Nonmotor comorbidities and somatic manifestations of Duchenne Muscular Dystrophy

IMPACT PARAGRAPH

This impact paragraph is a reflection in laymen's terms on the scientific impact of the research performed in this thesis. This thesis describes a series of studies that were undertaken to acquire a better understanding of the origin of comorbidties in patients with Duchenne muscular dystrophy (DMD). In this chapter the clinical and societal relevance of these findings will be discussed in a broad sense. It can therefore be used to inform a wider target group that is wider than patients, i.e., parents or caregivers, teachers, healthcare professionals and researchers.

RELEVANCE

Duchenne muscular dystrophy (DMD) is the most common neuromuscular disorder diagnosed in childhood, affecting approximately 8,29 per 100,000 boys. This dystrophinopathy is caused by X-linked recessive mutations in the *DMD* gene, resulting in functional loss of the dystrophin protein. It is characterized by progressive striated muscle weakness, leading to complete loss of ambulation around early adolescence, followed by scoliosis and loss of upper limb function. Next to the immobilizing skeletal muscle wasting, striated muscle of the lungs and heart is affected and will eventually lead to fatal respiratory and/or cardiac failure. So far, there is no cure available.

Nevertheless, life expectancy has increased due to improved supportive care. As a result of the increased life expectancy, patients with DMD nowadays face new comorbidities that may influence their quality of life significantly. Somatic symptoms including fatigue, pain, sleep disorders and problems with discharge of urine and faeces are increasingly reported. In addition to a physical burden, this may also affect the psychosocial functioning of patients, their families and caregivers. On top of this, existing brain-related comorbidities, such as behavioural and neurocognitive deficits become debilitating as patients grow older and threat academics and social functioning.

Overall, the large variety of these somatic manifestations (i.e. lower urinary tract symptoms [LUTS] and/or constipation) and nonmotor comorbidities (i.e. neurodevelopmental and learning disorders) may have a great impact on daily life functioning, thus having a negative influence on quality of life. However, there is as yet no standard screening nor a specific treatment of the majority of these comorbidities in DMD. They therefore often remain unrecognized and untreated. This may be due to the fact that their origin, which might be organ and/or mutation specific, is largely unknown. Also, their occurrence is scarcely included in existing diagnostic and therapeutic protocols. Increasing knowledge on the underlying pathophysiology may help to overcome these deficiencies and optimize DMD care from childhood to adulthood. Implementing clinical subtypes of DMD into future

research to investigate whether the dystrophin isoform that is affected and its tissue-specific expression play a role in the occurrence and severity of comorbidities may eventually lead to a more personalized approach.

We believe in the existence of dystrophin-associated bladder and bowel symptoms. This idea is supported by our finding of dystrophin in smooth muscle cells and neurons of the bladder and intestine (**Chapter 2 and 3**). Based on our preclinical studies together with our literature review of other molecular evidence of dystrophin in bladder and bowel dysfunction (BBD, **Chapter 5**), we conclude that there is some preclinical and clinical evidence for dystrophin-associated BBD, which may differ in relation to the function of these organs. The finding of not only dystrophin expression in muscle, but also in neurons underscores that bladder and bowel symptoms in DMD cannot solely be ascribed to muscle weakness and immobility. These findings are relevant for science and society as they may lead to a clinical paradigm shift, i.e. instead of muscular-targeted treatment of the nervous system for instance by (sacral) neuromodulation. Future studies may aim at diagnosing these comorbidities earlier in the disease course, for instance by histopathological examination. This may help to differentiate between a possible neurogenic or myogenic basis of BBD, may improve the understanding of the underlying pathophysiology and may eventually lead to more targeted and personalized treatment.

In addition, we systematically determined the prevalence of BBD in patients with DMD by using the validated Childhood Bladder and Bowel Dysfunction Questionnaire (CBBDQ, **Chapter 4)**. We presented data showing that BBD is more prevalent in patients with DMD than in healthy control subjects. Constipation was treated in a proportion of DMD patients, but LUTS often remained unrecognized and untreated. This emphasizes the need for the implementation of systematic screening for both bladder and bowel symptoms in the multidisciplinary guidelines for DMD care; in the current Standard of Care (Birnkrant et al 2018) only gastrointestinal management is mentioned. The use of validated screening tools such as the CBBDQ from an early age onwards could facilitate the diagnosis of possible LUTS and gastrointestinal (GI) problems at a later stage of the disease. This will not only optimize care of DMD, but could also be used in other neurological disorders associated with BBD.

A lesson learned from our Diffusion Tensor Imaging (DTI) study (**Chapter 6**) is that complex and multifactorial neurocognitive functions cannot solely be ascribed to a lack of dystrophin in the brain, which is mainly interesting for researchers trying to link brain structure to function. It implicates the importance of also taking dystrophin nonspecific factors into account. In line with this suggestion, we observed that methylphenidate treatment can be clinically just as effective to treat attention-deficit hyperactivity disorder (ADHD) symptoms in patients with DMD, as in patients without DMD (**Chapter 7**). Determining if there is a causal role for dystrophin in the neurocognitive profile of patients with DMD taking other possible contributing factors besides dystrophin into account, remains to be studied further. Various new insights could be obtained when investigating the role

of dystrophin in this process and whether or not these comorbidities are progressive. These insights could eventually improve DMD care.

Finally, we studied the presence of different symptoms and fluctuations of these symptoms during the day in relation to treatment with corticosteroids by using the Experience Sampling Method (ESM) smartphone application (**Chapter 8**). This showed that the ESM is a convenient and user-friendly method to capture extensive symptom fluctuations in the moment during on- and off-periods of intermittent corticosteroid treatment in patients with DMD. Thus far, most clinical studies have used retrospective questionnaires or diaries, which are unlikely to provide sufficiently detailed insights into possible correlations with treatment. The ESM may reveal potential pattern alterations in relation to treatment, which allows for a better timed and personalized interventions. Various new insights could be obtained when using the ESM in clinical research on rare diseases with a small sample size, as the ability of ESM to assess multiple repeated measurements within individual subjects makes single subject prediction possible.

TARGET AUDIENCE

It is essential that awareness increases, not only among patients, their parents or caregivers, their treating physicians, and researchers in the field, but also among a broader audience of healthcare professionals (i.e. paediatric neurologists, paediatricians, urologists, gastroenterologists, (neuro)psychologists, psychiatrists, rehabilitations physicians, general practitioners, paramedics such as physiotherapists) and other stakeholders of society, such as teachers. The findings from our clinical studies on the prevalence of bladder and bowel dysfunction using the CBBDQ, the extensive evaluation of methylphenidate use in ADHD comorbidity, and symptom monitoring in relation to treatment reactivity using the ESM (**Chapters 4, 7 and 8, respectively**) are relevant for all abovementioned stakeholders, since they can directly be incorporated in the screening for and monitoring of comorbidities. This thereby contributes to an increased recognition and facilitated diagnosis and treatment. The physical and psychosocial burden of BBD and neurodevelopmental deficits on patients, their families and caregivers, may decrease with the implementation of these screening methods, which could contribute to improving their quality of life. Also, educational achievements of patients may improve if teachers are more aware of the possible neurodevelopmental deficits and their potential treatment in case of a comorbid ADHD diagnosis. Healthcare professionals are the ones who should be aware of these additional symptoms, screen for them by using validated measurement tools such as the CBBDQ or ESM, and treat them or refer to a specialist if needed. Based on these results, researchers will hopefully be encouraged, in combination with additional findings from our preclinical studies and narrative review on the underlying molecular mechanisms of BBD (**Chapters 2, 3 and 5**), as well as from our DTI study

including the challenging aspects of linking brain connectivity to function (**Chapter 6**), to implement the insight of these findings in their research. And herewith to further determine if there is a relation between (1) bladder-, GI- and spinal cord- or (2) brain-specific dystrophin expression and the occurrence of BBD and neurodevelopmental deficits in DMD. Also, we hope to encourage researchers to evaluate the effectiveness of other existing symptomatic treatments, such as psychopharmacology use in the case of comorbid (neuro)psychiatric disorders like anxiety, depression or obsessive-compulsive disorder.

PRODUCTS/INNOVATION

The studies in this thesis can be considered innovative in several ways. Firstly, since BBD has yet no part in the multidisciplinary standards of care guidelines for DMD. This work included a validated and standardized screening tool (CBBDQ) based on the Internationally accepted Rome III criteria for functional gastrointestinal disorders and the International Children's Continence Society standardization. Implementing standard screening for BBD in DMD from childhood onward, is crucial for optimizing DMD care.

Furthermore, appropriate mental health screening, neuropsychological assessment and consideration of pharmacological treatment are recommended for the diagnosis and treatment of neurodevelopmental deficits in DMD. In this thesis we describe for the first time a systematic neuropsychological work-up consisting of objective neurocognitive (Wechsler Intelligence scale and symbol search subtest) and behavioural assessment (Childhood Behaviour Checklist-Attention Problems subscale) before and during short term and long term follow-up of the treatment of comorbid ADHD symptoms with short acting methylphenidate, next to standard prescribing guidelines with additional care considerations focusing on the general medical condition (i.e. disease status, cardiac status, medication interactions). Another innovative approach in this thesis to measure treatment reactivity, is the evaluation of symptoms and treatment effects by means of the ESM using mobile Health (mHealth) technology. Besides in DMD, ESM can also be used in other neuromuscular disorders (spinal muscular atrophy, myopathy and axonal neuropathy).

IMPLEMENTATION

The knowledge and new insights obtained from the research performed in this thesis has been and will be shared with health care professionals, patient organizations and scientific societies.

We will continue to encourage further investigation of the underlying pathophysiology of secondary symptoms in DMD by presenting our results at different neuroscientific congresses

as we have presented them at the XXIII World Congress of Neurology (Kyoto, Japan) in 2017, at the World Muscle Society (WMS) Congress (Mendoza, Argentina) in 2018, WMS Congress (Copenhagen, Denmark) in 2019 and MYO-MRI Conference (Berlin, Germany) in 2019, as well as at expert group meetings of the Duchenne Centre Netherlands (DCN). The DCN is a collaboration between researchers and clinicians from Leiden University Medical Centre, Radboud University Medical Centre, Maastricht University Medical Centre (MUMC+) and Kempenhaeghe Centre for Neurological Learning Disabilities. Health care professionals can contribute to these studies by incorporating standard evaluation of symptoms in patient care using the validated measurement tools, which are recommended in this thesis. Clinical observations at the neuromuscular outpatient clinic in collaboration with the urology department from MUMC+ have already shown that a standard urological evaluation and follow-up in the case of LUTS contributes to early recognition and treatment. For patient organizations, this provides valuable information and it will be reassuring to see that advances in diagnosis and treatment of secondary symptoms in DMD are still being made, as we have presented yearly updates of the research at the Duchenne Parent Project Congress.