Attention Deficit Hyperactivity Disorder and Cognitive Function in Duchenne Muscular Dystrophy: Phenotype-Genotype Correlation

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Objectives To assess attention deficit hyperactivity disorder (ADHD) in boys affected by Duchenne muscular dystrophy (DMD) and to explore the relationship with cognitive abilities and genetic findings.

Study design Boys with DMD (n = 103; 4-17 years of age, mean: 12.6) were assessed using a cognitive test (Wechsler scales). Assessment of ADHD was based on the *Diagnostic Statistical Manual, Fourth Edition, Text Revision* criteria and on the long version of the Conners Parents and Teachers Rating Scales.

Results ADHD was found in 33 of the 103 boys with DMD. Attention problems together with hyperactivity (17/33) or in isolation (15/33) were more frequent than hyperactivity alone, which was found in 1 patient. Intellectual disability (ID) was found in 27/103 (24.6%). Sixty-two of the 103 boys had no ID and no ADHD, 9 had ID but no ADHD, 14 had ADHD but no ID, and 18 had both. ADHD occurred more frequently in association with mutations predicted to affect Dp140 expression (exon 45-55) and in those with mutations predicted to affect all dystrophin product, including Dp71 (ie, those that have promoter region and specific first exon between exons 62 and 63 but were also relatively frequent).

Conclusions Our results suggest that ADHD is a frequent feature in DMD. The risk of ADHD appears to be higher in patients carrying mutations predicted to affect dystrophin isoforms expressed in the brain and are known to be associated with higher risk of cognitive impairment. *(J Pediatr 2012;161:705-9)*.

The mean IQ reported in children with Duchenne muscular dystrophy (DMD) is approximately 1.0-1.5 SDs below the mean. One-third of boys with DMD exhibit nonprogressive cognitive impairment compared with age- and sex-matched controls and with those with other neuromuscular disorders. There is a higher degree of impairment in verbal vs nonverbal performance both in older[1-3] and younger patients.[4]

The gene encoding dystrophin includes 79 exons interspersed with large introns. Several studies have reported the association between severe learning difficulties and mutations in the 3′ end of the gene.[5-8] Mutations occurring downstream of exon 44 affect the short isoform of dystrophin Dp140, largely expressed in the central nervous system, and mutations downstream of exon 63 disrupt all short isoforms, including Dp71, which is abundant in the brain.[9,10]

Other studies have also assessed autistic features,[11-13] obsessive-compulsive disorder, and more recently, attention deficit hyperactivity disorder (ADHD).[14-17] The frequency of ADHD in DMD reported varies in the literature, possibly reflecting the different methods used to test for ADHD. In a survey, 12% of parents reported that their boy had been diagnosed with ADHD[14]; in another study, the Child Behavior Checklist scales identified approximately 1 in 4 boys with significant attention problems.[15] In a small study, 10 boys with DMD were tested with the Conners Parent Rating Scale-Revised, and 5 were reported to have ADHD.[16] Other anecdotal reports by clinicians also suggest that ADHD is one of the most commonly observed psychiatric comorbidities in DMD, although a correlation with cognitive abilities has not been explored. Cognitive assessments in DMD showed that deficits in executive function, attention, and verbal memory are a frequent feature,[18-20] but it remains unclear whether this is a result of a specific cognitive deficit or a primary attention problem. Although the genotype/phenotype correlation for cognitive impairment in DMD has become increasingly clearer, the relationship between ADHD and genotype has not yet been systematically explored.

ADHD	Attention deficit hyperactivity disorder
CGI	Conners Global Index
CPRS-R:L	Conners Parents Rating Scales-Revised
CTRS-R:L	Conners Teachers Rating Scales-Revised
DMD	Duchenne muscular dystrophy
DSM IV	*Diagnostic Statistical Manual, Fourth Edition, Text Revision*
ID	Intellectual disability

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We assessed a cohort of boys with DMD using a battery of tests for cognitive functions and ADHD. We explored the prevalence of ADHD in DMD, and explored a possible relation with cognitive impairment and genotype.

Methods

This is prospective multicentric study involving 3 tertiary neuromuscular centers (Catholic University and Hospital Bambino Gesù, in Rome; Istituto Mondino, in Pavia). The study was approved by the Ethical Committee of each center. All patients with DMD between the age of 4 and 16 years regularly followed at the 3 centers were asked to participate. Inclusion criterion was genetically proven DMD. In all patients, diagnosis was confirmed by multiplex ligation-dependent probe amplification (ie, exons deletions and duplications) or by polymerase chain reaction amplification and direct sequencing of all 79 exons and adjacent introns (ie, intronic deletions, rearrangements). Mutations were classified according to the Leiden Muscular Dystrophy database (http://www.dmd.nl/) using the nomenclature system published in 2000 in Human Mutation.

Patients were broadly subdivided into 3 groups according to their steroid treatment: (1) no steroids: this included steroid-naïve boys or boys who had been on steroids for less than a year and had stopped treatment at least 1 year before the study; (2) intermittent steroid regime: boys on pulsed administration of steroids for over a year (alternate days, alternate weeks, 10 days on/10 days off); or (3) daily regime: boy on daily prednisolone 0.75 mg or deflazacort 0.9 mg/kg/day for over a year. Duration of steroids treatment was recorded.

Diagnosis of ADHD was first based on the *Diagnostic Statistical Manual, Fourth Edition, Text Revision* (DSM IV-TR)[21] criteria, administered to all 103 boys with DMD. The boys who met the criteria for ADHD were further assessed using the long version of the Conners Parents Rating Scales-Revised (CPRS-R:L) and of the Conners Teachers Rating Scales-Revised (CTRS-R:L).[22] Both the parents and school teachers were invited complete forms.

The CPRS-R:L and CTRS-R:L questionnaires use a categorical approach to rating symptoms of ADHD. The parents (and/or teachers) rate 80 items on a 4-point Likert-type scale. The result includes 7 subscales: (1) oppositional; (2) cognitive problems; (3) hyperactivity; (4) anxious–shy; (5) perfectionism; (6) social problems; and (7) psychosomatic. The questionnaires encompass 3 additional scales: the ADHD Index, the Conners Global Index (CGI), and the DSM-IV Symptoms Subscale. The ADHD Index, which consists of 12 items, is an effective screener for identifying children and adolescents meeting ADHD diagnostic criteria. The CGI is the index with the 10 items found to be most sensitive to treatment effects. The DSM-IV Symptoms Subscale consists of 18 items that directly parallel the DSM-IV criteria for diagnosing ADHD. In our study, we focused on to the 3 additional scales: the ADHD Index, the CGI, and the DSM-IV-TR Symptoms Subscale that provides a score for attention, hyperactivity/impulsivity, and a total score. For each of these subscales a score above 70 was considered abnormal.

All patients underwent a cognitive assessment using the Wechsler Scale.

To compare the presence of ADHD in relation to motor function, steroid treatment, and site and type of mutation, the Fisher exact test was used. The level of significance was set at $P < .05$.

Results

Consent was received for the 103 patients who were asked to participate in the study. Their ages ranged from 4-6 years (mean 12.6). Seventy-two boys were ambulatory and 31 were not. Eighty-three were on steroids (39 daily and 44 intermittent). All had been on steroids for longer than 12 months and treatment was commenced between the age of 5 and 7 years. Of the remaining 20, 2 had been on steroids but only for a short time over a year prior to enrollment into our study; 18 had never been on steroids.

Maternal carrier status was available in 84 with 73 mothers being carriers and 11 not.

Thirty-eight of the 103 patients met the criteria for ADHD on the DSM IV-TR: 3 for hyperactivity, 16 for attention, and 19 for both. The CPRS-R:L confirmed ADHD diagnosis in all but the CTRS-R:L only confirmed in 33 of the 38 boys. The other 5 showed high scores but did not reach the threshold for abnormality.

Of the 33 patients with ADHD confirmed on both CPRS-R:L and CTRS-R:L, 17 has attention problems together with hyperactivity, 15 has attention problems, and 1 has hyperactivity.

Fourteen boys were untestable because of severe intellectual disability (ID). The IQ of the 89 who could be assessed ranged from 45-128 (mean 88.4; median 90; SD 18.5).

Sixty-two of the 103 had normal IQ (85 or above), 14 borderline (70-84), and 13 had scores below 70 that including the 14 untestable boys makes a total of 27 boys with ID.

ADHD was found in 9 of the 62 boys with normal IQ (14.5%), in 5 of the 14 with borderline (35.7%), and in 18 of the 27 with ID (66%). Altogether, 62 boys had no mental retardation and no ADHD, 14 had ADHD but normal/borderline cognitive function, 9 had ID but no ADHD, and 18 had both.

ADHD was found in 7 of the 31 (22.5%) nonambulatory and in 25 of the 72 ambulatory boys (34%). No statistical difference was found between ambulant and nonambulant boys.

There was no clear relation between steroid regime and ADHD (**Figure 1**). In 9 of the 20 patients in the no steroids group, behavioral problems were already obvious when treatment was discussed and parents were reluctant to start treatment because of the possible behavioral problems reported in literature.

No statistical difference was observed between daily and intermittent steroids.

Maternal carrier status was available in 84 patients. ADHD was found in 29 children of 73 carriers, in none of the 11 noncarriers, and in 4 of the 19 with unknown carrier status.