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Cognitive and Neurobehavioral Profile in Boys With Duchenne Muscular Dystrophy

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Abstract

Duchenne muscular dystrophy is a progressive neuromuscular condition that has a high rate of cognitive and learning disabilities as well as neurobehavioral disorders, some of which have been associated with disruption of dystrophin isoforms. Retrospective cohort of 59 boys investigated the cognitive and neurobehavioral profile of boys with Duchenne muscular dystrophy. Full-scale IQ of < 70 was seen in 27%; learning disability in 44%, intellectual disability in 19%; attention-deficit/hyperactivity disorder in 32%; autism spectrum disorders in 15%; and anxiety in 27%. Mutations affecting Dp260 isoform and 5'untranslated region of Dp140 were observed in 60% with learning disability, 50% intellectual disability, 77% with autism spectrum disorders, and 94% with anxiety. No statistically significant correlation was noted between comorbidities and dystrophin isoforms; however, there is a trend of cumulative loss of dystrophin isoforms with declining full-scale IQ. Enhanced psychology testing to include both cognitive and neurobehavioral disorders is recommended for all individuals with Duchenne muscular dystrophy.

Keywords

Duchenne muscular dystrophy, Dp140 isoform, Dp71 isoforms, cognitive impairment, behavioral and developmental disorders

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Duchenne muscular dystrophy is a progressive neuromuscular disorder associated with cognitive and neurobehavioral deficits.[1] Mutations in the dystrophin gene (Xp21), which contains 79 exons, have been determined to be the genetic cause of Duchenne muscular dystrophy.[2] Dystrophin is expressed in skeletal, cardiac, and smooth muscle tissues. In addition, dystrophin isoforms are expressed in the human central nervous system.[3,4]

In the central nervous system the full length dystrophin isoform is expressed (Dp427). The dystrophin gene has at least 4 internal promoters that splice into exons 30, 45, 56, and 63, which give rise to shorter dystrophin products (Dp260, Dp140, Dp116, and Dp71).[5] The dystrophin isoform Dp260 is expressed mainly in the retina resulting in ophthalmic involvement.[3] Dp116 is expressed only in adult peripheral nerves, and its disruption has not been linked with a specific condition. Dp140 consists of the distal C-terminus of the 427-kDa dystrophin and is expressed in the brain, retina, and kidneys. Dp71 is expressed in the brain, retina, kidney, liver, lung, and cardiac muscles.

Boys with Duchenne muscular dystrophy display distinct cognitive profiles and also exhibit neurobehavioral comorbidities, including attention-deficit/hyperactivity disorder (ADHD); autism spectrum disorders, and obsessive-compulsive disorder.[3,6-8] There is a broad range of cognitive abilities among boys with Duchenne muscular dystrophy. The cognitive abilities have been described as nonprogressive, and one-third have a cognitive impairment.[3] The overall intellectual ability of boys with Duchenne muscular dystrophy is 1.0-1.5 standard deviations (SDs) below the mean.[9-14] The incidence of cognitive impairment is higher with deletions in exon 45 to 52 affecting both Dp140 and Dp427 isoforms.[15,16] The disruption of the Dp140 and Dp71 isoform is associated with intellectual disability in patients with Duchenne muscular dystrophy,[17-19] which highlights the

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importance of these isoforms on cognition and brain function.[20] It is reported that the verbal IQ is typically more affected than the performance IQ, both in older and younger boys with Duchenne muscular dystrophy.[3,10,21-23]

Fewer studies examined the academic skills in boys with Duchenne muscular dystrophy. The early studies showed that the academic achievement was consistent with overall IQ, as the mean scores on the academic tests were 1 SD lower than the general population.[24,25] In addition, further studies suggested that boys with Duchenne muscular dystrophy are at higher risk of learning disability as they demonstrate weaknesses in phonological awareness/processing, combined with problems in short-term verbal memory.[11,22,26] This explains the higher rate of reading problems in up to 40% of boys with Duchenne muscular dystrophy.[22,26,27] Writing and mathematics disorders are less well studied, but evidence suggests that these areas can also be problematic.[28,29]

ADHD is the most common neurobehavioral comorbidity associated with Duchenne muscular dystrophy.[6,30] The percentage of individuals with ADHD among patients with Duchenne muscular dystrophy was reported to be up to 50% in a pilot study of 10 children and adolescents with Duchenne muscular dystrophy.[31] A cohort study of 103 boys with Duchenne muscular dystrophy reported confirmed diagnoses of ADHD in 33/103 (32%),[13] compared to 8 to 10% prevalence in school age children.[32] The same study showed an association between ADHD and mutations predicted to affect the expression of Dp140 (mutations in exons 45-55) and Dp71 (mutations in exons 62 and 63).[13] In addition, the boys with mutations affecting the middle and 3′ end of the gene have a high risk of having cognitive impairment as well as ADHD.[13,33] An association between severe intellectual disability and ADHD in boys with mutations in exon 19 (2-point mutations and a deletion) was demonstrated as well.[13] There was no relation found between ADHD and the level of ambulation and steroid regime.

Autism spectrum disorders have been reported in boys with Duchenne muscular dystrophy,[34-36] with an incidence ranging from 4% to 37%.[34,36-38] A previous study showed that 16/85 (19%) of boys with Duchenne muscular dystrophy met the criteria for autism spectrum disorders using the Autism Diagnostic Interview–Revised. According to the latest estimates from the Centers for Disease Control and Prevention (CDC), 1 in 68 children in the general population is born with an autism spectrum disorders.[39,40] An association between autism spectrum disorders and Duchenne muscular dystrophy mutations has been reported previously.[36] Mutations disrupting the Dp140 dystrophin isoform (exon 45-55) were found in 5/8 (62.5%) of patients with autism spectrum disorders and Duchenne muscular dystrophy in a cohort study of 158 patients with Duchenne muscular dystrophy.[36] The cognitive profile of patients with Duchenne muscular dystrophy and comorbid autism spectrum disorders has not been described hitherto.

Most boys with Duchenne muscular dystrophy cope well with their medical condition and are described as emotionally well adjusted.[41] However, the risk of emotional problems, such as anxiety or depression, in this population is almost twice that among healthy children, as seen in patients with other chronic medical conditions.[42-44] The incidence of obsessive-compulsive disorder has not been thoroughly examined in boys with Duchenne muscular dystrophy; however, parents of boys with Duchenne muscular dystrophy have reported 4.8% obsessive-like qualities behaviors in their boys.[6,7]

The purpose of the current study is to describe the cognitive and neurobehavioral profile of boys with Duchenne muscular dystrophy treated at the regional neuromuscular clinic at Holland Bloorview Kids Rehabilitation Hospital (Holland Bloorview). In addition, the authors sought to explore the relation of the neurodevelopmental profile with the Duchenne muscular dystrophy genotype. The authors hypothesized that boys with Duchenne muscular dystrophy and mutations affecting the Dp71or Dp140 isoforms are at higher risk of learning disability or intellectual disability and/or ADHD than boys without Duchenne muscular dystrophy, and that autism spectrum disorders is more frequent in Duchenne muscular dystrophy patients with mutations affecting the Dp140 isoform.

Patients and Methods

Patients

Holland Bloorview is Canada's largest children's rehabilitation hospital and is a tertiary referral center for children with neuromuscular disorders in the greater Toronto area and communities north of Toronto. The medical records of all male patients managed at the neuromuscular clinic over the past 10 years for Duchenne muscular dystrophy were reviewed.

The inclusion criteria were as follows: (1) clinical diagnosis of Duchenne muscular dystrophy, (2) genetic mutation identified in the dystrophin gene, (3) psychological assessment completed by the psychologist in the neuromuscular clinic before 19 years of age.

The exclusion criteria were as follows: (1) medical or surgical history of any condition that can potentially impact neurocognitive functioning (eg, significant head injury or brain tumor), (2) symptomatic carriers, and (3) not followed on a regular bases in the neuromuscular clinic (ie, second opinions, intermittent visits).

Eligible cases were identified using specific diagnostic codes as stipulated by the institution. The health records of the selected patients were reviewed, and data were collected for individuals meeting the inclusion criteria based on a data collection sheet created for this project.

Genetic Analysis

Genetic mutation in the dystrophin gene was confirmed by multiplex ligation-dependent probe amplification, polymerase chain reaction amplification or direct sequencing of all 79 exons and adjacent introns. The dystrophin gene mutations were classified and effects of the mutations were predicted using the Leiden dystrophin gene reading frame checker (www.dmd.nl/index.html). Dystrophin gene isoform disruption was predicted as outlined by Taylor et al[33] (Table 1).

Cognitive and Academic Assessment

All boys had psychology assessments done by the neuromuscular clinic child psychologist. For boys aged 7 years and above, the

Table 1. Dystrophin Isoforms.

Isoform	Location of premature truncation codon
Dp427m	Proximal to c.4072-296
Dp260 or Dp140 (utr)	Between c.4072-296 and c.6438+61447 or between c.6438+61447 and c.7381
Dp140	Between c.7381 and c.8218-790
Dp116	Between c.8218-790 and c.9225-5813
Dp71	Distal to c.9225-5813

Wechsler Intelligence Scale for Children (WISC-III or WISC-IV) was administered.[45] The WISC-IV is divided into 15 subtests, 10 of which formed part of the previous WISC-III. The 5 new subtests include 3 core tests—Picture Concepts, Letter-Number Sequencing, Matrix Reasoning—and 2 supplemental tests—Cancellation and Word Reasoning. Full-scale IQ was based on the total combined performance of the Verbal Comprehension Index, Perception Reasoning Index, Working Memory Index, and Processing Speed Index.[45] For boys aged 3 years to 7 years, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III or WPPSI-IV) was administered.[46] The WPPSI consists of 14 subtests; the core subtests are required for the computation of the verbal, performance, and full-scale IQ. In boys aged 16 and above the WISC-IV or the Wechsler Adult Intelligence Scale (WAIS) was administered.[47] The WAIS consisted of 6 verbal and 5 performance subtests. Verbal IQ, performance IQ, and full-scale IQ were obtained from it.

The cognitive function full-scale IQ was also measured by using the Stanford–Binet–IV in boys who couldn't perform any of the above IQ scales because of their ability. It's a standardized test that measures intelligence and cognitive ability children and adults, from age 2 through mature adulthood.[48] In addition the Leiter International Performance Scale – R was used.[49,50] This scale usually used for individuals with autism spectrum disorders, speech/language disorders, as well those with English as a second language.[51,52] It evaluates the nonverbal cognitive, attention, and neuropsychological abilities and targets typical as well as atypical children, adolescents and adults. It uses an engaging, nonverbal format and provides an IQ score, as well as percentile and age-equivalent scores for each subtest.

The Verbal Comprehension Profile measures the ability to analyze information and solve problems using language-based reasoning. The authors used the Verbal Comprehension Index scores from the WISC, WAIS, and WPPSI-IV plus Verbal Index scores from the WPPSI-III to evaluate the Verbal Comprehension Profile. The Perceptual Reasoning Index scores from the WISC and the WAIS plus Visual Spatial Index scores from the WPPSI-IV and the Performance Index scores from the WPPSI-III were used to evaluate the Visual Perception Profile, which looks at the ability to interpret and organize visual material and to produce and test hypotheses related to problem solving. The Verbal Comprehension–Visual Perception discrepancy was not measured because of the heterogeneity of the measures used.

The Wechsler Individual Achievement Test (WIAT-II and WIAT-III) was used to assess the academic achievement of the children and adolescents. It is a standardized test that is validated for children as young as 4 years to 85 years. The test assesses 4 basic skills: reading, math, writing, and oral language. For these items, there are a total of 9 subtest scores; however, the core subtests varied depending on the version of the WIAT that was administered.[53] The patients included in this study were not tested for all areas, but only in the areas of concern as reported by parents, the school, or a psychologist.

Cognitive and Neurobehavioral Comorbidities

Learning disability encompasses a number of disorders that can affect the acquisition, organization, retention, and understanding or use of verbal or nonverbal information. These disorders affect learning in individuals who otherwise demonstrate at least average abilities essential for thinking and/or reasoning. They are recognized by the academic achievement scores being significantly lower than expected on the basis of their level of cognitive functioning, or in some cases, average or stronger academic achievement that is attained only at the expense of unrealistically high levels of effort and/or support.[54,55]

Intellectual disability was defined according to the guidelines of the American Association of Intellectual and Developmental Disabilities on the basis of the following 3 criteria: (1) intellectual functioning level (IQ) below 70-75, (2) significant limitations exist in 2 or more adaptive skill areas, and (3) manifestation of the condition before the age of 18 years.[56]

The diagnosis of ADHD was made based on criteria of the Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision).[57,58] To assess symptoms of ADHD, the Conners 3rd Edition[59] was used in 4 of 19 boys; the long version of the Conners Parents Rating Scales–Revised and Conners Teachers Rating Scales–Revised[60,61] were used in 15 of the 19 boys diagnosed with ADHD. Out of the 15 boys who had the Conners Parents Rating Scales–Revised and Conners Teachers Rating Scales–Revised, 10 also had assessments of attention with the Test of Everyday Attention for Children.[62]

Autism spectrum disorders was diagnosed in all boys with autism spectrum disorders utilizing both the Diagnostic and Statistical Manual of Mental Disorders criteria[57,58] and the Autism Diagnostic Observation Schedule.[63]

Anxiety disorders and obsessive-compulsive disorder were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders criteria.[58,64]

Statistical Analysis

Statistical analyses were performed using SAS 9.3 and graphs were created in R 3.0.3. Frequency of comorbidities across the control and mutation group is reported along with 95% confidence limits estimated using exact methods. Equality of proportions across mutation groups was assessed using Fisher's exact test. The ranges of mean full-scale IQ and age are reported across groups according to the presence and absence of ADHD and autism spectrum disorders. The distribution of IQ is represented graphically as individual points for the different mutation groups separately. Overall, a modified boxplot was used so that the values in the upper and lower 25th percentiles are represented as individual points rather than whiskers.

Results

Patient Demographics

There were 201 individuals identified with dystrophinopathy seen in the neuromuscular clinic over the past 10 years. The authors excluded 74 of the 201 after the initial review; 8 of 74 had different or comorbid diagnoses, 28 were followed primarily by another institution, 13 had no psychology assessment (6 are less than 5 years of age, and 7 are on the waiting list for psychology assessment), 25 were older than 18 years of age. Of the 127 remaining, 90 had a neurodevelopmental diagnosis including 24 had either an ADHD, autism spectrum disorders,

Table 2. Demographic Information at Time of Psychology Assessment.

Age	Mean (minimum; maximum)
Age of DMD diagnosis	5.1 (1.3; 11.1)
Age of psychological assessment	9.8 (4.2; 18.9)
Corticosteroids (Deflazacort)	51/59 (86%)
School and educational support	N = 59 (%)
Public school	51 (86)
Regular class	52 (88)
Educational support	56 (94)
Formally recognized school exceptionality	56 (94)
Formal writing assessment	21 (35)
Computer access at school	23 (39)
Motor function	
Brooks scale (upper extremity)	N = 59 (%)
Arms at side, abducts arms in full circle until they touch above head	42 (71)
As above, but flexes elbows or uses accessory muscles	12 (20)
Raises 8 oz bottle/cup with liquid to mouth (1-2 hands)	1 (2)
Raises hands to mouth, but can't raise 8 oz bottle/cup	3 (5)
Used hands to hold pen, pick up small objects	1 (2)
Vignos scale (lower extremity)	N = 59 (%)
Walks and climbs stairs (minimum 1 step) independently	27 (46)
Walks and climbs stairs with railing	12 (20)
Walks and climbs stairs slowly with railing (>12 sec 4 standard stairs)	2 (3)
Walks unassisted, rises from chair but cannot climb stairs	7 (12)
Walks unassisted, cannot rise from chair or climb stairs	3 (5)
Walks only with assistance	2 (3)
Fulltime use of wheelchair	6 (10)

Abbreviation: DMD, Duchenne Muscular Dystrophy.

or anxiety diagnosis given by a developmental pediatrician but no psychology assessment done, 66 underwent psychological assessment. Seven were excluded in the analysis, as they did not have genetic testing. Demographic information was obtained for the 59 individuals who met the inclusion criteria (Table 2).

Psychological assessment was not part of the clinic routine assessment until 5 years ago. There were 3 main concerns raised by the parents and or the school at the time of the psychological assessment listed in (Table 3).

Genetic Analysis

Dystrophin gene mutation analysis predicted full-length dystrophin protein was not produced in all cases. The majority of mutations were intragenic deletions (74.5%). Single or multi-exon duplications accounted for 11.8% of patients, and point mutations, small deletions or insertions accounted for 13.7%. The Dp260_140utr isoform was disrupted in 76% while the fully translated Dp140 isoform was disrupted in only 28% of the patients. Only 5% had disruption of the Dp71 isoform (Figure 1).

Table 3. Family Concerns at the Time of the Psychological Assessment.

Cause of referral	N = 59 (%)
Academic concerns	46 (77)
Attention and hyperactivity	19 (32)
Behavioral ± social concerns	14 (23)

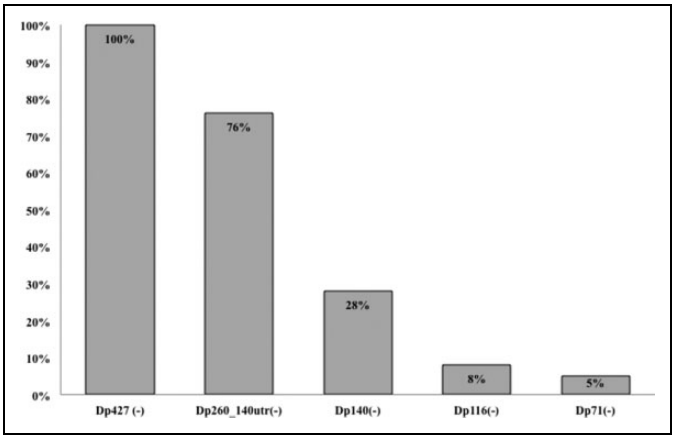

Figure 1. Dystrophin isoforms (N = 59): The distribution of the predicted dystrophin isoforms affected.

Cognitive Profile and Its Relation to the Dystrophin Isoforms

Sixteen of the 59 boys had full-scale IQ <70 (27.1%) with an overall mean full-scale IQ of 84.0 (with a 95% CI of 79.1; 89.0) (Figure 2). Disruption of Dp427 had a mean full-scale IQ of 82.0, the addition of Dp260_140utr had a similar average full-scale IQ of 85.0 and the addition of Dp140 had a lowered full-scale IQ of 75.0. Disruption of Dp71, in addition to the other isoforms had an even lower full-scale IQ of < 50.0. The mean Visual Perception Profile was 89.3 (with a 95% CI of 84.4; 94.3) and Verbal Comprehension Profile was 87.7 (with a 95% CI of 82.9; 92.5) (Figure 3).

The analysis of Verbal Comprehension Index and Verbal Index scores, which reflects the Verbal Comprehension Profile in the authors' cohort, and Perception Reasoning Index and Performance Index scores indexes, which reflect the Visual Perception Profile, showed that there was greater variation in the distribution with respect to the various dystrophin isoforms however, showed the same isoform trend as full-scale IQ (Figure 3).

Comorbidities and Their Relation With Dystrophin Isoforms

Learning disability was diagnosed in 44.0% (n = 26), intellectual disability in 18.6% (n = 11), ADHD in 32.2% (n = 19),

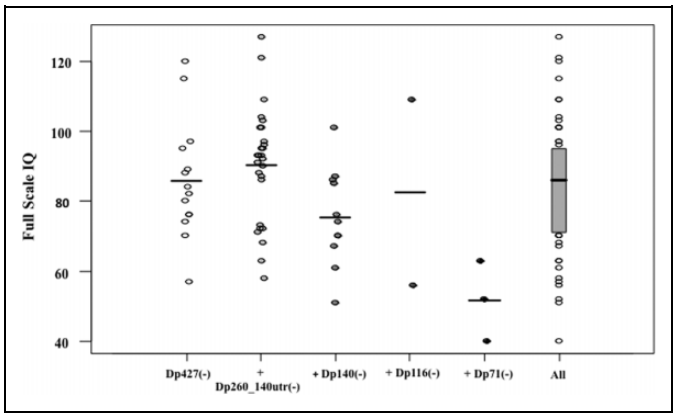

Figure 2. Observed full-scale IQ scores by mutation group. The overall distribution is shown using modified boxplot. The box extends from the first quartile to the third quartile, with a horizontal line representing the median value. Observations in the lower and upper 25 percentiles are represented as points, with filled circles to represent outliers.

autism spectrum disorders in 15.3% (n = 9), anxiety disorder in 27.1% (n = 16), and obsessive-compulsive disorder in 5.1% (n = 3) (Table 4).

ADHD was found in 9 of the 26 boys diagnosed with a learning disability (34.6%) and in 4 of the 11 boys with intellectual disability (36.3%). Eight of the 19 boys with ADHD (42.1%) took stimulant medication and 17 (89%) were taking corticosteroids. A similar proportion of boys without ADHD (85%) were also on corticosteroid medication (34/40). Ten of the 16 boys diagnosed with anxiety (62.5%) were treated with a selective serotonin reuptake inhibitors or serotonin-specific reuptake inhibitor.

In the boys with autism spectrum disorders, 4/9 had a comorbid learning disability (44.4%) and 1 had intellectual disability (11.1%). Anxiety was found in 4/9 (44.4%) and ADHD in 3/9 (33.3%). There were more than 2 comorbidities in addition to autism spectrum disorders in 33.3%.

The cognitive profile of boys diagnosed with ADHD and autism spectrum disorders showed that boys with Duchenne muscular dystrophy and ADHD had similar full-scale IQ compared with boys with only Duchenne muscular dystrophy (Table 6). However, boys with Duchenne muscular dystrophy and autism spectrum disorders had higher full-scale IQ scores compared to boys with only Duchenne muscular dystrophy. There were only 6 boys with Duchenne muscular dystrophy who had no other comorbidities. Their full-scale IQ was greater than the full-scale IQ of all boys with Duchenne muscular dystrophy. This was also seen with the Verbal Comprehension Profile and the Visual Perception Profile (Table 6). Only 1 of 6 had full-scale IQ less than 80.

There was no statistically significant relation between comorbidities and dystrophin isoforms (Figure 4). Although the analysis suggested the dystrophin isoform Dp427 contributes to learning disability ($P = .07$) and Dp260-140utr to anxiety ($P = .03$). Neither of these observations is considered statistically significant after adjusting for multiple comparisons. ADHD, autism spectrum disorders, and obsessive-compulsive disorder were much less affected by their mutations. Three boys had mutations disrupting the Dp71 isoform and 2 of them had an intellectual disability (Figure 4).

Discussion

Over the past 20 years, there has been increased focus on the cognitive and neurobehavioral profile in Duchenne muscular dystrophy. Previous studies suggest that this profile is non progressive, does not correlate with the severity of muscle disease, and primarily involves verbal rather than nonverbal intelligence.[3,10,65] Only a few studies have addressed the cognitive and neurodevelopmental profile in relation to the affected dystrophin isoforms.[16,18,19,33]

In the present study, 59 boys with Duchenne muscular dystrophy were assessed for cognitive and neurobehavioral disorders. In addition, the authors sought to determine the association between the disrupted Duchenne muscular dystrophy isoforms and the cognitive and neurodevelopmental profile. Similar to the authors' results, boys with Duchenne muscular dystrophy have been described to have a broad range of IQ scores however; they are more likely to have lower IQ and lower academic test scores than other children their age.[21,66] In the authors' population there was a lower mean full-scale IQ and a high proportion of boys with a learning disability. Although learning disability was not specifically diagnosed in other studies, it has been described that boys with Duchenne muscular dystrophy have challenges characterized by poor use of phonetic word analysis, and are at increased risk of academic challenges in math, reading, and writing skills.[22,26,28] In the current study a total of 62.6% of boys with Duchenne muscular dystrophy had a learning disability or intellectual disability. Secondary to the large proportion of the authors' cohort having learning issues, the authors strongly support the consensus care guidelines for Duchenne muscular dystrophy recommending formal psychological assessment.[67] In the authors' study population, the majority (94%) were formally recognized with exceptionality at their local schools. However, the authors feel that assistive technology (eg, writing aids, computers and appropriate software) is underutilized to optimize their learning.

When comparing full-scale IQ with disruption of the dystrophin isoforms, there was a trend toward a cumulative effect. This is consistent with Taylor et al's[33] observation when more dystrophin isoforms are disrupted there is a resultant decrease in full-scale IQ. This study further supports that the risk of cognitive deficit based on full-scale IQ can be attributable to the cumulative loss of dystrophin isoforms expressed in the central nervous system. Similar to the trend noted with full-scale IQ, the Visual Perception Profile (Perception Reasoning Index, Performance Index, and Visual Spatial Index scores) were lower for mutations that disrupt the Dp71 isoform compared to mutations that disrupted the other isoforms.

Previously, there have been reports of discordance between Performance IQ and Verbal IQ. This difference is not universally detected and when present, it is not considered to be

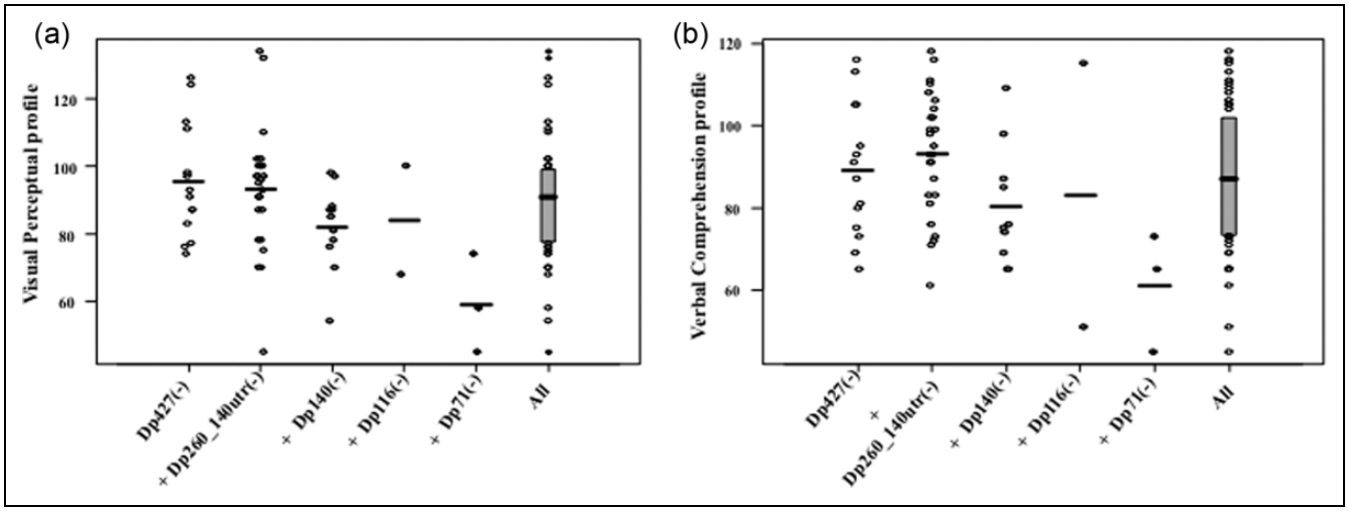

Figure 3. Observed IQ scores (Perception Reasoning Index/performance IQ/Visual Spatial Index = Visual Perception Profile, Verbal Comprehension Index/verbal IQ = Verbal Comprehension Profile) by mutation group. The overall distribution is shown using modified boxplot. The box extends from the first quartile to the third quartile, with a horizontal line representing the median value. Observations in the lower and upper 25 percentiles are represented as points, with filled circles to represent outliers.

Table 4. Prevalence of Comorbidities.

Comorbidity	% (95% CI)
LD	44.0 (31.2; 57.6)
ID	18.6 (9.7; 30.9)
ADHD	32.2 (20.6; 45.6)
ASD	15.3 (7.2; 27.0)
Anxiety	27.1 (16.4; 40.3)
OCD	5.1 (1.1; 14.2)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorders; ID, intellectual disability; LD, learning disability; OCD, obsessive-compulsive disorder.

significant.[21,65] This is not consistent with the authors' data, which can reflect the changes over time in how this is evaluated, the authors' sample size and the age when the psychological assessment was completed. Verbal Comprehension Profile (Verbal Comprehension Index and Verbal Index scores) was lower in boys with mutation disrupting the Dp71 isoform, while that of those with mutations affecting Dp427 and Dp260_140utr was slightly greater than the other isoform disruption.

The diagnosis of ADHD was confirmed in 32.2%, which is increased compared to typical school age children (8 to10%).[32] This is consistent with the previous reports of ADHD in boys with Duchenne muscular dystrophy (12% to 50%).[6,31,68] It has been reported that ADHD is diagnosed in up to 20% of childhood illnesses that involve the brain, for example, epilepsy.[69] It is important for clinicians, parents and educators who follow boys with Duchenne muscular dystrophy to be aware that ADHD is present at a higher frequency in boys with Duchenne muscular dystrophy. Teenagers and young adults with untreated ADHD can have ongoing issues with impulsivity, can fail to think through the consequences of their decisions, can be unable to finish what they start, and can have poor judgment. The consequence of untreated and unrecognized ADHD impacts the quality of life, social interactions with peers, and smooth transition to adulthood.[70]

The effect of corticosteroid on behavior is controversial; it has been reported that the long-term effect of prolonged corticosteroid exposure on behavior might be associated with initial mood swings and memory and attention problems that stabilize with time.[71] In this study, the authors found no significant relation between corticosteroid therapy and ADHD; as 85% of boys without ADHD were on corticosteroids therapy at the time of the psychology assessment. This is consistent with previous reports on Duchenne muscular dystrophy and ADHD.[13] The authors did not analyze their results for the groups on corticosteroid therapy comparing the untreated group, as there was no obvious bias in the authors' result.

Anxiety and obsessive-compulsive disorder has been described as more frequent in Duchenne muscular dystrophy.[6,7] Anxiety was present in 27% of the authors' cohort, which is consistent with the range estimated in childhood (10 to 30%).[72] The frequency of obsessive-compulsive disorder behaviors has been reported in boys with Duchenne muscular dystrophy to be 4.8%,[6] which is consistent the diagnosis of obsessive-compulsive disorder with the authors' cohort (5%). This is double the rate described in typical children (2 to 3%).[73] Anxiety disorders and obsessive-compulsive disorder are often chronic conditions when left untreated. The nature of the symptoms can change across child and adolescent development; however, both anxiety and obsessive-compulsive disorder put individuals at higher risk of educational underachievement, increased risk for depression,[74] substance abuse and/or dependence and suicide, as well as other significant functional impairments that can extend into adulthood.[75,76] Anxiety disorders are often co-occurring with other disorders such as depression, and ADHD.[77,78]

Table 5. Cognitive Profile of Boys With DMD and Boys With DMD ± ADHD and ASD.

Mean (minimum; maximum)	No ADHD or ASD (n = 34)	ADHD only (n = 16)	ASD only (n = 6)	ADHD and ASD (n = 3)
Full-scale IQ	82.5 (40; 121)	85.0 (52; 127)	91.5 (73; 120)	81.0 (70; 87)
Verbal Comprehension Profile (VCI+VI)	87.2 (45; 118)	86.7 (65; 113)	91.3 (69; 116)	[a] (91; 93)
Visual Perception Profile (PRI+VSI+PI)	89.3 (45; 134)	87.3 (45; 132)	93.5 (78; 126)	[a] (91; 95)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorders; DMD, Duchenne muscular dystrophy; ID, intellectual disability; LD, learning disability; OCD, obsessive-compulsive disorder; PI, Performance Index; PRI, Perceptual Reasoning Index; VCI, Verbal Comprehension Index; VI, Verbal Index; VSI, Visual Spatial Index.
[a]Only 2 values available; observed values are given.

Table 6. Cognitive Profile of Boys With DMD and No Cognitive or Neurobehavioral Comorbidities.

Variable	n	Mean	95% CI
Full-scale IQ	6	94.3	(76.8; 111.9)
Verbal Comprehension Profile	6	94.7	(77.7; 111.6)
Visual Perception Profile	6	99.3	(79.3; 110.3)

Abbreviation: DMD, Duchenne Muscular Dystrophy.

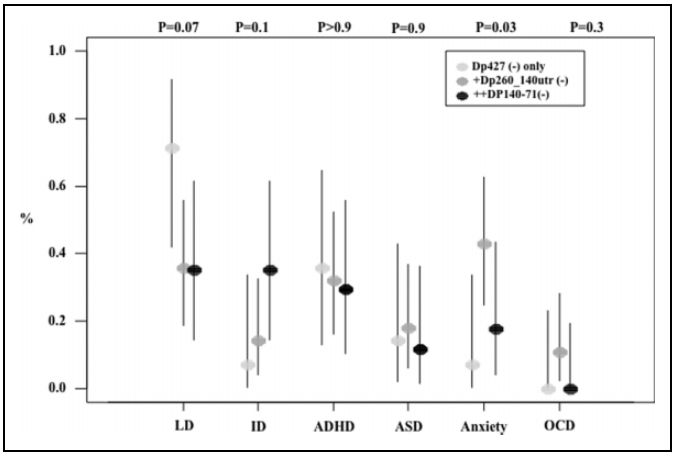

Figure 4. Prevalence and 95% confidence limit of comorbidities by affected dystrophin isoform. *P* value is obtained using Fisher's exact test to look for differences in prevalence for each comorbidity across the 3 groups.

It has been suggested that boys with Duchenne muscular dystrophy are at increased risk of autism spectrum disorders with an incidence up to 19% to 26%.[36,38] In the present study, 15% (9/59) of boys with Duchenne muscular dystrophy met the criteria for autism spectrum disorders. This rate is considerably elevated compared to latest estimates from the CDC (1 in 68 live births).[40] Therefore, it is important to screen for autism spectrum disorders when assessing patients with Duchenne muscular dystrophy as early identification facilitates referral to the appropriate programs and resources and impacts their overall care. The majority of boys with Duchenne muscular dystrophy and autism spectrum disorders had near normal intellectual function. In contrast other genetic neurodevelopmental disorders including tuberous sclerosis, fragile X, Angelman, Prader-Willi, De Lange, Smith-Lemli Opitz, and velocardiofacial syndromes, that have higher than expected rates of autism spectrum disorders (16 to 65%) but generally do not have normal intellectual function.[79] One child of the 9 diagnosed with autism spectrum disorder) in the present cohort had a full-scale IQ of 70 and a comorbid diagnosis of intellectual disability. Further studies that systematically assess autism spectrum disorders in Duchenne muscular dystrophy are required to better understand this profile.

Another important finding in this study is the overlap of diagnoses. A total of 12 of the 59 (20%) boys had 2 comorbidities and 3 of the 59 (5%) had a comorbidity between the 3 neuropsychiatric disorders. The combination of learning disability and ADHD is also quite common in the literature, up to 20% to 25%,[80] and was the most prevalent comorbidity in the authors' study 34.6%.[67] Only 10% did not have cognitive or neurobehavioral diagnosis supporting the importance of comprehensive screening.

There is no statistically significant relationship between the cognitive and neurodevelopmental profile and isoform disruption in the authors' population however this might be a reflection of the small sample size. However, the authors found that the Dp71 and Dp140 isoforms are associated with a high risk of learning disability or intellectual disability and/or ADHD and that autism spectrum disorders is more frequent in Duchenne muscular dystrophy patients with mutation of the Dp140 isoform, which is similar to what has been reported.[36] In addition, this study explored the cognitive profile of boys with Duchenne muscular dystrophy and comorbid autism spectrum disorders, which has not yet been described in the literature.

Pathophysiologically, the decreased average full-scale IQ, and increased risk of learning disability, intellectual disability, ADHD, autism spectrum disorders, anxiety and obsessive-compulsive disorder in boys with Duchenne muscular dystrophy can be related to dystrophin expression in the brain or the effect of dystrophin on other central nervous system proteins.[81,82] The Dp427 isoform is disrupted in all patients with Duchenne muscular dystrophy. This isoform is expressed in the hippocampus and purkinje cells of the cerebellum.[83,84] Both structures are part of a network that connects with the frontal lobe, which plays an important role in human memory[85] and is responsible for executive functions such as planning for the future, decision-making skills, judgment, attention span, and inhibition.[86] In addition, it has been reported that Dp140 is expressed in the brain and plays an important role in synaptic transmission.[15,87-90] A recent study used quantitative magnetic resonance imaging to study brain microstructure in Duchenne

muscular dystrophy[91] showed that Duchenne muscular dystrophy patients had smaller total brain volume, smaller gray matter volume, lower white matter fractional anisotropy, and higher white matter mean and radial diffusivity than healthy controls. In addition, they reported that the disruption of the Dp140 isoforms contributed mostly to the gray matter volume differences and poor performed on information processing. This supports the important role for the Dp140 dystrophin isoform in cerebral development.[91] Dp71 is expressed in the hippocampus and some layers of the cerebral cortex however, the function of Dp71 remains unknown.[90,92,93] Although the authors do not know the specific relationship between the loss of dystrophin isoforms in the brain and function, there appears to be a trend toward the cumulative affect associated with a higher risk of cognitive impairment and disruption of Dp427 in individuals with learning disability, and Dp260_140 with anxiety.[16,18-20]

Conclusion

Secondary to the decreased mean full-scale IQ and elevated rate of learning disability in boys with Duchenne muscular dystrophy, the authors recommend routine educational psychology screening, which is consistent with the consensus care guidelines. Furthermore, the authors recommend expanding the evaluations to ensure the neurobehavioral comorbidities including ADHD, autism spectrum disorders, anxiety, and obsessive-compulsive disorder are evaluated. Both the cognitive and neurobehavioral comorbidities impact quality of life if not recognized or addressed. Early identification facilitates education planning, provisions for family support, management of family stress, and delivery of appropriate medical care and treatment of associated conditions. The cognitive and neurodevelopmental profile also impacts the skills that need to be developed for a successful transition to adulthood.

At this time, it's clear that the disruption of the dystrophin gene impacts brain function. However, the relationship between dystrophin isoforms and the cognitive and neurobehavioral profile is not definitive. A thorough cognitive and neurobehavioral evaluation and development of appropriate interventions needs to be tailored to the individual regardless of the dystrophin gene mutations.

Future studies could include longitudinal data to examine if cognitive function in Duchenne muscular dystrophy is static or changes overtime, which is important in counseling and future planning.

Limitations

There are several variables that might have influenced the outcome of this study. The sample size is small although similar in numbers to other studies in Duchenne muscular dystrophy. Therefore, the study might not have the power necessary to evaluate the influence of dystrophin isoforms on the cognitive and neurodevelopmental profile. In addition, since this is a retrospective study some of the standardized assessments changed versions and not all assessments were consistently completed. Last, the psychology assessment was not routinely ordered in the neuromuscular clinic until 5 years ago. Therefore, this can overrepresent the frequency of learning disability; however, the rate of ADHD and obsessive-compulsive disorder is consistent with what has been previously reported in the literature.

Author Contributions

RB contributed to the study conception and design, wrote the proposal, and applied for Research Ethics Board approval. She collected the main data, helped with psychology data collection, prepared all the data for analysis, and participated in the data analysis and interpretation. She also wrote the first draft and edited and finalized the manuscript after all the contributing authors reviewed it. She presented the research project design and preliminary results at Holland Bloorview resident research day. SS contributed to the study conception and design, reviewed the initial proposal, and assisted with Research Ethics Board application. She was involved in the data analysis and interpretation. In addition, she provided a critical revision of the manuscript. GY contributed to the study conception and design, confirmed the genetic mutation, predicted the Duchenne muscular dystrophy gene mutation on isoform disruption, and assisted with the genetic description in the manuscript. In addition, she provided a critical revision of the manuscript. AD performed the more advanced statistical analysis and interpretation of data. She generated the first draft of the figures and statistical tables. In addition, she provided input regarding the statistical analysis portion of the manuscript and provided a critical revision of the whole manuscript. MM collected the psychoeducational assessment data and reviewed the manuscript. AS provided her psychology input to the study design as the neuromuscular clinic child psychologist and revised the psychology assessment data collection sheet and the cognitive and academic assessment part in both the initial study proposal and final manuscript. She assisted in the psychology assessment data collection. In addition, she reviewed the final version of the manuscript. LM built the study conception and design, as a primary investigator, selected the collaborators, and supervised the first author in ongoing management of the project. In addition, she was involved in the collection, analysis and interpretation of data and the revision and edition of the manuscript and finalizing it with the first author to be ready for publication. She presented preliminary results at an international congress. She is the Duchenne muscular dystrophy specialist in the neuromuscular clinic.

Declaration of Conflicting Interests

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The Research Ethics Board of the Holland Bloorview Kids Rehabilitation Hospital, Toronto, Ontario, Canada approved the study. Research Ethics Board approval 13-378.

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