Neuropsychiatric Disorders in Males With Duchenne Muscular Dystrophy: Frequency Rate of Attention-Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder, and Obsessive–Compulsive Disorder

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Using a questionnaire-based study, we assessed the parent-reported prevalence of attention-deficit hyperactivity disorders (ADHDs), autism spectrum disorders, and obsessive–compulsive disorders in a group of 351 males with Duchenne muscular dystrophy. Of the 351 males with Duchenne muscular dystrophy, 11.7% were reported to have a comorbid diagnosis of ADHD, 3.1% had autism spectrum disorder, and 4.8% had obsessive–compulsive disorder. It can be concluded that the incidence of these neuropsychiatric disorders is higher in Duchenne males than in the normal population. This finding, together with recent reports on the higher prevalence of cognitive and learning problems in Duchenne, supports the view that Duchenne muscular dystrophy is not only a muscular disorder but also a disorder affecting the brain. It is important for clinical practice to take into account this heightened association. More research is needed to examine this association and its consequences.

Keywords: attention-deficit hyperactivity disorder; autism spectrum disorder; obsessive–compulsive disorder; males; Duchenne muscular dystrophy

Duchenne muscular dystrophy is an X-linked condition caused by the absence or disruption of the protein dystrophin due to a mutation of the Duchenne muscular dystrophy gene. Dystrophin is part of a large, tightly associated glycoprotein complex containing other proteins, the so-called dystrophin-associated proteins or dystrophin-associated protein complex. The functional features of the various dystrophin isoforms in different tissues differ because of their localization and type specificity (e.g., muscles, brain, retina, and so on). In skeletal muscle, the primary role of dystrophin is probably mechanical stabilization of the plasma membrane.

In a review, Anderson et al stated that, in males with Duchenne muscular dystrophy, there is evidence of disordered architecture of the central nervous system, abnormalities in dendrites, and loss of neurons, all associated with neurons that normally express dystrophin. As early as 1994, Uchino et al reported that dystrophin has a certain distribution and function in different parts of the central nervous system. No dystrophin was detected in the cerebrum and cerebellum in males with Duchenne muscular dystrophy who had intellectual disturbance. Approximately one-third of the males diagnosed with Duchenne show signs of dyslexia and mild mental retardation, deficits in verbal working memory, and impairment in the ability to perform automatic motor tasks, functions that are thought to depend on the cerebellum. Several recent publications, using the dystrophin-deficient mdx mouse (a murine model of Duchenne muscular dystrophy), showed that there is a certain functional interaction and the role for dystrophin and dystrophin-associated proteins related to Purkinje cells and cerebellar mossy fiber synaptic glomeruli in the granular layer.

Until now, only a few studies have systematically addressed the incidence of neuropsychiatric comorbidity in a population of males with Duchenne muscular dystrophy.
In an extensive review article on dystrophin, Mehler states that “patients exhibit significant developmental cognitive and behavioral abnormalities, including increased frequencies of infantile autism and attention deficit disorders” (p. 279). Recently, 6 males with Duchenne muscular dystrophy having autism were identified by using the Diagnostic and Statistical Manual of Mental Disorders-IV criteria in a total population of 158 Duchenne males representing the total number of Duchenne patients in the state of Massachusetts, which corresponds with a frequency rate of 3.8%. Darke et al reported 5.4% of the Duchenne males (n = 37) in their study having a pre-existing autism spectrum disorder.

No studies on the incidence of attention-deficit hyperactivity disorder (ADHD) in Duchenne males have been published until now. It was not until 2004 that the first case-report of a Duchenne boy with ADHD was described in literature. The aim of that case report was to illustrate the medical, behavioral, and cultural aspects of a boy with muscular dystrophy and disruptive classroom behavior, emphasizing the importance of further research on this association. ADHD is a neurodevelopmental disorder in children, which makes them unable to inhibit motor or emotional responses to an event. This results in the core symptoms of the classification of the Diagnostic and Statistical Manual of Mental Disorders-IV, Text Revision, that is, attention deficit and/or hyperactivity and impulsivity, also called the “holy trinity of attention-deficit hyperactivity disorders.” Epidemiological studies reveal different prevalence rates of ADHD in the general population. The Diagnostic and Statistical Manual of Mental Disorders-IV, Text Revision, reports rates from 3 to 7%. Wolraich and colleagues found an overall prevalence rate of 6.8% when each of the subtypes of ADHD was included (primarily inattentive type, combined type, and primarily hyperactive/impulsive type). Schneider and Eisenberg using parent-reported diagnoses found a prevalence of 5.4% of ADHD in a study of 9278 elementary school children (all subtypes were coded as ADHD). On the basis of clinical practice, it is hypothesized that obsessive–compulsive disorders also have a higher prevalence in males with Duchenne muscular dystrophy. Obsessive–compulsive disorders are characterized by distressing intrusive thoughts and/or repetitive actions that interfere with the individual’s daily functioning, representing 1 of the most incapacitating anxiety disorders. Compulsions are meant to relieve anxiety to a dreaded event and as such might have a higher incidence in children confront with progressive physical disability, experiencing some distress at 1 point or another in their life when coping with their disease. No research on this topic has been published until now. The aim of the present study is to report the frequency rate of ADHD, autism spectrum disorders, and obsessive–compulsive disorders in a population of American and Dutch males with Duchenne muscular dystrophy, using parent-reported diagnosis.

**Material and Methods**

**Patients**

The parents from the Dutch and American Duchenne Parent Project were contacted by letter or e-mail to participate in the study. Parent Project Muscular Dystrophy is a nonprofit organization focused entirely on Duchenne and Becker muscular dystrophy founded in 1994 by the parents of these children. Approval was obtained from the local ethics committee of Maastricht University. Of the 112 Dutch parents who were contacted by letter, 63 of them participated (56%) by completing the questionnaire. Of the 1725 American parents contacted by e-mail, 317 participated (18%). Of the total of 380 males, only the 351 males with Duchenne muscular dystrophy were included in further analysis; the 29 males with Becker dystrophy were excluded. The participating parents lived in areas spread throughout the Netherlands and the United States. The mean age of the males was 11.9 years (SD = 5.2), with a minimum age of 3 years and a maximum of 38 years. The diagnosis Duchenne muscular dystrophy was set at a mean age of 3.8 years (SD = 2.1). A total of 181 males used steroids (52%), 155 of them (44%) did not use steroids, and the remaining 15 males (4%) had used steroids before, but stopped using them for a variety of reasons. Parents were asked to give their educational status (highest grade of school that they completed) on a 5-point scale from “some high school or less” to “professional or graduate degree” as is done in the Child Health Questionnaire. The Kolmogorov-Smirnov test was performed to test whether the distribution of education was normal in both the US and Dutch sample. Educational status in the US sample (D[280] = 0.22; P < .001) and the Dutch sample (D[62] = 0.23; P < .001) were both significantly different from normal. This result reflects the positive skewed distribution in the educational status of our sample. As parents participated anonymously, further data on the sample characteristics and the characteristics of the nonparticipants were not available.

**Method**

Parent-reported neuropsychiatric diagnosis is the dependent variable in the current study. The parent responders (in 71% of the cases the mother, in 15% of the cases the father, and in 14% of the cases both parents) were asked by means of a questionnaire whether their child had ever received a professional neuropsychiatric diagnosis. Parents were asked to indicate whether their son has been diagnosed with “attention-deficit hyperactivity disorder,” “autism spectrum disorder,” or “obsessive–compulsive disorder.” When the answer was “yes,” the parent was asked to indicate who made this diagnosis. Only formal diagnoses made by health care professionals (psychiatrists, psychologists, pediatricians, and neurologists) were scored for the purpose of this study.
NOTE: ADHD = attention-deficit hyperactivity disorder; ASD = autism spectrum disorder; OCD = obsessive–compulsive disorder.

Results

As can be seen in Table 1, parents reported a total of 69 neuropsychiatric diagnoses. Of these 69 diagnoses, 44 males got 1 diagnosis (30 with ADHD, 7 with autism spectrum disorder, and 7 with obsessive–compulsive disorder), 8 males got 2 diagnoses (1 male was reported to have both ADHD and autism spectrum disorder, and 7 males were reported to have ADHD and obsessive–compulsive disorder), and 3 males were reported to have all 3 diagnoses. Thus, a total of 55 males were given 1 or more of the 3 investigated neuropsychiatric diagnoses, which corresponds to a total and overall frequency rate of 15.7% of the Duchenne males who had been given a neuropsychiatric diagnosis at the time of our study. Table 1 describes the mean age and SD of the males who received a neuropsychiatric diagnosis at the time of our study. Furthermore, the frequency rates of the 3 neuropsychiatric disorders are reported as well as the prevalence rates of these disorders as reported in general population studies.10,14,16 A 1-sample \( t \) test was performed to test whether there were a significant difference between frequency rates in Duchenne males and in the normal population.

It can be seen in Table 1 that ADHD, autism spectrum disorders, and obsessive–compulsive disorders are significantly more prevalent in males with Duchenne muscular dystrophy than in the general population. To test whether there is a relation between the diagnosis of ADHD and the use of corticosteroids, we performed a \( \chi^2 \) analysis. No significant relationship between ADHD and corticosteroids was found (\( \chi^2 = 0.00; p = .998 \)). In 2 of the 15 males (13.3%) in whom corticosteroid treatment was stopped, the diagnosis of ADHD was given, which reflects a percentage not significantly different from 11.7%. For autism spectrum disorders and obsessive–compulsive disorders, \( \chi^2 \) analysis could not be performed because of cells with less than 5 cases included.

Educational status of the parents of the males who were reported to have a neuropsychiatric disorder did not significantly differ from those without a neuropsychiatric disorder (\( t = -0.23; p = .82 \)). For this indicator of socioeconomic level, an effect on the reported neuropsychiatric diagnosis could, therefore, be ruled out.

Discussion

Research in Duchenne muscular dystrophy has primarily focused on muscle degeneration and its treatment. Studies examining neuropsychiatric functioning have been relatively sparse. Three studies7,8,17 have reported on the association between autism spectrum disorders and Duchenne. Our frequency rate of autism spectrum disorders based upon parent report does not significantly differ from the 3.8% reported by Wu et al7 using the criteria from the Diagnostic and Statistical Manual of Mental Disorders-IV: 1-sample \( t \) test \( t = 0.72; p = .475 \). This finding (1) suggests that parent-reported diagnoses do not result in under-reporting or over-reporting of the diagnosis of autism spectrum disorders in Duchenne males and (2) confirms the prevalence rate reported by Wu and his colleagues.7

The present study also demonstrates an association between Duchenne and parent-reported diagnoses of ADHD in 12% of the males. This rate is more than twice as high as the prevalence rate in the study of Schneider and Eisenberg,13 who also used parent-reported diagnosis as the method of gathering diagnosis data in a large sample in US elementary school children. Furthermore, it was found that reducing the concentration of free serotonin in plasma by using corticosteroids is not linked to a higher association rate of Duchenne muscular dystrophy with ADHD. Steroids are used in males with Duchenne muscular dystrophy to improve functional impairment such as ambulation and pulmonary function to improve quality of life.1 Although mood disturbances as a side effect of steroids have been reported, no studies have been published on the association between the use of corticosteroids and the occurrence of ADHD in males with Duchenne.

Before this study, the association of Duchenne and ADHD had not been described. ADHD has been reported to co-occur with other childhood illnesses involving the brain. For example, at least 20% of patients with epilepsy may present with features of ADHD.14 It is assumed that the cognitive profile of ADHD is a consequence of a deficient inhibitory control system, which reflects abnormalities in the frontal lobes. Based on the cognitive and behavioral heterogeneity of ADHD, Castellanos et al19 proposed a more extensive neuroanatomical circuitry (medial and dorsolateral
prefrontal cortex, frontal, premotor, motor, and striatum). We hypothesize that, in males with Duchenne muscular dystrophy and ADHD, the neurocognitive profile will be more linked to cerebellar dysfunction. The evidence of disordered cerebellar structure, the loss of dystrophin in the cerebellum, and the experimental findings in the mdx mouse support this assumption, which needs further investigation.

Finally, the frequency rate of obsessive–compulsive disorders is also twice as high as compared with the general population, meriting further attention in future research and confirming our hypothesis of obsessive–compulsive disorders as being a diagnosis of clinical relevance in males with Duchenne muscular dystrophy.

An important diagnostic concern in this study is the overlap of diagnoses: a total of 11 males were reported by parents to have a comorbidity between the 3 neuropsychiatric disorders. In looking at this comorbidity, it is important to keep in mind that, by using the criteria from the Diagnostic and Statistical Manual of Mental Disorders-IV for ADHD, it cannot be diagnosed in individuals with autism spectrum disorders, a comorbidity that has been reported by 1 parent in our study. The comorbidity between obsessive–compulsive disorders and autism spectrum disorders has not been reported in our study, although 3 parents reported their boys to have all 3 diagnoses. The association between obsessive–compulsive disorders and ADHD, which is also quite common in literature, is the most prevalent comorbidity in our study.

There are several extraneous variables that might have influenced the outcomes of this study. Even though the sample in our study is large, it does not necessarily mean that it is representative. For instance, the differences in response rates for the Dutch and American samples is not fully understood. Furthermore, given that ADHD can be both underdiagnosed and overdiagnosed and many clinicians do not use rigorous diagnostic methodologies, apart from differences between European and US clinicians, further research using other methods for assessing neuropsychiatric diagnosis are needed. We recommend the use of standardized questionnaires such as the Revised Conners Parent Rating Scale (CPRS-R), Childhood Autism Rating Scale (CARS), and the children’s Yale-Brown Obsessive-Compulsive scale (CY-BOCS). It could be argued that, as our sample also includes older individuals, comparison with the general population and criteria from the Diagnostic and Statistical Manual of Mental Disorders-IV may not be applicable as was done in Table 1. Our data, however, show that the mean age of the males with a neuropsychiatric diagnosis is within the elementary school age. Furthermore, as we do not have objective data on the intelligence of the males in our study, we are not able to analyze the relationship between intelligence and neuropsychiatric symptoms, which is a research question meriting further attention. Finally, the role of corticosteroids is also not conclusive, given that things such as dose and duration of taking medication have not been controlled for.

In conclusion, our results describe a higher association between Duchenne muscular dystrophy and 3 neuropsychiatric disorders. A neurobiological mechanism is suggested, but not yet fully understood. It may be that only males with intellectual impairments or with specific deletions may be at risk for neuropsychiatric disorders. This highlights that Duchenne muscular dystrophy is a heterogeneous population and that specific subgroups of Duchenne males may be those at risk for ADHD. Further research on neuropsychiatric comorbidity is of great importance for effective psychological treatment and follow-up of males with Duchenne muscular dystrophy and their quality of life. This importance is further emphasized by the fact that the introduction of assisted ventilation in the late 1980s and onward has resulted in a new population of adults with Duchenne.

Our research data are not pretending to be all-conclusive; they rather are to be seen as a starting point for future research on this clinically important topic. These data and the data of other recent studies suggest that, in addition to the well-known motor disabilities and the recently described neurocognitive problems, there is also a higher incidence of neuropsychiatric problems in males with Duchenne muscular dystrophy. Knowledge of these associated, nonmotor, problems is of utmost importance for caregivers and clinical practitioners.

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References


