Myotonic dystrophy type 1

Summary

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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.