Duchenne Muscular Dystrophy: a neurocognitive and behavioral perspective

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Abstract

Duchenne muscular dystrophy is a progressive neuromuscular disorder associated with neurocognitive and behavioral difficulties. In the past, the focus of research and clinical care was mainly on the devastating physical consequences of this disease. Recently, more attention goes to the neurocognitive and behavioral aspects that affect boys with Duchenne muscular dystrophy and their families. Boys with Duchenne muscular dystrophy are more vulnerable for cognitive deficits, learning difficulties and behavioral problems. The combination with their physical problems can be a heavy burden for these patients and their families. Research tries to reveal the complex mechanisms between genotype, dystrophin deficiency, brain structure and functioning, and behavior and cognition. Meanwhile, clinical care should focus on early detection and intervention. This paper reflects about what we know thus far about these aspects, which research is ongoing and how these issues can be handled in clinical care.

Introduction

Duchenne Muscular Dystrophy (DMD) is a progressive neuromuscular disorder caused by mutations in the *dystrophin* gene on the X-chromosome. With an estimated incidence of 1 in 3500-6000 live born boys, it is one of the more common neuromuscular diseases, however still rare. Due to the X-linked inheritance, mainly boys are affected. Female carriers can develop relatively mild muscular symptoms and they have a risk for cardiomyopathy, but female cases with a severe phenotype are rare (1).

The *dystrophin* gene is one of the biggest genes in humans and it is responsible for the expression of different isoforms of the protein dystrophin. A mutation in this gene causes a disruption in the production of one or more of those isoforms, depending on the location of the mutation (2). The full-length isoform of dystrophin is expressed in muscles and other isoforms are expressed throughout different body tissues, like the kidneys, the retina and the brain (3). In muscles, dystrophin has key functions in maintaining cell membrane stability and cell functioning. Without dystrophin, muscle tissue gets progressively damaged, leading to a gradual loss of motor function (2).

Boys with DMD typically are referred to a specialist before the age of four, often with a history of delayed motor or global development. The disease is characterized by progressive muscle weakness resulting in a typical clinical evolution of motor decline. After the first symptoms of delayed motor development and/or muscle weakness, young boys with DMD develop a typical waddling gait pattern. Most DMD boys lose ambulation around the age of 13 years. In the following years total wheelchair dependence, progressive muscle weakness of the upper limbs, respiratory muscle weakness and cardiomyopathy will follow. Due to the muscle weakness and motor difficulties secondary orthopedic complications (e.g., scoliosis, joint contractures, …) will develop. DMD patients have a reduced life expectancy with an early death around 30 to 40 years most often due to cardiorespiratory failure (2).

DMD should be taken in consideration in young boys with motor difficulties or a global developmental delay and raised creatine kinase (CK) levels (more than 10 times the upper limit of normal). Nowadays, genetic confirmation finalizes the diagnosis, avoiding the need for a muscle biopsy to demonstrate dystrophin deficiency (2).

Currently, DMD cannot be cured and treatment exists merely of symptomatic management. A multidisciplinary approach is essential to support children and adults with DMD and their families. Corticosteroids have been proven effective in slowing down the progression of the disease, altering the typical clinical evolution and increasing life expectancy. Best clinical practice guidelines were developed and published in 2010 and frequently updated since (4).

Due to the enormous impact on physical functioning, DMD has long be considered as an exclusively muscular disease. However, even in the first descriptions of this disease by Edward Meyron in 1851 and Duchenne de Boulogne in the late 19th century, intellectual comorbidities were mentioned (5). For decades, this aspect of DMD was somehow neglected in clinical care and in research. Only few papers explored cognitive and behavioral functioning of DMD boys in the second half of the 20th century and only in the late '90s more structural research was performed. A lot of explorative research has been done in the first two decennia of the current century. With improving therapeutic options and increasing survival rates, we are now aware that the cognitive and behavioral phenotype of DMD is very important. However, little is known about the pathophysiological mechanisms and the impact of dystrophin deficiency on the brain. This paper gives an overview of what is known about the cognitive and behavioral phenotype in DMD, where to focus on in clinical care and the research currently ongoing regarding this topic.

Cognition & learning

In the first reports about DMD, boys were described as having a "dull intellect" and "difficult speech" (6). Intelligence is one of the most intensively researched cognitive domains in boys with DMD. Dozens of studies have investigated the intelligence profile of this population. The consensus is that boys with DMD have a higher risk of a lower full scale intelligence quotient (FSIQ), than healthy peers (7–9). Moreover, most studies support the findings that boys in the DMD population have a normally distributed FSIQ with a mean of 85, which is one standard deviation under the normative population FSIQ (8). This FSIQ seems stable throughout life, however studies about intelligence in adult men with DMD are scarce. Most evidence supports the idea that the FSIQ does not correlate with motor functioning or severity of the physical symptoms (8). More specifically, boys with DMD tend to have a significant discrepancy between their verbal intelligence quotient (VIQ) and their performance intelligence quotient (PIQ) with lower scores on the verbal tasks (10). As most studies have been conducted with

relatively small samples sizes using multiple different instruments, it is difficult to generalize the results. Furthermore, most researchers are convinced that there is a direct effect of *dystrophin* mutations on intellectual functioning. Moreover, some studies found a significant correlation between gene mutation site and FSIQ (9,11). The hypothesis is that the more the mutation is located at the end of the gene, the more production of protein dystrophin isoforms is disrupted (also those isoforms expressed in the brain) and the more cognitive impact there is. However, the whole image is not that straightforward, as discussed below.

Intelligence is a very broad cognitive concept and some studies have investigated more specific cognitive domains in DMD boys. These findings are somewhat inconsistent and reflect the great heterogeneity in cognitive and neuropsychological functioning in DMD patients. Nevertheless, it is clear that they are more vulnerable to neuropsychological deficits and should be monitored closely. One of the most constant findings is problems with short term auditive memory and verbal working memory (12,13). Especially this last feature is thoroughly described in literature and this is of great clinical relevance, as this is a capacity which is widely used in daily life. For example, usually in a classroom auditive instructions by the teacher are supposed to be processed by the pupils while retrieving new information from further instructions. In general, boys with DMD will perform badly in such situations and teachers have to be advised to deliver information in short bits or use visual cues to support them. Another frequently reported difficulty is automatization of new information and procedures (14–16). Boys with DMD seem to need more repetition, explanation and explicitation in order to learn new skills, compared to their peers. Additionally, some studies found difficulties in implicit learning, information processing and executive functioning (17,18). Combined, these problems seem to lead to deficits in school accomplishments, like reading and mathematics as well as in less obvious social behaviors. Indeed, boys with DMD are at high risk for reading and other learning disorders. Reading problems have been reported in up to 30% of DMD boys, and difficulties with maths in up to 10% (19). A good follow up, early detection and interventions and an open communication with all stakeholders (parents, teachers, student counseling, DMD experts, …) are crucial to optimize school functioning of boys with DMD and give them a fair chance of regular education (see below for more).

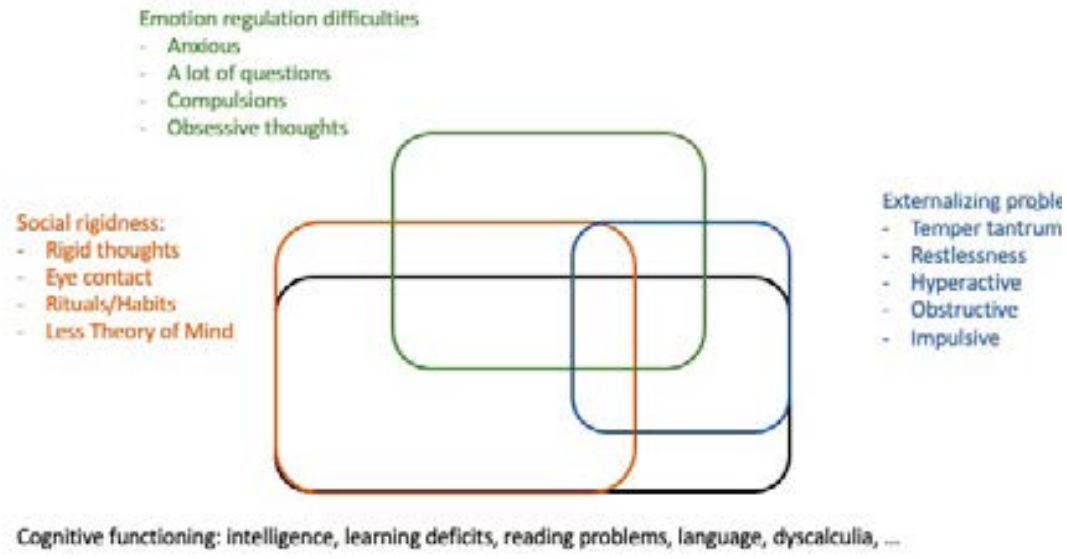
Finally, boys with DMD seem to be at risk for a delayed language development and language problems later on in life (20). More specifically, some studies reported speech delay (33%), significant lower expressive and receptive language capacities and deficits in verbal working memory performance (21,22). In clinical care it is striking that many boys and young adults with DMD have difficulties with verbal communication and rely on their parents to express their experiences. Generally, they experience difficulties with expressing their emotions, wishes and thoughts through verbal communication. However, it remains unclear if this is a matter of language performance or rather a matter of communication skills and feeling comfortable to speak in unfamiliar circumstances. Currently, this group is investigating language performance and the connectivity of language networks in the brain in DMD patients in UZ Leuven.

Behavioral difficulties

Not only cognition, learning and language are affected in DMD, but also behavioral problems have been documented frequently, as well in clinical care as in scientific literature. However, the use of different methodologies and even more different instruments makes it difficult to draw general conclusions and most studies report only small samples without control groups. Despite these considerations, the general conclusion is that boys with DMD are more at risk for psychopathologies like Attention Deficit and Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Obsessive Compulsive Disorder (OCD) and anxiety and depressive disorders (7,23). Estimations of the prevalence of ADHD within the DMD population differ from 11 to 30%, being higher than prevalence rates in the normal population (7,9,24). The same conclusions, however with lower percentages, can be drawn about the prevalence of ASD (2-21%) and OCD (5-14%) in DMD patients (23,25). Whereas studies have investigated these conditions separately, clinical reality is more complex, with many boys (over 30%) being diagnosed with more than one psychiatric diagnosis (9). This of course has a major impact on the boys themselves and their families. From a clinical point of view, behaviors reported in boys with DMD can be classified in four different but overlapping clusters as we illustrate in *figure 1*. Common behavioral characteristics seen in DMD are rigid thinking, asking many questions, looking for predictability and control, obsessions, difficulties with being alone, lower social skills, anger tantrums, anxiety issues and difficulties falling asleep. They can appear simultaneously and vary between different age periods, with changing intensity. Regular screening, early detection and early intervention to prevent severe problems are key in clinical care (see below). The burden of those behavioral aspects can be very high for a family and during some age periods even more manifest than the physical problems. Awareness of these aspects is not only required in the family setting, but also in other social contexts, like school and leisure activities, especially because children and adolescents with DMD tend to have more difficulties with acquiring and maintaining social relationships caused by a combination of above behavioral vulnerabilities and a higher threshold for social participation due to physical limitations.

In clinics, it is important to screen for these problems on a regular basis during history taking and by observing. The behavioral issues in DMD are not easily classified based on existing behavioral classification models, like the DSM-V, as there are many comorbidities and there is overlap between these behaviors.

Figure 1: *Visual representation of different, but overlaying clusters of behaviors in DMD*



Referral to a specialized child psychiatric setting should be done carefully and with good documentation of what we know about DMD and behavioral problems thus far.

Brain involvement in DMD

The cognitive and behavioral complications in DMD cannot be explained as a consequence of limited motor functioning as these specific behaviors are not described in other neuromuscular pathologies similar to DMD (26). In this complexity, they seem to be inherent to and specific for DMD. Researchers have been studying the link between *dystrophin* mutations and neurocognition and –psychology in DMD patients as some dystrophin isoforms are expressed in the brain (9). Different isoforms are expressed in different brain regions through different developmental stages. Dp140, for example, is expressed in the cerebral cortex only in fetal life stages, whereas in the cerebellum it is expressed after birth as well (3). Which role the different dystrophin isoforms exactly play in the brain remains unknown thus far. Different brain imaging techniques have been used to study brain structure, connectivity, blood flow and metabolism in DMD patients, however so far, in an exploratory manner. However, this kind of research is scarce in this population and has been done only with exploratory aims. Boys with DMD seem to have smaller total brain volumes and smaller grey matter volumes, measured with T1-weighted magnetic resonance imaging (27). Diffusion weighted imaging revealed smaller fractional anisotropy and higher mean diffusivity in white matter in boys with DMD on a whole brain level, possibly indicating small changes in white matter tracts in DMD patients (27). Other brain imaging modalities support the hypothesis that DMD is also influencing brain function. A perfusion study showed 17% reduction in cerebral blood flow in the DMD group (28). While the specific function of dystrophin and the impact of a reduced expression of this protein in muscles is well understood, this is absolutely not the case in the brain. Muscle pathology and its complications (cardiac and respiratory, orthopedic,…) can be treated, but the brain-related pathology is still mainly neglected. Nevertheless, over the last decade there was a growing interest to investigate the brain-related pathology in DMD. Not only in humans, but also in dystrophin deficient mdx mice the effects of *dystrophin* mutations on brain development, structure and functioning are being investigated (29). The international multicenter Brain Involvement iN Dystrophinopathies (BIND) study started in January 2020 and focusses on this topic (https://cordis.europa.eu/project/id/847826). Our group currently conducts a brain imaging study with primary focus on the language tracts.

Corticosteroid treatment

Currently, glucocorticosteroid (GCS) treatment is the golden standard for DMD, being initiated already early in the ambulant stage of the disease. GCS have been proven to increase muscular strength and slow down the progression of the disease, delaying the moment of loss of ambulation and the progression of orthopedic, cardiac and respiratory complications (2). Two different GCS compounds are widely used in DMD treatment, namely prednisolone and deflazacort. Both have been proven effective, but each show a slightly different pattern of efficiency. Research has mainly focused on the physical effects of chronic GCS use and some studies have compared these two compounds. Cushingoid features, weight gain, growth inhibition, osteoporosis, cataract, … are well-known side effects (2). However, it is well known that chronic GCS treatment also has significant psychological side effects. Less understood is the influence on behavior and wellbeing. Use of high doses of GCS for long periods can induce behavioral problems. A study conducted by our group in cooperation with the Leiden University Medical Center (LUMC) aims to investigate these behavioral and psychological side effects of chronic GCS treatment. The DMD population in Leiden is traditionally treated with prednisolone, while the standard of care in UZ Leuven exists since more than 30 years of daily deflazacort treatment. The aims of this study are 1) to investigate physical changes due to GCS treatment and their impact on self-perception, body image and illness perception, 2) to explore if differences can be detected in neuropsychological and behavioral functioning between both GCS regimes, and 3) to evaluate the impact of chronic GCS use on brain structure and functioning. Indeed, scientific evidence in other pathologies suggests that GCS cross the blood-brain barrier, possibly having consequences for brain development, such as cortical atrophy (30). More insight into the consequences of starting chronic GCS treatment in early childhood on outcome in adulthood is urgently needed.

Clinical approach

The above overview of neurocognitive and behavioral complications in patients with DMD is only an indication of the complexity families with DMD are confronted with. Besides the already existing evidence, there are many aspects of DMD that have not been studied yet: the great heterogeneity of these deficits in the DMD population, the burden on the family, the impact of having to cope with progressive loss of physical functioning and a set future of premature death, difficult participation in society, problems with functioning at school, … The clinical complexity of DMD requires a multidisciplinary approach, management and longitudinal follow-up (4). The progressive nature of this disease requires constant adaptation, on a physical level as well as in educational, social and familial functioning. Screening for possible difficulties is key in order to prevent more severe problems in the future. Screening should include regular standardized neuropsychological testing as well as questions about behavior, sleep, school and social functioning, and family burden. Prevention consists of early initiation of parent counseling, advise for schools, multidisciplinary therapies, psychoeducation about DMD of the boys themselves, … In some cases, psychopharmacological interventions can be necessary to relief the burden on the families and help the boys. Relatively low doses of fluoxetine have been suggested being effective in boys who suffer from anxiety and OCD-like behaviors, and methylphenidate seems to be effective for boys with attention and concentration problems (29,31). Melatonin supplementation can be helpful to support falling asleep.

Conclusion and future perspectives

In conclusion, DMD is a complex disease and many aspects of the neurocognitive and behavioral problems are still poorly understood. Currently, a cure is not available, but promising therapies such as exon skipping and gene therapy are being tested in clinical trials (32). However, these therapies target the skeletal (and cardiac) muscles, but not the brain-related comorbidities. Filling the research gap about neurocognitive and behavioral aspects in DMD may pave the road towards treatments also targeting those important aspects of this complex disorder. In the meanwhile, clinical awareness of neurocognitive and behavioral vulnerabilities in boys with DMD is extremely important. Raising this awareness in healthcare professionals, schools, parents of boys with DMD and society in general is also one of the priorities on the agenda of the World Duchenne Organization (www.worldduchenne.org) and the Duchenne Parent Project (www.DPPbelgium.be & www.duchenne.nl). These patient driven organizations fund scientific research, facilitate networking between patients and professionals, are an advocacy for patient's rights and create more awareness about Duchenne muscular dystrophy in the general population. In 2020, the main topic on the World Duchenne Awareness Day (7th September) was Duchenne and the brain. Indeed, networking, creating awareness and working together are important strategies to optimize the overall care for boys with DMD and their families. The little evidence and expertise about cognitive and behavioral issues in boys with DMD should be shared as much as possible in order to learn faster, develop interventions and ultimately treating DMD as a whole, including the brain.

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