Understanding and Management of Neurobehavioral Difficulties in Patients with Duchenne Muscular Dystrophy

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Abstract

Patients with Duchenne muscular dystrophy (DMD) face an increased risk to develop neurobehavioral problems linked to brain dystrophin deficiency. This PhD thesis explores the impact of corticosteroid treatment and genotype on brain morphology and their correlations with neurobehavioral outcomes. Using MRI, significant differences in gray matter volumes, subcortical volumes, and brain morphology were found between DMD patients treated daily with corticosteroids and those treated intermittently. Additionally, differences were observed based on genotypes. A new term, Duchenne Muscular Dystrophy-Associated Neurobehavioral Difficulties (DuMAND), and the DuMAND Checklist were introduced for systematic screening of neurobehavioral difficulties in DMD. Finally, clinical experiences with psychopharmaceuticals to treat severe neurobehavioral difficulties in DMD patients were investigated.

Introduction

Duchenne muscular dystrophy (DMD) is the most frequent muscular dystrophy (1). In addition to the severe and progressive muscular loss, patients with DMD face a heightened risk of developing neurobehavioral problems (2). These issues not only significantly impact the daily functioning of patients but also contribute to a substantial burden on both the affected individuals and their families (3). The etiology of these neurobehavioral problems has been associated with the absence of dystrophin expression in the brain, but till now effective treatments for these neurobehavioral problems remain elusive. To enhance clinical care for this burdensome aspect of DMD, new insights regarding the DMD brain, and the screening for and treatment of neurobehavioral difficulties, are urgently needed (4).

The overarching objective of this PhD project is to contribute to various domains of understanding and management of neurobehavioral challenges in patients with DMD.

Different studies

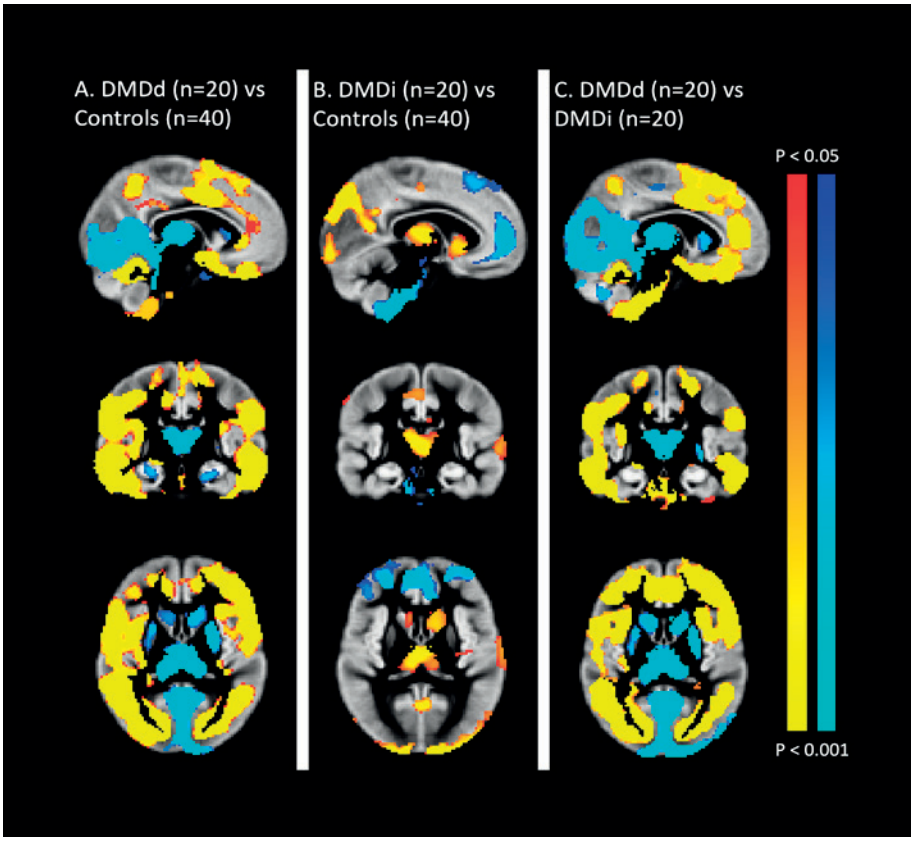
In the first study, we investigated the impact of different corticosteroid regimens on brain volumetrics in DMD using Magnetic Resonance Imaging (MRI). In a cross-sectional, two center study, T1-weighted MRI scans were obtained from three age-matched groups (9-20 years): DMD patients treated daily with deflazacort (DMDd, n=20, scan site: Leuven), DMD patients treated intermittently with prednisone (DMDi, n=20, scan site: Leiden), and healthy controls (n=40, both scan sites). FSL (the FMRIB Software Library) was used to perform voxel-based morphometry analyses and to calculate intracranial, total brain, gray matter, white matter, and cerebrospinal fluid volumes. A MANCOVA was employed to compare global volumetrics between groups, with site as covariate.

Voxel-based morphometry analyses revealed notable differences between patient groups and controls (Figure 1). Specifically, daily corticosteroid treatment in DMD patients exhibited more pronounced alterations in gray matter volumes compared to intermittent treatment. Global volume quantification further demonstrated significant differences in gray matter, white matter, and cerebrospinal fluid volumes in daily treated patients compared to controls, underscoring the need to consider corticosteroid treatment as a confounding variable in future brain imaging studies in DMD (5).

In the second study, we looked into specific regions of gray matter in the brain of DMD patients and explored whether variation in gray matter characteristics within the DMD population was influenced by corticosteroid treatment and genotype. The CAT12 toolbox in SPM was used for detailed MRI segmentations, assessing subcortical structures, cortical thickness, gyrification, and sulci depths. Comparisons were made between DMD (n = 40) vs. controls (n = 40), daily vs. intermittent corticosteroid treatment (n = 20 each), and Dp140+ vs. Dp140- gene mutations (n = 15 vs. 25). MANCOVA, CAT12 3D statistics and Pearson correlations were conducted. DMD patients showed significant differences in volumes of distinct subcortical volumes, left hemisphere cortical thickness, and gyrification in multiple brain areas compared with healthy controls. The daily treated DMD group exhibited differences in subcortical volumes and different patterns of cortical thickness, sulci depth, and gyrification compared to the intermittent treated DMD group. DMD Dp140+ patients displayed altered gyrification and sulci depth compared to DMD Dp140- patients. Finally, we found significant correlations between neurobehavioral outcomes and brain areas that showed significant differences in cortical morphology associated with corticosteroid treatment.

This study demonstrated that both genotype and corticosteroid treatment are associated with variations in subcortical volumes and cortical

Figure 1: Results of gray matter (GM) voxel-based morphometry (VBM)
(A) Brain regions expressing lower (red-yellow) or higher (blue) GMV in the DMDd group compared with controls; (B) brain regions expressing lower (red-yellow) or higher (blue) GMV in the DMDi group compared with controls; (C) brain regions expressing lower (red-yellow) or higher (blue) GMV in DMDd group compared with the DMDi group. (p < 0.05, TFCE-corrected)



morphology, albeit in different ways. Corticosteroid treatment appears to have a more profound association with differences in gray matter characteristics of brain regions that are associated with functional outcomes.

In study 3, we explored the strategies used by healthcare professionals to address neurobehavioral symptoms in DMD patients. Twenty-eight respondents from 16 different countries completed an online survey. Only 35% of the centers systematically screened for neurobehavioral difficulties in their DMD population. Predominant screening methods included history taking and clinical observation, mostly done by physicians relying on their own expertise and experience. Common neurobehavioral difficulties encompassed learning challenges, dependency from adults, anxiety, concentration difficulties, and social deficits. The participating centers frequently employed parental counseling and liaison with psychosocial healthcare professionals for psychosocial intervention. This study underscores the complex behavioral landscape in DMD, highlighting the need for validated screening, assessment and management strategies and collaborative efforts in implementing these. We advocate for international consensus recommendations for screening, assessment and management of neurobehavioral difficulties in DMD to enhance patient care and communication across healthcare settings (6).

In study 4 we introduced the term Duchenne Muscular Dystrophy-Associated Neurobehavioral Difficulties (DuMAND) and the DuMAND Checklist, which will facilitate comprehensive screening for neurobehavioral symptoms in DMD. DuMAND categories were derived through literature review, parent (48 mothers and 37 fathers), and expert (n = 28) input and feedback. The DuMAND Checklist subscales were developed iteratively, incorporating item selection, expert panel (n = 10) assessment for face validity, comprehensiveness, and a pilot validation study in a DMD sample (n = 20).

DuMAND encompasses five categories: cognition and learning, social responsiveness, emotion regulation, externalizing behavior, and eating and sleeping. Preliminary validation of the DuMAND Checklist indicates acceptable-to-excellent internal consistency and construct validity. By introducing the DuMAND concept, this study seeks to inspire a consensus approach for screening, assessing, and managing neurobehavioral issues in DMD. Incorporating screening, using the DuMAND Checklist, in addition to medical follow-up will facilitate early intervention, addressing a critical gap in identification of neurobehavioral disorders in DMD. Future research is needed to further evaluate psychometric properties of the DuMAND Checklist and investigate the natural course of DuMAND (7).

Finally, we reported on the clinical experience with psychopharmaceutical treatment in 52 DMD patients, assessing its efficacy in improving neurobehavioral symptoms. Electronic patient files were searched for patients with DMD that had been treated with psychopharmaceuticals between 2008 and 2022. Information about neurobehavioral symptoms, type of medication, side effects, and behavioral changes were collected. Two independent clinicians used the clinical global impression scale (CGI) to assess severity of the neurobehavioral problems before and the change in symptoms after treatment. Descriptive statistics were used. Our results include 52 males with DMD (mean age 11 years) treated with psychopharmaceuticals of which 55.8% had four or more comorbid neurobehavioral symptoms. The clinical condition was much improved on the CGI in 54.2% treated with methylphenidate, in 38.9% of the patients treated with fluoxetine, and in 22.2% treated with risperidone. Minimal effects and side effects were also reported.

Patients with DMD may experience severe neurobehavioral symptoms interfering with learning and/or development. Treatment with psychopharmaceuticals can improve these neurobehavioral symptoms, but further research is needed to gain better insights in psychopharmaceutical treatment in patients with DMD(8).

Conclusion

This thesis aimed to address symptoms of Duchenne muscular dystrophy (DMD) beyond the physical components, which understandably receive priority in a disease with such devastating physical consequences. However, the disparity between physical and psychosocial research is intriguing, as it does not reflect the conversations we have with boys with DMD and their parents in clinical care. Naturally, everyone holds high hopes that new medical advances will lead to a cure, but there is also a sense of realism and acknowledgment that living with the disease will remain a significant challenge in the near future. Many struggle with the high burden of neurobehavioral difficulties, navigating the school system, accessibility, societal understanding, participation, isolation, social contacts, and self-fulfillment.

The physical symptoms of DMD may be devastating, but so is the psychosocial impact on daily life—not only for the patients but also for their families. This thesis aimed to shed light on these often-overlooked aspects, but a lot of work still needs to be done.

In conclusion, this thesis demonstrated the multifaceted factors contributing to variations in distinctive parts of gray matter in the DMD brain, emphasizing the importance of considering both genetic and treatment-related factors as confounding variables in future studies. Furthermore, our findings highlight the lack of a standardized approach to address neurobehavioral problems in DMD patients. To address this gap, we introduced the term DuMAND and developed the DuMAND Checklist, providing a tool for systematic screening of neurobehavioral difficulties in clinical practice. Lastly, our research demonstrates the potential of psychopharmacological treatment as a safe and effective approach to alleviating neurobehavioral difficulties in patients with DMD.

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