Neurocognition and behaviour

Impact paragraph

Introduction

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are hereditary neuromuscular disorders covering the spectrum of X-linked dystrophinopathies. Both disorders are caused by mutations in the *DMD* gene, that encodes multiple dystrophin isoforms in various tissues (e.g. skeletal striated and smooth muscles, kidney, retina, urinary and the brain). Depending on mutation location the production of one or more dystrophin protein isoforms are disturbed. The absence of the full-length dystrophin is responsible for the progressive muscle pathology in DMD. By contrast, in BMD, gene mutations cause variable levels of partially functional dystrophin, resulting in a milder and more variable phenotype ranging from adult onset muscle cramps to severe muscle weakness. An aberrant expression of dystrophin isoforms in the brain has recently been related to the frequently observed comorbid neurocognitive impairments, neurodevelopmental- (e.g. attention-deficit hyperactivity disorder or autism spectrum disorders) and behavioural disorders (e.g. depression or obsessive-compulsive disorder) in DMD and BMD. However, these features differ between patients. Furthermore, since the muscle pathology is progressive, questions arise concerning the neurocognitive features: are these progressively deteriorating as well or do they remain stable over time reflecting a developmental stagnation?
Treatment of muscle functioning currently consists of corticosteroid treatment and physiotherapy for maintaining and strengthening muscles. This is also described in the DMD standards of care. There are some recommendations in the 2018 updated DMD standards of care on treatment of the features i.e. neurocognitive impairments and neurodevelopmental-, and behavioural disorders, but scientific research is lacking. It would be valuable to evaluate neurocognitive or behavioural treatment options, especially when the cognitive impairments develop progressively over time or are caused by a developmental delay and when the behavioural problems negatively affect development and/or quality of life of patients. This paragraph describes the aims and results of this thesis and it relevance for science and practical applications.

Aim, results and conclusions

Current thesis has focused on the neurocognitive impairments and neurodevelopmental and behavioural disorders in both dystrophinopathies (**chapter 2-5**). Furthermore, we evaluated and systematically reviewed assessment tools used to establish behavioural and psychosocial problems in males with DMD (**chapter 6**). Finally, we explored whether nonmotor treatment options i.e. cognitive training and

pharmacological treatment used in other (chronic) patient populations may be effective and safe for males with DMD (**chapter 7-8**).
The findings of present thesis acknowledge that in DMD and BMD, problems may arise in neurocognition, particularly in intellectual functioning, processing speed and verbal short-term memory/ verbal span capacity. This latest problem is suggested to remain present over time in DMD patients (**chapter 3**). However, no typical neurocognitive or behavioural dystrophinopathy profile was found within our paediatric DMD and BMD males and adult BMD males when they were compared to normative data or patients with other neurogenetic disorders (**chapters 2-4-5**). With regard to treatment options, results of this thesis display positive effects of cognitive interventions such as working memory training (**chapter 7**) and pharmacological treatment such as stimulant medication (**chapter 8**) in paediatric DMD patients with comorbid working memory problems or ADHD. Furthermore, we found that behavioural and psychosocial assessment in DMD and BMD has been performed increasingly in the last two decades. However, the reported prevalence rates of behavioural disorders or psychosocial problems vary extensively. This may depend on (1) the different instruments used by previous studies and (2) a lack of good psychometric properties of the instruments used (**chapter 6**).

This thesis confirms that both dystrophinopathy disorders are not only characterized by (progressive) myopathy. For now, the name Duchenne muscular dystrophy should be adapted and appointed as Dystrophin Multi-organ Disease. Neurocognitive impairments may be important features as well. It remains unclear whether these impairments progressively deteriorate or whether they are caused by a developmental stagnation due to alterations in maturation. Based on a first longitudinal analyses of findings of DMD patients, we found indications for a developmental stagnation with respect to working memory. Future longitudinal studies are required to further explore this developmental profile. Concerning treatment of the neurocognitive and behavioural features we recommend using evidence-based interventions i.e. cognitive training or psychopharmacological treatment as these may stimulate (academic) development and increase quality of life.

Relevance

The research described in this thesis can be considered innovative in several ways.
Results acknowledge that patients with dystrophinopathies (DMD and BMD) may exhibit neurocognitive impairments and behavioural disorders. In particular impairments in intellectual abilities, processing speed and verbal short-term memory/

verbal span capacity (**chapter 2-5**). These may even remain present over time, suggesting that the cognitive impairments may be caused by a developmental delay. This emphasizes that (re) evaluation of cognitive functioning is important, since these impairments may (eventually) impact academic skills development (i.e. reading and math) and successes.

Results of present thesis displays the effect of training i.e. computerized working memory training on verbal short-term memory impairments in paediatric DMD patients. Improvements were shown in academic skills as well as on parent reports using a SCED design (**chapter 7**). For treatment of these impairments, health-care professionals may implement this training in standard care when working memory problems are stagnating development. However, generalizations to daily life situations i.e. academic skills and development at school should be further investigated. Previous studies in other populations using computerized cognitive training, show that generalizations to daily life situations can be achieved by using strategies such as explicit strategy instruction. This promotes using strategies on computerized training tasks and it additionally ensures that patients relate new acquired strategies to relevant daily life areas. Future research, should evaluate the combination of training and explicit strategy instruction when treating cognitive impairments.

Furthermore, results of present thesis have shown that stimulant medication may be effective and safe for paediatric DMD males with attention problems. Recent updated standards recommend the use of this pharmacological treatment in patients with attention problems. However, since these patients are more at risk for cardiovascular problems, it is important that treatment efficacy and safety is evaluated beforehand. Our study (**chapter 8**) describes scientific data showing that simulant medication i.e. methylphenidate considerably improves attention in DMD patients, without major medical side effects (in cardiac status). Though, future studies should evaluate the efficacy and safety of stimulant medication in this population, using a randomized controlled trial or single case design with additional and more complete neuropsychological outcomes.

Finally, results of the review study in the present thesis show that neurodevelopmental- , behavioural disorders as well as psychosocial problems of DMD and BMD patients have been evaluated frequently by previous studies using various instruments. Our systematic review (**chapter 6**) gives an overview of all instruments being used and results showed that three instruments: the Psychosocial adjustment and Role Skills Scale 3rd edition (PARS-III), the Paediatric Quality of Life Inventory

Generic Module (PedsQL GM) and the Life Satisfaction Index for Adolescents with DMD (LSIA) have good psychometric properties and should be implemented in standard psychosocial screening of DMD care. However, unknown psychometric information (e.g. construct validity or test-retest reliability) of these psychosocial instruments should be further evaluated. Concerning behavioural screenings instruments, we encourage researchers to further evaluate the psychometrics and applicability of instruments to determine which should be implemented during standard screening. In case of diagnosing behavioural disorders, our review suggests that researchers and clinicians should not use one instrument for establishing a definite diagnosis, but should apply the multi-method, multi-source, multi-setting approach. Approximately 20-30% of DMD patients display more than one neurodevelopmental or behavioural disorder and the overlapping symptoms may result in under or overdiagnosis when disorders are diagnosed based on one screening instrument.

Target population

The findings presented in this thesis are of interest for several target groups. To patients (and their parents/caregivers) with Duchenne or Becker muscular dystrophy and educational professionals, it provides additional information on the presence and variable severity of neurocognitive impairments, neurodevelopmental-, and behavioural problems in both dystrophinopathies. Awareness for cognitive and behavioural disfunctions may lead to increased referrals to health professionals.

All health care professionals (paediatric neurologists, paediatricians, (neuro)psychologists, psychiatrists, rehabilitation physicians, general practitioners, paramedics such as physiotherapist) treating patients with DMD or BMD are important stakeholders as well. They are the ones who should be aware of the risk for developing neurocognitive impairments, neurodevelopmental- and behavioural disorders during different life stages and should inform patients and caregivers appropriately. Early screening and diagnosis of these problems may contribute to better academic achievements and an increased health-related quality of life of DMD and BMD patients. Additionally, psychologist and other professionals may take the results of our review in account when applying behavioural screening and assessment. Results of this thesis also informs health care professionals about psychological or pharmacological interventions and their possible (side) effects, when paediatric DMD patients display verbal working memory or attention problems.

The findings from this thesis are also relevant for researchers in the DMD and BMD field, as they may shed more light on the variable severity and development of neurocognitive- and behavioural problems in DMD and BMD. Our data may encourage researchers to further assess the role of abnormal brain functioning (i.e. aberrant brain dystrophin expression or brain structure abnormalities) on neuro- cognition, development and behaviour. Additionally, researchers may be encouraged to further evaluate (1) psychometrics of behavioural and psychosocial instruments for the DMD and BMD population and (2) treatment effects of other known evidence-based interventions. For instance the effectiveness of pharmacological treatment i.e. selective serotonin-reuptake inhibitors in DMD or BMD patients with comorbid anxiety, depression or obsessive-compulsive disorders. Furthermore, it is valuable to know that research designs such as single case experimental design studies may be useful tools to analyse treatment effects in relatively small groups of patients with dystrophinopathies. It is often difficult to include large DMD or BMD sample sizes and follow them longitudinally. Patients are also frequently contacted by several researchers, which may overburden them. SCED designs may diminish these problems.

Implementation and future work

The knowledge derived from the studies presented in this thesis will be used for continuation of research on one hand and implemented in health care on the other hand. Researchers should connect (longitudinal) neurocognitive and behavioural data to neurophysiological and neuroimaging alterations, to assess the relation of the underlying aetiology and neuro- cognitive, developmental and behavioural disfunctions in both dystrophinopathies. With respect to diagnostic work-up, additional evaluation of psychometrics of psychosocial screening instruments (i.e. the PARS-III, PedsQL GM and LSIA) and behavioural screening instruments should be performed to determine a gold standard protocol. With respect to interventions researchers can further focus on the efficacy and safety of known evidence-based psychological or pharmacological interventions for DMD and BMD patients.

In clinical practice the results of this thesis can by implemented by health care professionals during diagnostic work-up of cognitive and behavioural functioning. Furthermore, the review of instruments being used as described in this thesis may encourage health care professionals (1) to adequately use screening instruments and (2) to implement the multi-method, source, setting approach in case of definite diagnostics. The intervention i.e. computerized working memory training can be implemented during DMD care by educational and health care professionals when

DMD patients exhibit problems in this domain. Furthermore, prescribing health care professionals may implement the use of stimulant medication such as methylphenidate in DMD patients with comorbid attention problems, with awareness for both the neuropsychological and medical (side) effects, in particular to cardiovascular adverse events.

Activities and products

The findings of this thesis have been presented at national and international conferences. These conferences were attended by health care professionals and researchers. Moreover, results have been discussed at (clinical) symposia and expert meetings in clinical settings. Some results have for instance been presented to a network of health care professionals (psychologists ad educationalists) working with males with DMD in special education schools, rehabilitation centres and university hospitals in the Netherlands and Belgium. New insights were communicated to health care professionals, researchers as well as to patients and their caregivers at (1) the Dutch parent platform, (2) the annual organised symposia (Duchenne Parent Project) and (3) working conferences of the Duchene Center Netherlands (which is a collaboration of the Leiden University Hospital, Radboud University Hospital, Maastricht University Hospital and Kempenhaeghe Center of Neurological Learning Disabilities. Results of this thesis are also available at the website of the Duchenne Center Netherlands.