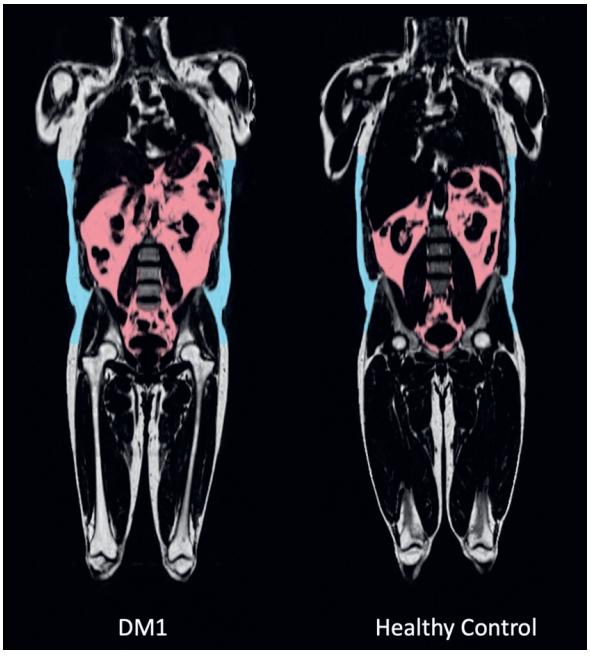

Figure 7.3 Comparison of full body MRI images between a myotonic dystrophy type 1 (DM1) patient and a healthy age-, sex- and BMI-matched control. Visceral adipose tissue (VAT) deposition is highlighted in pink. VAT volume was 5,59L in the displayed DM1 patient versus 4,28L in the healthy matched control. Subcutaneous fat deposition is highlighted in blue, as part of the total adipose tissue volume. Also note the difference in shoulder and leg musculature: thigh lean muscle volume was 11,1L in the DM1 patient versus 15,1L in the healthy control, as part of total lean tissue volume.

Energy expenditure

Median 24-hour resting EE determined by RC did not differ between DM1 patients (1948 [1742-2146] kcal/24h) and healthy controls (2001 [1853-2425] kcal/24h; p=0.466; **Figure 7.4A**). After correction for lean tissue volume, resting EE per liter lean tissue was 89 [86-100] kcal/L in DM1 patients and 90 [84-97] kcal/L in matched controls (p=0.715). In contrast, total EE assessed under free living conditions via DLW measurement was 23% lower in DM1 affected individuals (2162 [1794-2494] kcal/24h) when compared with healthy controls (2814 [2424-3310] kcal/24h; p=0.027; **Figure 7.4B**).

Physical activity

There was a significant difference in the amount of habitual daily physical activity performed between both groups. DM1 patients had a 63% lower amount of steps per 24 hours, with a median number of 3090 [2263-5063] steps/24h vs. 8283 [6855-11485] steps/24h in healthy adults (p=0.003, **Figure 7.4C**). Individuals in the DM1 group were sedentary 86 [82-91] % of the time, in comparison to 79 [75-84] % in the matched control group (p=0.027).

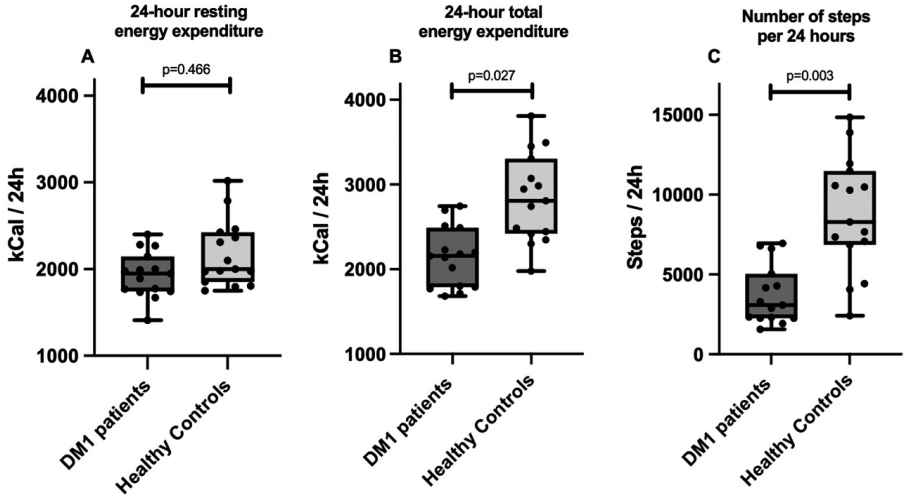

Figure 7.4 Comparison between A) 24h resting energy expenditure measured by whole room calorimetry, B) 24h total energy expenditure under free living conditions measured using doubly labeled water, and C) number of steps per 24h measured by accelerometer, in myotonic dystrophy type 1 patients and healthy age-, sex- and BMI-matched controls.
DM1, myotonic dystrophy type 1

Muscle oxidative capacity

DM1 patients had a significantly lower median VO_2 peak of 22 [17-24] mL/min/kg in comparison to 33 [26-39] mL/min/kg in healthy matched adults (p=0.003). Median VO_2 peak stratified according to sex is displayed in **Table 7.2**. There was a statistically significant difference in the absolute values at which the ventilatory anaerobic threshold and respiratory compensation point were reached (**Table 7.2**). These differences were no longer significant when expressed as percentages of the VO_2 peak (**Table 7.2**). Also, there was a statistically significant difference in maximal workload

and oxygen uptake efficiency slope (**Table 7.2**). Median respiratory exchange ratio did not differ between groups (**Table 7.2**).

Muscle biopsy

CS activity in muscle biopsy material did not differ significantly between groups, with a median of 15.4 [13.3-20.0] µM/g/min in DM1 patients versus 20.1 [16.6-25.8] µM/g/min in healthy adults (p=0.449).

Table 7.2 Exercise testing results.

	DM1 patients ***n*****=15**	**Healthy controls** ***n*****=15**	**P value**
VO_2 peak, mL/min/kg	22 [17-24]	33 [26-39]	0.003
Males	23 [19-33]	39 [30-41]	
Females	21 [14-23]	31 [25-37]	
Ventilatory anaerobic threshold, mL/min/kg	15 [11-17]	20 [16-22]	0.011
% of VO_2 peak	57% [53-60]	60% [53-62]	1.000
Respiratory compensation point, mL/min/kg	22 [18-28]	31 [24-34]	0.019
% of VO_2 peak	91% [84-95]	89% [86-95]	0.414
Respiratory exchange ratio	1.22 [1.06-1.28]	1.18 [1.12-1.11]	1.000
Maximal workload, W	139 [111-160]	217 [191-275]	0.003
Oxygen Uptake Efficiency Slope, ([mL/min O_2]/[L/min VE])	1851 [1689-2201]	2711 [2298-3306]	0.003

DM1, myotonic dystrophy type 1.

Discussion

In the present study we observed a higher fat ratio in patients affected by DM1 when compared to healthy, matched controls. The difference in body composition was accompanied by a 23% lower total EE in DM1 patients when compared to healthy matched controls, assessed under free living conditions. In line, habitual physical activity level was 63% lower in patients compared to healthy controls, with substantially more time spent in a sedentary state. The lower EE could not be attributed to any metabolic derangements as 24h EE under standardized conditions did not differ between groups. Aerobic capacity, assessed by oxygen uptake capacity, was substantially reduced in DM1 patients when compared to sex- and age-matched controls.

Apart from overweight in more than 50% of the general DM1 population[6-9], body composition has been described to be altered with increased fat mass, decreased lean body mass and visceral obesity.[6,7,10,28,29] In line with previous studies[6,7,10,28], we performed DEXA to assess body composition. We observed that DEXA-derived total fat

and lean mass were not statistically different between groups. However, given that DEXA scans have been demonstrated to consistently underestimate fat mass[28,30], we considered it relevant to assess body composition by full body MRI as well, especially in a patient population with fat infiltration into atrophic muscle tissue. With full body MRI, differences in total adipose tissue volume nor total lean tissue volume were statistically significant between groups. Still, we consider the observed differences to be clinically relevant, especially since they are in line with previous research.[7,8,10] In support, fat ratio was significantly higher in DM1 affected individuals, which seems to be of greater relevance as fat ratio takes loss of lean muscle volume into account. Visceral adipose tissue volume was also significantly higher in DM1 patients, as suggested in literature.[7,10,31] The current study is the first to assess body composition in DM1 patients by means of full body MRI, as previous data were based on DEXA or bioelectrical impedance analysis. In the present study we also performed CT to assess upper leg muscle atrophy, demonstrating a difference in CSA of the quadriceps between groups, even though this did not reach statistical significance.

Both 24h resting EE and corrected resting EE per liter lean tissue were comparable between DM1 affected individuals and matched controls. Even though resting EE of DM1 patients had been researched in three small studies, measurements were based on only short intervals using ventilated hood method.[11,28,29] While there seemed to be a difference in resting EE between DM1 patients and healthy matched controls in these other studies, this difference was no longer present after correction for lean muscle volume which is comparable to our data.[11,28,29] Since the current study used 24h whole room calorimetry under standardized circumstances, resting EE estimates can be considered more accurate and precise.[32]

Apart from EE under standardized circumstances, DLW was used to asses total EE under free living conditions. While the DLW technique is considered the gold standard for determination of total EE, it had not yet been used in DM1 patients nor in patients diagnosed with other neuromuscular diseases. A study using continuous heart rate registration, with subsequent heart rate VO_2 calculations, did estimate EE under free living conditions in patients with slowly progressive neuromuscular disease (including DM1) and matched controls.[29] This study described a decreased total EE as a result of a reduced amount of physical activity, in comparison to healthy matched adults, as is in line with our results.[29]

The hypothesis of lower total EE in DM1 being the result of relative inactivity, can be confirmed by comparing collected accelerometer data between both groups. Indeed,

there was a clear distinction in the amount of physical activity between DM1 affected individuals and healthy adults, with DM1 patients registering less than half the number of steps per day. A previous study measuring physical activity in DM1 patients using accelerometers had similar results, even though data was collected over a shorter seven day period.[33] By extending this period to 15 days in the current study, the effects of possible behavioral adjustments were minimized. Possible causes for a decreased amount of physical activity in DM1 patients do not only consist of muscular impairment, but also participation restrictions in daily and social activities and cognitive impairment[34], even though this was not objectified in the current study.

VO_2 peak values confirmed a clear distinction in exercise capacity between DM1 affected individuals and healthy controls. When comparing test results to normative values in the Dutch population, DM1 affected individuals' scores were lower than the lower limit of normal P3 percentile, while healthy individuals' scores were between P10-P25.[35] Despite the fact that DM1 patients had a reduced exercise capacity, all of the included participants completed the test until maximal effort based on respiratory exchange ratio.[36] Absolute ventilatory anaerobic threshold and respiratory compensation point values seemed to indicate an early switch to anaerobic metabolism in DM1 patients, yet these differences no longer remained when values were expressed as percentages of the VO_2 peak. Only one other study has described cardiovascular exercise testing in DM1 patients, even though this was a retrospective evaluation of exercise testing based on clinical indications.[37] Approximately 35% of included DM1 patients was unable to reach maximal effort and the ascertained limited exercise tolerance was presumed to be the result of cardiac and ventilatory deficiencies.[37] In our study, oxygen uptake efficiency slope was also significantly different between groups.[38,39] The difference in oxygen uptake efficiency slope may indicate pulmonary and/or cardiac involvement with suboptimal O_2 uptake in the included DM1 participants, yet cardiac and pulmonary data (from regular disease follow-up) was not included in the study.

Oxidative capacity was also evaluated at the level of muscle tissue through CS activity analysis. CS activity is considered a biomarker for muscle metabolic capacity.[40,41] Even though maximal CS activity was not statistically different between patients and healthy controls, possibly resulting from insufficient statistical power, median values suggest a lower oxidative capacity of muscle tissue of DM1 patients. A lesser oxidative capacity would be secondary to a lower physical activity level as CS activity has been demonstrated to increase after training interventions.[42] Apart from CS, mitochondrial content and function have been demonstrated to increase after aerobic training in

DM1 as well.[43] Still, research on DM1 mitochondrial functioning has demonstrated conflicting results[44] while there seems to be an increasing amount of evidence suggesting that mitochondrial dysfunction is part of the DM1 phenotype.[12,44-46] Interestingly, this did not seem to affect resting EE in our study population.

The main limitation of this study consists of the relatively small sample size. Moreover, we deliberately chose not to collect data on energy intake, which would facilitate the assessment of a potential mismatch in energy intake and expenditure, as the 15-day trial period was already relatively demanding, considering the neuropsychological status of DM1 patients. Also, we did not include cardiopulmonary characteristics and cardiovascular risk profiles, as this would necessitate a large amount of additional analyses in healthy controls. By combining several advanced research techniques in one study, however, we did manage to get a complete overview of metabolic function of DM1 patients, which we were able to compare to healthy, matched controls. Still, results might have been influenced by the fact that six DM1 patients had an impaired glucose tolerance. Finally, thyroid function was not assessed in DM1 affected individuals as part of the study although thyroid function screening is part of standard DM1 patient follow-up. The relationship between thyroid dysfunction and DM1 still remains unclear.[2,47]

The current study did not find a difference in resting EE, but did find a difference in total EE under free living conditions, in oxidative capacity and in the amount of physical activity between both groups. Therefore, overweight in DM1 seems to be the consequence of a structural more positive energy balance. Since CTG repeat expansions of included participants were mostly on the lower end of the scale and only patients with the adult-onset subtype were included in the study, total EE might even be lower in the DM1 population. Moreover, as muscle wasting continues over the course of disease, caloric needs continue to decrease during DM1 patients' lifetimes. As a result, patient management in DM1 should focus on correcting the caloric mismatch to prevent weight gain, or even on creating a temporary negative energy balance in case of desired weight loss. Ideally, this could be accomplished through a combination of dietary changes and increased physical activity. Due to muscle weakness, fatigue and neuropsychological symptoms (such as lack of motivation and apathy)[48,49], the ideal type of lifestyle intervention and preferred exercise training modalities remain to be determined. Even though cardiopulmonary fitness was very poor in DM1 affected individuals, patients did manage to complete exercise testing as part of the current study protocol. Moreover, other studies have established the feasibility of long-term exercise interventions and have demonstrated positive effects on patients-reported

outcomes, muscle endurance, mitochondrial functioning and functional testing in DM1.[43,50,51] Still, there are insufficient data available to determine an optimal exercise training intervention for DM1 patients at this time.[50] Based on a high level of heterogeneity in DM1 manifestations both on a muscular and neuropsychological level, a personalized intervention seems to be the most suitable. With regards to the lesser muscle mass and low oxygen uptake capacity, exercise interventions should focus both on improving muscle mass and strength as well as increasing endurance performance. Moreover, it would be of added value to determine if weight loss could be beneficial not only on a physical level, but also on the level of social participation and quality of life as these effects have been established in the general population.[52,53]

Apart from a subjective desire to lose weight in many DM1 patients, the data in this study stresses the need for cardiovascular risk management as well. While overweight is known to impose cardiovascular risk on the long-term, specifically visceral obesity has also been linked to insulin resistance, hypertension and atherogenic dyslipidemia.[54,55] In our study, glucose tolerance was abnormal in 6 out of 15 DM1 patients. Data on the prevalence of subsequent cardiovascular disease in DM1 is scarce, which might be the result of it being considered less important due to reduced survival.[56] As patient management has been improving over the last decade, cardiovascular risk management will become of greater importance.

In conclusion, whole-body EE does not differ in DM1 affected individuals when compared to healthy age-, sex- and BMI-matched controls when assessed under strict dietary and physical activity standardization. However, under free living conditions, daily EE is severely reduced in DM1 patients which can be attributed to a low physical activity level. The low physical activity status, accompanied by a low physical fitness level, represents a key factor responsible for the undesirable changes in body composition in this patient population. In clinical practice, DM1 patient management should include promotion of a more active lifestyle combined with an exercise intervention program to increase physical fitness, increase EE and, as such, prevent overweight and reduce cardiovascular risk.

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Supplementary table

Table S7.1 Body composition determined by DEXA scan.

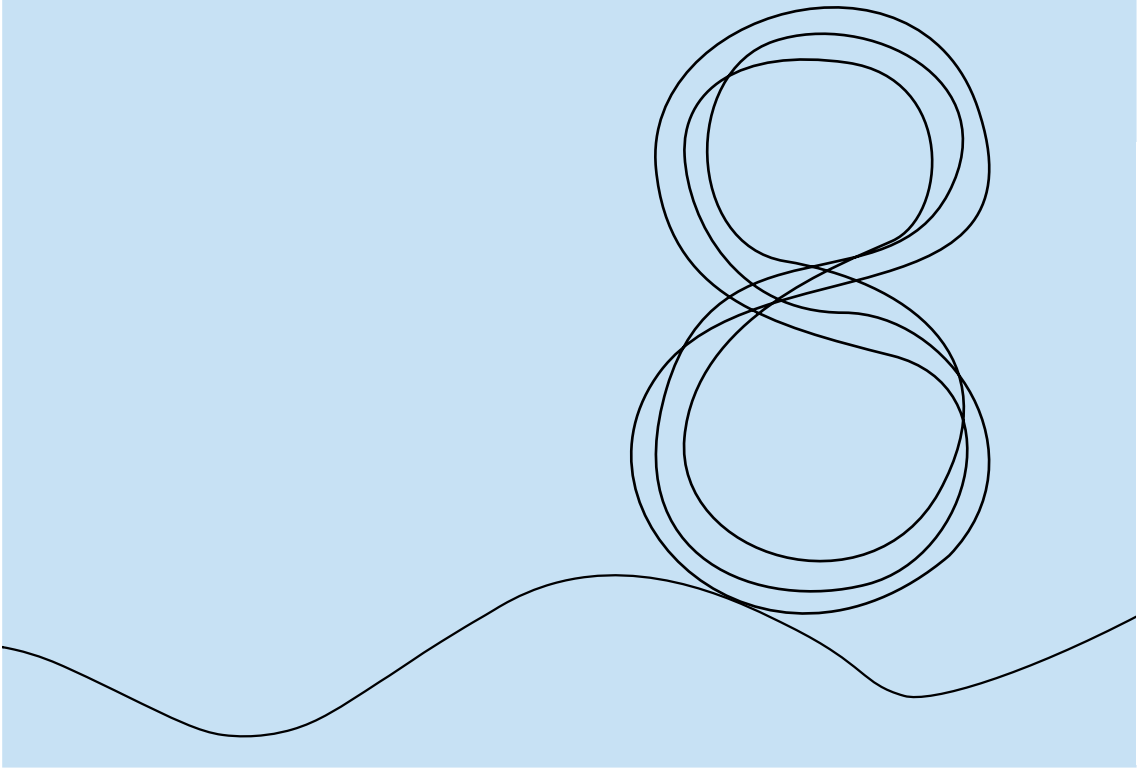
	DM1 patients (*n*=15)	**Healthy controls (*n*=15)**	**P value**
Total lean mass, kg [IQR]	46.74 [43.60-56.16]	48.94 [44.30-60.22]	1.000
Total fat mass, kg [IQR]	29.42 [24.05-36.63]	23.99 [18.75-28.79]	0.466

Section 4

Addenda

Chapter 8

General Discussion



General discussion

The current thesis focused on clinical genetics and multisystem involvement in myotonic dystrophy type 1 (DM1). In **Section 2**, we presented a comprehensive overview of DM1 including its medical management and described the intergenerational instability of DM1 pre- and protomutation alleles. In **Section 3**, multiorgan involvement was discussed including the usefulness of cardiac screening modalities and an evaluation of metabolic functioning in DM1-affected individuals. As DM1 is a slow progressive disorder without curative treatment options at this time, adequate patient follow-up is essential for the establishment of possible complications and adequate treatment at an early stage.

Various studies have demonstrated, that patients affected by chronic diseases often receive less than optimal care.[1] Although the management of different conditions requires an approach that is in-part disease-specific, some general requirements have been composed for chronic disease management (CDM) [1]. CDM can be defined as an '*organized, proactive, multi-component, patient-centered approach to healthcare delivery that involves all members of a defined population who have a specific disease entity'.*[1] In order to provide high-quality CDM, several essential management elements are addressed in literature, such as: the availability of (1) decision support through the implementation of disease-specific guidelines or performance standards, (2) self-management support including systematic attention for the information needs of patients, (3) redesigned healthcare systems in order to meet the needs of patients who require more time, a broad array of resources, and close follow-up, (4) clinical information systems able to monitor disease outcomes, and (5) healthcare provider education.[1-3]

For the management of patients affected by DM1, efforts have been devoted to enhance several aspects of CDM over the last decade. As we aimed to improve DM1 patient management by adding to the current knowledge of clinical genetics and multisystem involvement, this thesis can be placed in the CDM context as well (**Figure 8.1**).

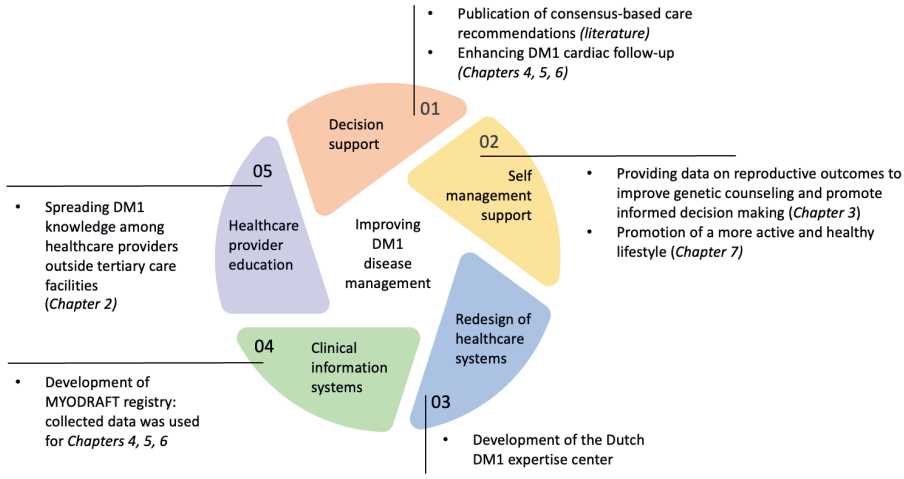


Figure 8.1 **Improvements in the management of myotonic dystrophy type 1.**
The current thesis is placed in the context of chronic disease management, demonstrating how the content of this thesis and recent literature have added to improving myotonic dystrophy type 1 (DM1) disease management.

An important step forward in DM1 disease management was taken with the publication of the *Consensus-Based Care Recommendations for Adults with Myotonic Dystrophy Type 1* in 2018[4], adhering to the first CDM essential element of available decision support.[1,2] These recommendations include practical information on both DM1 genetic counseling and multisystem involvement.

Genetic counseling

Genetic counseling is advised for all DM1 patients of child-bearing age and parental counseling is recommended in case of an active wish to conceive.[4] Genetic counseling aims to promote informed choices: this is possible only if disease-specific reproductive outcome data are available to caregivers and patients.[5] In *Chapter 3,* data on the intergenerational instability of DM1 pre- and protomutations were described. Even though a small number of studies on this topic had been published[6-8], *Chapter 3* gives an overview of the largest sample of parent-child pairs carrying such small repeat expansions so far. In clinical practice, the presented data add to the information needs of patients as reproductive outcomes of pre- and protomutation carriers can be included in genetic counseling. Through the availability of this information, the second CDM element of self-management is promoted and informed decision making is enhanced (**Figure 8.1**).[1,2] Moreover, a recently published paper has demonstrated that

DM1 premutations are far more common than previously presumed, with a newly mentioned prevalence of 1 in 525 births in Northern America.[9] Based on this information, our data on the intergenerational instability of such small repeat expansions may become of greater relevance. The noted prevalence of 1:525 results from additional analysis performed on blood collected for a regular newborn screening program however, meaning that some of these repeat expansion carriers would probably not have been identified outside of the study due to lack of symptoms.[6,7,9,10] Because pre- and protomutation carriers are often asymptomatic at a reproductive age, the expanded repeat can unknowingly be transferred to offspring. As described in *Chapter 3,* we found that the transmission of pre- and protomutations leads to CTG repeat lengths associated with clinical symptomatology (CTG>80) in a large proportion of offspring, with paternal transmission as an additional risk factor. Adding to the newly mentioned prevalence of premutations, the study by Johnson *et al.*[9] demonstrates that 1 in every 2100 newborns had a CTG repeat >50, leading to a combined prevalence of DMPK repeat expansions that is five times higher than previously estimated. As such, standard newborn screening could be considered with subsequent follow-up and counseling to prevent DM1 transmission, even in case of small sized repeat expansions.[9] On the other hand, as a large proportion of patients with small sized repeats remain asymptomatic, this raises several ethical concerns.

Multisystem involvement

While the consensus-based care recommendations for adults with DM1 published in 2018 include advise on the management of organ involvement, organ-specific care recommendations have been published thereafter as well. In 2020, both *Clinical Care Recommendations for Cardiologists Treating Adults with Myotonic Dystrophy* by McNally *et al.*[11] and *Consensus-Based Care Recommendations for Pulmonologists Treating Adults with Myotonic Dystrophy Type 1* by Boentert *et al.*[12] became available.

As described in the cardiac care recommendations[11] and stressed in the current thesis, electrocardiogram (ECG) should be used as an annual screening tool in all DM1 patients independent of cardiac symptomatology (*Chapters 4 and 6*). Based on ECG results, the need for an electrophysiological study (EPS) and subsequent pacemaker (PM) or Implantable Cardioverter Defibrillator (ICD) implantation is determined.[11] While PM or ICD implantation was advised in case of abnormal EPS results in international cardiac pacing guidelines, these guidelines did not include information on when to perform an EPS in clinical practice.[13,14] *Chapter 4* demonstrated that a specific combination of ECG abnormalities (PR >200ms and QRS >120ms) has a high positive predictive value for abnormal EPS results. After the publication of *Chapter 4,* the 2021 ESC Guidelines on

Cardiac Pacing and Cardiac Resynchronization Therapy were published, including more specific indications for PM and ICD implantation in DM1 patients.[15] Still, the appropriate timing of EPS was not discussed, as was the case in the 2013 ESC guidelines.[13,15] The lack of advice on the timing of EPS was subsequently addressed by two cardiologists with DM1 expertise in a letter to the editor, arguing that EPS should be performed in all DM1 patients with an abnormal PR interval or widened QRS complex based on the results of *Chapter 4* and a previously published paper by Wahbi *et al*..[16,17] Still, the question remains if EPS is necessary at all, due to the high positive predictive value of the presented ECG abnormalities in *Chapter 4.*[18] As our study is based on a retrospective data set however, we believe that a prospective study will be necessary to investigate the option of direct PM implantation in the future. Moreover, it is important to note that during EPS not only the His-Ventricle interval is measured, but also arrhythmia inducibility is assessed. Currently, arrhythmia inducibility is being used to differentiate between the need for a PM or combined PM/ICD, even though the exact role of this assessment in DM1 patients has not yet been validated.

As cardiac arrhythmias may have a paroxysmal character in DM1[11,19], 24 h Holter monitoring is included in DM1 cardiac screening as well. The exact role of Holter monitoring has remained unclear, as the previously mentioned care recommendations give conflicting advice on when this screening modality should be used.[4,11,20] *Chapter 5* of the current thesis demonstrated that Holter monitoring frequently establishes new findings that may warrant treatment alteration, even in patients with normal baseline ECGs. Unfortunately, consensus on the utility of Holter monitoring has not yet been reached, which is most likely the result of the small amount of evidence available on this topic.

Even less data are available on the follow-up of specific subgroups within the DM1 patient population, as is the case for DM1 small sized repeat carriers. Patients affected by late-onset DM1, carrying such small CTG repeat expansions, often remain asymptomatic or present with a mild muscular phenotype while the extent of multi-organ involvement has not been well-studied. However, in *Chapter 6* we have demonstrated in a large sample of DM1 patients, that the prevalence of cardiac conduction delay was comparable between late-onset and adult-onset DM1. Also, a relatively large proportion of late-onset DM1 patients required non-invasive ventilation as a result of respiratory involvement.

Apart from organ complications, DM1 can have several metabolic consequences such as insulin resistance and abnormal lipid levels.[21] Also, overweight and obesity are

frequently observed.[22-25] In *Chapter 7* we demonstrated that differences in weight and body composition in DM1 patients do not seem to result from direct metabolic consequences of disease, but rather from a decreased amount of habitual physical activity. The observed sedentary lifestyle appears to be an important risk factor for cardiovascular disease in this patient population as well. Consequently, we consider the promotion of a more active and healthy lifestyle to be important in DM1 follow-up, which can be considered a part of self-management support (*second CDM element*, **Figure 8.1**). Unfortunately, only little attention is paid to lifestyle management in available DM1 care recommendations at this time.[4,11] While Ashizawa *et al*.[4] state that moderate intensity exercise should be encouraged and that patients should be referred to a physical therapist, these recommendations are given as management options for skeletal muscle weakness. Moreover, lifestyle interventions are only mentioned once for patients that have already been diagnosed with insulin resistance.[4] The clinical care recommendations for cardiologists by McNally *et al.*[11] give some advice on the management of metabolic syndrome and hyperlipidemia, but the authors state that larger studies are needed to evaluate the benefits of exercise. Unfortunately, lifestyle management in general is not addressed, as is the case in the Dutch DM1 guidelines.[20] We believe that not enough attention is paid to lifestyle management in DM1 in clinical practice. To ensure that lifestyle management will become part of DM1 follow-up, future studies are required to confirm its effects.

Patient management

In order to make DM1 disease follow-up as adequate as possible, it is important to develop a suitable healthcare environment that is *organized, proactive, multi-component, and patient-centered,* as described in the CDM definition.[1-3] The previous sections of this discussion have made it apparent that, apart from a neurologist, at least specialized cardiologists, pulmonologists and clinical geneticists should be part of the DM1 care system. When looking back at Table 1.1 of *Chapter 1* however, it becomes clear that a much larger team of specialized healthcare providers is required, such as gastroenterologists, ophthalmologists, neuropsychologists, physical therapists, occupational therapists and so on. As a result of new insights, even more members might need to be added to the team, for example specialized lifestyle coaches.

Since organizing such complex care can be quite challenging, a decision was made to centralize DM1 care in the Netherlands by founding the Dutch DM1 expertise center in 2017. The DM1 expertise center is comprised of the Radboudumc Nijmegen and Maastricht UMC+, with a DM1 specialized care team available at each location. The formation of the expertise center is in line with the third essential management

element of CDM, namely the redesign of healthcare systems for a specific patient population (**Figure 8.1**). Apart from aiming to provide the most optimal form of care for DM1-affected individuals, the expertise center aims to enhance DM1-related research activities as well. One of the most important research activities so far has been the development of a joint DM1 disease registry: the Myotonic Dystrophy type 1: Dutch Registry and Follow-up study, or MYODRAFT in short. Through the formation of the MYODRAFT, another CDM essential management element was added to the Dutch DM1 care system, as a clinical information system became available to monitor disease outcomes (*fourth CDM element,* **Figure 8.1**). As of January 2023, a total of 600 patients have been included in the registry, collecting data on demographics (age, sex and education) and clinical features (such as data on the diagnosis, genetic confirmation, age at onset, DM1 subtype, medical history, neuromuscular, cardiac and pulmonary status, gastrointestinal complaints, cataract, fatigue, cognition and behavior, and activity and participation restrictions). Through the development of the MYODRAFT and expertise center, a strong collaborative team with specific DM1 knowledge has been formed, that is able to determine important knowledge gaps in the DM1 field. As a direct result of this collaboration, the studies in *Chapters 4, 5 and 6* of this thesis were performed using MYODRAFT data. Even though these studies have added to improving DM1 patient follow-up, we believe there is still ample work to be done.

Future perspectives

To further optimize DM1 care, it would be of great value if long term, prospectively collected, cardiac follow-up data became available. Ideally, data on all screening modalities currently used in DM1 cardiac follow-up would be collected and utilized for risk stratification of mortality. In part, the data are already being collected in the Dutch MYODRAFT registry. As the MYODRAFT is a strictly observational study however, more comprehensive diagnostics such as EPS are performed only if this is considered necessary by treating cardiologists, as part of routine clinical care. Based on the results of *chapters 4 and 5,* it would be ideal to perform a study in which a subgroup of MYODRAFT participants undergoes standard EPS screening, including patients with normal ECG and Holter results. Such a study could either validate the role of ECG and Holter screening, or determine if standard EPS screening should be considered in the future. Also, prospective follow-up data could be used to determine the ideal ECG and Holter screening interval, as this could not be determined based on the data presented in *Chapters 4 and 5*. As soon as long-term follow-up data has been collected, the impact of preventive measures on patients' prognosis should be evaluated as well.

Apart from screening for arrhythmias and conduction delay, it could be necessary to include standard screening for cardiovascular risks in future DM1 follow-up (*Chapter 7*). Nevertheless, data on cardiovascular risk profiles in DM1 patients are scarce and the prevalence of, for example, metabolic syndrome, hypertension, transient ischemic attacks, stroke and myocardial infarction have not been well-studied.[11,26] Due to the improvement of DM1 disease management in the last decade and its expected positive effects on survival, cardiovascular risk management and lifestyle interventions will become of greater importance. Still, future studies are needed to define the ideal type of lifestyle intervention and preferred exercise training modalities (*Chapter 7*).[27,28] Due to the heterogeneity of the DM1 population both on a muscular and neuropsychological level, a personalized approach seems to be the most suitable. The effects of lifestyle interventions and exercise training would need to be assessed through forthcoming studies as well, to determine their impact on cardiovascular risk reduction, functional outcome measures and quality of life. Moreover, as some clinicians have a cautious approach towards structured exercise training[27] due to the possible arrhythmogenic nature of exercise in DM1[29], these studies should also confirm safety.

It can be expected that the DM1 field will undergo great changes with the development of genetic treatment options in the upcoming years. Due to the monogenetic origin of DM1, potential therapies consist of oligonucleotide-based drugs and gene-based approaches.[30] Also, repurposing of existing drugs such as tideglusib, mexiletine or metformin seem promising and phase III trials are currently being performed.[30] To adequately evaluate the effects of treatment options however, it is of great importance that DM1 research maintains focus on the validation of DM1-specific outcome measures, such as the DM1-Activ^{C} used in *Chapter 6.*[31] Also, it could be contemplated that DM1 disease follow-up may become less relevant in the future as therapeutic treatment options may become available. Nevertheless, marketing authorization is most likely to be received for repurposed small molecules at first, which improve symptomatology, but do not seem able to cure DM1.[30,32] Even if gene-based approaches are able to cure DM1 patients in the future through genome editing, it remains unclear if preexisting damage such as myocardial fibrosis and muscle wasting are reversible. Moreover, DMPK repeat expansions will continue to be transmitted to offspring, since small sized repeat carriers often remain asymptomatic and undiagnosed as described in *Chapters 2 and 6.* Consequently, new DM1 patients will unfortunately continue to arise and DM1 disease follow-up will not become redundant just yet.

At last, we believe that more attention should be paid to the fifth CDM element of healthcare provider education (**Figure 8.1**). Even though we have taken significant steps forward in DM1 care through the development of the DM1 expertise center and availability of disease-specialized healthcare providers, we should remember that this type of healthcare is not available to every patient in any given location. Therefore, it is important that knowledge of DM1 is spread among other doctors that are likely to encounter DM1 patients in clinical practice, such as cardiologists, pulmonologists, and rehabilitation physicians. Only through the education of healthcare providers outside of tertiary care centers, chances of timely referral to specialized facilities will increase. In order to contribute to healthcare provider education, *Chapter 2* of this thesis has been published as a book chapter in a reference guide for health care professionals worldwide (**Figure 8.1**). Finally, the development of comprehensive international evidence-based guidelines for the follow-up of DM1 patients are essential for the management of this multisystemic disorder.

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Summary

Summary

Section 1 Introduction

Myotonic dystrophy type 1 (DM1) is a multisystem disorder affecting patients of all ages, as described in **Chapter 1**. The two main clinical findings consist of myotonia (inability to relax muscles) and muscle weakness, while DM1 can potentially affect almost every organ system in the human body. DM1 is caused by an autosomal dominantly inherited cytosine-thymine-guanine (CTG) repeat expansion in the dystrophia myotonica protein kinase (DMPK) gene. Although the number of CTG repeats in healthy individuals ranges from 5 to 35, repeat expansions larger than 50 are associated with DM1.

Survival in DM1-affected individuals is significantly reduced, primarily as a result of multisystem involvement of cardiac and pulmonary origin. Cardiac complications consist of cardiac conduction delay and/or (ventricular) arrhythmias, which may even result in sudden cardiac death. Apart from cardiac and respiratory complications, the brain, eyes, gastro-intestinal system and metabolism may become involved.

Curative or disease-modifying treatment options are not yet available, even though great changes are expected with the development of gene therapy in the upcoming years. As of now, disease management focuses on monitoring progression and early detection of possible complications. Moreover, providing adequate information to the patient and their caregivers, including expectation management, is of great importance.

The current thesis aimed to improve DM1 patient management by adding to the current knowledge of clinical genetics and multisystem involvement. The results were later placed in the context of chronic disease management.

Section 2 Clinical Genetics

In **Chapter 2** a comprehensive overview of DM1 was presented as a reference for clinicians involved in DM1 care. The chapter includes a description of the four clinical subtypes, genetic background, advice for genetic counseling and an extensive summary of disease manifestations. For each organ (system), the most important features of follow-up and management were summarized as a guideline for clinical practice. The extensiveness of this book chapter emphasizes the clinical heterogeneity of DM1 and its widespread effects. The chapter accentuates that the involvement of multiple

healthcare providers with DM1 expertise is indispensable for adequate disease management.

Chapter 3 describes the intergenerational instability of DM1 pre- and protomutation alleles, focusing on the influence of parental sex. DM1 premutation (36-50 repeats) and protomutation (51-80 repeats) allele carriers are often clinically asymptomatic, but are at risk of transferring a lengthened CTG repeat to offspring due to intergenerational instability of the repeat expansion. By reviewing pedigrees of DM1-affected families, 146 parent-child pairs in which a pre- or protomutation was transmitted to a successive generation were selected. While 72% of paternal transmissions led to a symptom-associated repeat length (CTG >80) in offspring, only 23% of maternal transmissions led to a symptom-associated repeat length in offspring. Moreover, CTG repeat length instability occurred for paternal repeats of $n \geq 45$, while maternal instability did not occur until CTG repeats of $n \geq 71$. Based on these findings, we conclude that paternally transmitted pre- and protomutations are more unstable than maternally transmitted pre- and protomutations. Consequently, we suggest addressing sex-dependent factors in genetic counseling of small-sized CTG repeat carriers, since male carriers have an increased risk of symptomatic offspring.

Section 3 Multisystem involvement

Nearly every organ system can be affected by DM1. In clinical practice, most attention is paid to the management of cardiac and pulmonary disease complications, as these may have life-threatening effects.
For DM1 cardiac follow-up, annual electrocardiogram (ECG) is recommended and regular echocardiography and 24 h Holter monitoring are commonly carried out. Despite the advice to use these specific screening modalities in DM1 cardiac follow-up, it has remained unclear what the clinical effectiveness of 24 h Holter monitoring is and which patients require a more extensive measure of the cardiac conduction system.

Chapter 4 describes 100 DM1-affected individuals undergoing an invasive investigation of the cardiac conduction system, known as an electrophysiological study (EPS). Through the comparison of ECG parameters of patients with normal EPS results and abnormal EPS results, we determined that a specific combination of ECG abnormalities (PR >200ms and QRS >120ms) has a high positive predictive value (78%) for abnormal EPS results in DM1 patients. In other words, the presence of these ECG abnormalities can predict abnormal cardiac conduction that may warrant pacemaker implantation. Accordingly, we conclude that these ECG parameters could be used as a screening tool

to determine the need for referral to a specialized multidisciplinary cardiac and neuromuscular team, with EPS capacity.

In **Chapter 5**, we aimed to evaluate the clinical effectiveness of routine 24 h Holter monitoring to screen for cardiac conduction disturbances and arrhythmias in patients with DM1. A total of 235 patients were included and abnormal Holter results were discovered in 126 (54%) patients after a mean follow-up of approximately 5 years. Out of 126 patients with abnormal Holter findings, 74 (59%) patients had Holter findings that had not been previously ascertained on ECG. Moreover, abnormalities on Holter monitoring were not only present in patients with previous ECG abnormalities, but also in patients with normal ECGs upon yearly follow-up. Based on these results, we conclude that 24 h Holter monitoring is of added value to routine cardiac screening for all DM1 patients. Still, the ideal frequency of Holter monitoring is yet to be determined.

Although the extent of muscle weakness and organ complications has been well-studied in patients affected by adult-onset DM1, data on cardiac and respiratory complications in late-onset DM1 remains scarce. In **Chapter 6**, we aimed to compare the clinical phenotype of adult-onset vs late-onset DM1, focusing on the prevalence of cardiac, respiratory, and muscular involvement. A total of 275 adult-onset and 66 late-onset DM1 patients were included. While muscular phenotype was milder in late-onset patients than in adult-onset patients, the prevalence of cardiac conduction delay was comparable. Also, subtype was unable to predict the presence of cardiac conduction delay. Although adult-onset patients had an increased risk of having an indication for respiratory support (non-invasive ventilation), 17% of late-onset patients required respiratory support as well. We conclude that, despite different muscular phenotypes, screening for multiorgan involvement should be equally thorough in late-onset as in adult-onset DM1.

Apart from organ complications, DM1 is known to have metabolic consequences such as insulin resistance and increased levels of cholesterol. Weight issues and overweight are frequently observed as well. Possibly, weight issues result from lowered resting energy expenditure (EE) and impaired muscle oxidative metabolism.
In **Chapter 7,** we assessed EE, body composition, and muscle oxidative capacity in 15 patients with DM1 compared to 15 age-, sex- and BMI-matched controls. A prospective case control study in which all participants underwent state-of-the-art methodologies including 24 h whole room calorimetry, doubly labeled water and accelerometer analysis under 15-days of free-living conditions, muscle biopsy, full body magnetic resonance imaging (MRI), dual-energy x-ray absorptiometry (DEXA), computed

tomography (CT) upper leg, and cardiopulmonary exercise testing, was performed. We observed that whole-body EE did not differ in DM1-affected individuals when compared to healthy age-, sex- and BMI-matched controls when assessed under strict dietary and physical activity standardization. However, under free living conditions, daily EE is severely reduced in DM1 patients which may be attributed to a low physical activity level. The low physical activity status, accompanied by a low physical fitness level, represents a key factor responsible for undesirable changes in body composition, as confirmed in our study. Consequently, DM1 patient management should include promotion of a more active lifestyle to prevent overweight and reduce cardiovascular risk. At this time, the prevalence of cardiovascular risk factors and cardiovascular events in DM1-affected individuals remains to be established. Additionally, further research is needed to determine which training interventions are suitable for this specific patient population.

Section 4 Addenda

Finally, in **Chapter 8**, the current thesis was placed in the context of chronic disease management, demonstrating how its contents and recent literature have added to improving DM1 disease management over the last decade. By adding to the current knowledge of DM1 reproductive outcomes and multisystem involvement, this thesis contributes to the availability of decision support for healthcare providers and to informed decision making for patients. Moreover, through the formation of the Dutch DM1 Expertise Center and Dutch DM1 disease registry (MYODRAFT study), a clinical information system became available to monitor disease outcomes. MYODRAFT data has formed the basis for several papers included in the current thesis. Furthermore, we aim to spread DM1 knowledge among healthcare providers worldwide, through the publication of a DM1 specific book chapter (**Chapter 2**) and by disseminating this thesis's conclusions.

Samenvatting

Samenvatting

Deel 1 Introductie

Myotone dystrofie type 1 (DM1) is een erfelijke spierziekte met als hoofdkenmerken het vertraagd ontspannen van spieren (myotonie) en langzaam toenemende spierzwakte (dystrofie). Behalve in de spieren, kunnen er ook problemen ontstaan in andere organen, zoals in het hart, de longen, het maagdarmstelsel, het brein en de ogen (**Hoofdstuk 1)**. Om deze reden, kan er in het geval dan DM1 beter gesproken worden van een systeemziekte dan van een spierziekte. DM1 wordt veroorzaakt door een verlenging van het erfelijk materiaal (DNA) in het DMPK gen. Aan het einde van dit gen bevindt zich een stuk DNA, dat bestaat uit tripletten met een combinatie van de bouwstenen C, T en G. Bij mensen zonder DM1, herhaalt het CTG-triplet zich tussen de 5 en 35 keer, bij mensen met DM1 komt deze herhaling echter vaker dan 50 keer voor. DM1 erft autosomaal dominant over, wat betekent dat ieder kind van een aangedane ouder 50% kans heeft om tevens drager te zijn van een verlengd CTG-triplet en klachten te ontwikkelen.

Mensen met DM1 hebben een verkorte levensverwachting, dit is met name het gevolg van betrokkenheid van het hart en de longen. Cardiale complicaties bestaan uit geleidingsstoornissen (vertraging van elektrische prikkels in het hart) en hartritmestoornissen, welke beiden kunnen leiden tot acute hartdood.

Genezing van DM1 is helaas nog niet mogelijk, hoewel gentherapie hier in de toekomst mogelijk verandering in zal brengen. Op dit moment, worden patiënten met DM1 jaarlijks opgevolgd door een team van deskundigen om eventuele achteruitgang in kaart te brengen en complicaties van de ziekte zo snel mogelijk te kunnen behandelen. Een voorbeeld hiervan is het tijdig opsporen van geleidingsstoornissen in het hart, waarvoor een pacemaker geïmplanteerd kan worden. Daarnaast is het van belang dat patiënten, hun naasten en betrokken zorgverleners, zorgvuldig geïnformeerd worden over DM1 en de mogelijke gevolgen hiervan.

Het doel van dit proefschrift betrof het vergroten van de kennis over de erfelijke achtergrond van DM1 en het beter in kaart brengen van orgaanbetrokkenheid bij DM1. Uiteindelijk vergeleken we de zorg voor patiënten met deze ziekte, met de zorg voor mensen met een chronische ziekte in het algemeen.

Deel 2 Klinische Genetica

In **Hoofdstuk 2** werd er een uitgebreid overzicht gegeven van alle aspecten van DM1, zoals de genetische (erfelijke) achtergrond, de vier verschillende subtypen, adviezen voor genetische counseling (erfelijkheidsadvies) en een samenvatting van alle bekende uitingsvormen. Voor elk orgaan (systeem), werden de belangrijkste aandachtspunten voor follow-up beschreven als leidraad voor betrokken zorgverleners. De omvang van dit hoofdstuk, benadrukt het sterk wisselend klinisch spectrum van deze ziekte, welke ook nog eens grote individuele verschillen laat zien. Het hoofdstuk benadrukt daarnaast dat zorg voor DM1 patiënten een multidisciplinaire aanpak behoeft.

Hoofdstuk 3 beschrijft de erfelijke overdracht van DM1 pre- en protomutaties, waarbij de nadruk ligt op de mogelijke invloed van het ouderlijk geslacht. Er wordt gesproken van een DM1 premutatie wanneer er 36-50 herhalingen van het CTG-triplet in het DMPK-gen voorkomen. Wanneer er tussen de 51-80 herhalingen voorkomen, wordt er gesproken van een protomutatie. Dragers van pre- en protomutaties hebben zelf meestal geen uitingsvormen van DM1. Wanneer een pre- of protomutatie echter van ouder op kind wordt doorgegeven, kan er een verlenging van het erfelijk materiaal ontstaan. Zo is het mogelijk dat een kind van een asymptomatische ouder, wel symptomen ontwikkelt. In **Hoofdstuk 3** beschrijven we de resultaten van stamboomonderzoek in families waar DM1 voorkomt. In totaal werden er 146 ouder-kind paren teruggevonden, waarbij de ouder een pre- dan wel protomutatie doorgaf aan de volgende generatie. Bij 72% van de paternale transmissies was er sprake van een CTG-triplet >80 bij het nageslacht, wat geassocieerd wordt met klinische uitingsvormen van DM1. Bij maternale transmissies, was er slechts bij 23% van het nageslacht sprake van een CTG-verlenging >80. Ook observeerden we dat instabiliteit van het aantal CTG-herhalingen bij vrouwen later optrad dan bij mannen (geobserveerd vanaf 45 CTG-herhalingen bij overdragende vaders ten opzichte van 71 CTG-herhalingen bij overdragende moeders). Op basis van deze bevindingen, concludeerden wij dat paternaal overervende pre- en protomutaties vaker een instabiel karakter hebben dan maternaal overgedragen pre- en protomutaties. Mannen met een pre- of protomutatie hebben dus een grotere kans op symptomatisch nageslacht. Het effect van ouderlijk geslacht en de kansen op een aangedaan kind, zullen daarom besproken moeten worden met dragers van pre- en protomutaties die een kinderwens hebben.

Deel 3 Orgaanbetrokkenheid

Bijna elk orgaan in het lichaam kan gevolgen ondervinden van DM1. Bij het opvolgen van patiënten, ligt de nadruk vooral op het vroegtijdig opsporen van mogelijke cardiale

(in het hart) en pulmonale (in de longen) complicaties omdat deze levensbedreigende gevolgen kunnen hebben.
Cardiale opvolging bestaat in ieder geval uit een jaarlijks ECG (hartfilmpje), waarbij een 24-uurs Holter registratie (24-uurs hartfilmpje) en een echo van het hart ook regelmatig worden uitgevoerd. Hoewel geadviseerd wordt om alle drie de genoemde onderzoeken toe te passen binnen de screening van DM1 patiënten, is het tot op heden onduidelijk wat de toegevoegde waarde is van een 24-uurs Holter registratie en welke patiënten in aanmerking zouden moeten komen voor (invasief) vervolgonderzoek van het hart.

In **Hoofdstuk 4** beschrijven wij een groep van 100 DM1 patiënten die allen een invasieve meting van het geleidingssysteem in het hart ondergingen, ook wel een elektrofysiologisch onderzoek (EFO) genoemd. We vergeleken vervolgens de ECG's van patiënten met een normale EFO-uitslag, met de ECG's van patiënten met een afwijkende EFO-uitslag. Hiermee stelden we vast dat een specifieke combinatie van afwijkingen op het ECG (PR >200ms en QRS >120ms), een hoge positief voorspellende waarde heeft (78%) voor het hebben van afwijkingen op het EFO. Met andere woorden, de aanwezigheid van deze specifieke ECG-afwijkingen kan voorspellen of er sprake zal zijn van een afwijkend EFO en of er bij de patiënt een pacemaker moet worden geïmplanteerd. Op basis van deze data, concludeerden wij dat de genoemde ECG-parameters een geschikte screeningstool zijn om te bepalen of DM1 patiënten verwezen moeten worden naar een multidisciplinair cardiaal en neuromusculair team met de mogelijkheid tot het verrichten van een EFO.

Het doel van **Hoofdstuk 5** was om te bepalen wat de toegevoegde waarde is van het verrichten van een 24-uurs Holter registratie bij patiënten met DM1. Voor deze studie includeerden wij 235 DM1 patiënten: bij 126 (54%) van hen werden er afwijkingen vastgesteld middels de Holter registratie na een gemiddelde follow-up duur van 5 jaar. Bij 74 van de 126 (59%) DM1 patiënten waarbij er sprake was van een afwijkende Holter, bleek het om niet eerder vastgestelde veranderingen te gaan. Deze afwijkingen werden dus niet eerder op het ECG gezien. Ook stelden we vast dat een deel van de patiënten met een afwijkende Holter, een normaal ECG bleef houden gedurende jaarlijkse follow-up. We concludeerden dat 24-uurs Holter registratie van toegevoegde waarde is voor de cardiale screening van DM1 patiënten, maar dat toekomstig onderzoek zal moeten aantonen met welke frequentie de Holter registratie verricht dient te worden.

Eerder onderzoek naar de uitingsvormen van DM1 werd vooral verricht in patiënten met het volwassen subtype. Als gevolg hiervan, was er tot op heden weinig data

beschikbaar over het voorkomen van cardiale en pulmonale complicaties bij patiënten met het milde subtype van DM1.

In **Hoofstuk 6**, vergeleken we de uitingsvormen van het volwassen subtype van DM1 met die van het milde subtype, waarbij de nadruk lag op de prevalentie van cardiale -, pulmonale - en spierbetrokkenheid. In deze studie werden 275 patiënten met het volwassen subtype en 66 patiënten met het milde subtype geïncludeerd. Hoewel patiënten met het milde subtype duidelijk minder krachtsverlies en beperkingen ervaarden, was de prevalentie van cardiale geleidingsstoornissen vergelijkbaar tussen de twee subtypen. Nadere analyse toonde tevens aan dat subtype niet kon worden gebruikt als voorspellende factor voor het hebben van cardiale geleidingsproblematiek. Hoewel patiënten met het volwassen subtype daarnaast vaker een indicatie hadden voor respiratoire ondersteuning (non-invasieve beademing), bestond deze indicatie ook bij 17% van de patiënten met het milde subtype. Deze studie toont aan dat de screening voor orgaanbetrokkenheid even zorgvuldig moet worden uitgevoerd bij beide subtypen, ondanks beperkte uitingsvormen op spierniveau bij het milde subtype.

Naast betrokkenheid van multipele organen, kunnen er ook veranderingen optreden in het metabolisme (stofwisseling) van mensen met DM1 zoals insuline resistentie en verhoogde cholesterolwaarden. Ook komen gewichtsproblematiek en overgewicht regelmatig voor. Deze gewichtsproblemen zouden mogelijkerwijs het gevolg kunnen zijn van een afname in energiegebruik bij DM1 patiënten.

In **Hoofstuk 7** vergeleken we het energiegebruik en de lichaamssamenstelling (hoeveelheid vet- en spiermassa) van 15 DM1 patiënten met 15 gezonde leeftijd-, geslacht-, en BMI-gematchte controles. In deze prospectieve studie ondergingen de deelnemers een 24-uurs meting van het energiegebruik in een respiratiekamer, een 15-daagse meting van het energiegebruik in de thuissituatie met behulp van dubbel-gelabeled water en een stappenteller, een spierbiopt, een MRI van het gehele lichaam, een DEXA-scan, een CT-scan van het bovenbeen en een fietstest. De verzamelde gegevens toonden aan dat het energiegebruik vergelijkbaar was tussen beide groepen, wanneer deze gemeten werden in de gestandaardiseerde omgeving van de respiratiekamer. In de thuissituatie, was het energiegebruik van DM1-patiënten echter duidelijk verlaagd ten opzichte van hun gezonde gematchte controles, ten gevolge van verminderde fysieke activiteit. Op basis van de verzamelde data concludeerden wij dat de afname in fysieke activiteit en fysieke fitheid, verantwoordelijk zijn voor het geobjectiveerde verschil in lichaamssamenstelling tussen de twee groepen. Met andere woorden, de verminderde hoeveelheid lichaamsbeweging in de groep van DM1-

patiënten leidt tot een toename van vetmassa en gewicht. Er waren in deze studie geen aanwijzingen voor een verschil in energiegebruik op celniveau ten gevolge van DM1. Gebaseerd op de conclusies van dit artikel, raadden wij aan dat patiënten met DM1 worden gemotiveerd voor leefstijlveranderingen om overgewicht en cardiovasculaire risico's te verminderen.

Deel 4 Addenda

In **Hoofdstuk 8** werd de zorg voor patiënten met DM1 vergeleken met de zorg voor patiënten met andere chronische ziekten. Verschillende elementen zijn hierin essentieel, waaronder het beschikken over objectieve informatie waarop zorgverleners hun beslissingen kunnen baseren, het voorlichten van patiënten zodat zij geïnformeerde keuzes kunnen maken, en het verspreiden van kennis over de specifieke aandoening. Samenvattend draagt dit proefschrift bij aan de verbetering van zorg voor mensen met DM1, door zorgaanbieders te voorzien van handvaten voor follow-up en door richting te geven aan de screening voor orgaanbetrokkenheid. Daarnaast ondersteunt de data ten aanzien van pre- en protomutaties, zorgaanbieders in de reproductieve counseling van DM1-patiënten, waardoor patiënten meer ruimte krijgen voor geïnformeerde keuzes. Tenslotte droeg dit proefschrift bij aan het vergroten van de kennis omtrent DM1, door de publicatie van **Hoofdstuk 2** in een internationaal boek en door het uitdragen van de opgedane kennis middels meerdere wetenschappelijke publicaties en presentaties op (inter)nationale congressen.

Impact paragraph

Impact paragraph

This thesis focused on patients affected by myotonic dystrophy type 1 (DM1) and aimed to improve patient management, by adding to the current knowledge of clinical genetics and multisystem involvement. The results of the included studies are not solely of interest to neurologists, serving as coordinating physicians for this patient population, but to a larger audience as well due to the multisystemic nature of disease. The current chapter states the added value and (potential) impact of the performed research.

Scientific relevance

We have demonstrated how this dissertation adds to the improvement of DM1 chronic disease management. In particular, we have provided reproductive outcome data for the genetic counseling of DM1 small sized repeat carriers that wish to conceive healthy offspring. Our paper on pre- and protomutations describes the largest study population of small sized repeat carriers so far, which is relevant since reproductive outcome data for this specific patient population was scarce. Moreover, recent literature has demonstrated that DM1 pre- and protomutations are more prevalent than previously assumed, adding to the relevance of our work.

Based on our study results, we have also presented electrocardiographic (ECG) parameters as a screening tool for patient referral to a multidisciplinary neuromuscular team. Such parameters have the potential to significantly enhance DM1 care and might be implemented in future guidelines on cardiac conduction disorders. The incorporation of these parameters, would most likely prevent patients with ECG abnormalities to be followed-up for long periods of time without required comprehensive diagnostics, in non-specialized care centers.

Furthermore, we have established that patients who are only mildly affected by DM1 on a muscular level often exhibit cardiac abnormalities. As such, we draw attention to the fact that screening for multisystem involvement should be equally thorough in each DM1 subtype, including regular ECG and Holter monitoring. While Holter monitoring has been accepted as a screening tool in the DM1 cardiac work-up, evidence for its use was scarce and care recommendations suggested to use this modality only in case of ECG abnormalities. Our study has confirmed the added value of 24 h Holter monitoring for DM1 patients with both normal and abnormal ECGs, expanding its use through the detection of possible life-threatening conduction disorders and arrythmias (heart rhythm abnormalities) in the entire DM1 population. Based on this thesis's findings,

even the overview of DM1 cardiovascular disease management presented in *Chapter 2* has become somewhat outdated, underlining the impact of the conducted research.
Finally, our study on metabolic functioning is the first to use several state-of-the-art methodologies for the evaluation of the DM1 patient population. With this approach, we have provided a framework that may be useful not only for DM1 research but for research on the potential metabolic involvement of other neuromuscular disorders as well.
The scientific relevance of the included work is reflected by the fact that our research has received attention on both a national and international level, as described below. Despite the added value of the current work, this thesis has also provided several new research questions and serves as a foundation for future studies.

Target groups and societal relevance

In clinical practice, a large group of healthcare providers is involved in DM1 related care, such as neurologists, clinical geneticists (*Chapters 2 and 3*), cardiologists (*Chapters 4, 5 and 6*), pulmonologists (*Chapter 6*), rehabilitation physicians (*Chapters 2 and 7*) and paramedics (*Chapters 2 and 7*). Consequently, the content of the current thesis is relevant to all of the specialties within the multidisciplinary spectrum of DM1.

With the involvement of such a large group of healthcare providers, comes a high amount of healthcare resource utilization and costs. Even though costs associated with DM1 have only been studied in the United States, one study describes mean all-cause healthcare costs to range between $14,640–$16,704 per patient per year, which is approximately three times higher than the US population average (1). Moreover, expenses tended to increase over time, as a result of the chronic and progressive nature of disease. In another study taking all costs of disease into account, including medical, nonmedical, and loss of income, the annual per-patient cost for DM1-affected individuals was estimated as high as $32,236 (2). Even though the effects of improved patient management have not been studied in the DM1 population, it can be expected that improving patient follow-up with early detection of disease complications can decrease medical expenses over time. Specifically, since cardiac arrhythmias are among the most frequent causes of death in DM1-affected individuals, the validation and improvement of cardiac management for this patient population is crucial. Also, we demonstrated that observed changes in weight and body composition do not seem to be a direct consequence of disease, but rather occur due to a decreased amount of physical activity. It is therefore likely that tailored lifestyle interventions can reduce

disease morbidity over time. Eventually, this may lower healthcare resource utilization and costs in the DM1 population as well.

Apart from outcomes that may be utilized by healthcare providers and may lead to a reduction of healthcare resource utilization in the future, this dissertation also provides information that is directly relevant for the DM1 patient population. Study results may be used to improve self-management support as part of chronic disease management.

Communication of research findings and translation into practice

In order to improve DM1 patient management and to add to the current knowledge of clinical genetics and multisystem involvement, this thesis' content must be spread among involved healthcare providers and the DM1 patient population. Through the development of the Dutch DM1 Expertise Center (comprised of the Radboudumc Nijmegen and Maastricht UMC+) in 2017, a strong collaborative bond has been formed between DM1-dedicated professionals in The Netherlands. As part of this collaboration, study results were discussed in joint meetings involving DM1-related healthcare providers. As a result, study outcomes are already being used in the setting of our Expertise Center, such as the data on pre- and protomutation inheritance for genetic counseling and the proposed ECG criteria. However, it is important that knowledge is spread among all doctors that are likely to encounter DM1 patients, also outside the setting of specialized (tertiary) care centers. This has been accomplished through the publication of the conducted studies in peer-reviewed journals and by the publication of *Chapter 2* in an international reference guide for healthcare professionals worldwide. Moreover, study results were presented at national and international conferences. The presented data has been well-received by the scientific community, as is reflected by the fact that we received a prize at the International Annual Congress of the World Muscle Society in 2019 (please see the attached Curriculum Vitae) and by the fact that our study on ECG screening was featured in a letter to the editor by two expert cardiologists suggesting that our study should have been included in the 2021 ESC Guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy (3). On a national level, we have attended the "Prinses Beatrix Spierfonds" conference each year, which is a symposium organized particularly for Dutch patients affected by neuromuscular disorders including DM1. During the course of this PhD, patients have been kept up-to-date on study progress and outcomes through presentations and Q&A sessions at the Spierziekten Nederland / Prinses Beatrix Spierfonds patient meetings. In

short, the results derived from this PhD-trajectory will have an important impact on the clinical care of DM1 patients, may be implemented in future guidelines, and emphasize the importance of a multidisciplinary team in the follow-up of DM1 patients.

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Dankwoord

Dankwoord

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List of publications

List of publications

Vosse BAH, Horlings CGC, **Joosten IBT**, Cobben NAM, van Kuijk SMJ, Wijkstra PJ et al. Role of respiratory characteristics in treatment adherence with noninvasive home mechanical ventilation in myotonic dystrophy type 1, a retrospective study. Article in Press, Neuromuscular Disorders, https: //doi.org/10.1016/j.nmd.2023.08.004.

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Curriculum vitae

Curriculum vitae

Isis Joosten was born on the 14th of May 1993 in Maastricht, the Netherlands. She graduated from secondary school at Sint-Maartenscollege Maastricht in 2011. In the same year, she started studying Medicine at Maastricht University and received her bachelor's degree in 2014. During her master's in Medicine, she performed a scientific internship under supervision of Prof. dr. C. Faber at the Neurology department of the Maastricht University Medical Centre+. During this internship, she developed a special interest in neuromuscular disorders. After graduating with distinction (cum laude), she started a PhD-trajectory in the same research group, with a focus on myotonic dystrophy type 1 (DM1). Throughout this trajectory, she remained involved in clinical work consisting of outpatient follow-up of DM1 patients. In 2019, she pursued an International Master in Peripheral Nervous System Disorders at the Università degli Studi di Milano in Milan, Italy. She successfully completed this program in 2020. She continued her PhD under the supervision of Prof. dr. C. Faber, Prof. dr. L van Loon and Prof. dr. K. Vernooy and was involved in the development of the Dutch DM1 Registry and Follow-up study as part of the formation of the Dutch DM1 Expertise Centre. At this time, she is working as a resident (ANIOS) at the Clinical Genetics department of the Maastricht University Medical Centre+. Isis happily lives with her partner Sam and daughter Alva in Cadier en Keer.