Myotonic dystrophy type 1

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.

References

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