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Association of Autistic Spectrum Disorders With Dystrophinopathies

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Parents of 85 boys with dystrophinopathies and 51 sibling controls completed the Social Communication Questionnaire, describing child behaviors associated with autism spectrum disorders and a rating of parental stress. Twenty-one boys with dystrophinopathies and no siblings received scores above the cut-point for possible autistic spectrum disorders. Mothers of identified children were given detailed interviews using the Autism Diagnostic Interview-Revised, and 16 boys (about 19% of the sample) met the criteria for autism spectrum disorders. Significant qualitative abnormalities in reciprocal social interactions and communication were evident in all, whereas restricted and repetitive behaviors were generally less pronounced in the group. Moreover, parents of boys with dystrophinopathy and autism spectrum disorders demonstrated significantly higher ratings of stress than parents of boys with dystrophinopathy alone. Increased attention to behavioral concerns associated with dystrophinopathies is necessary to ensure the well-being of the whole family. © 2009 by Elsevier Inc. All rights reserved.

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Introduction

Autistic spectrum disorders (defined as children less than 3 years of age presenting with significant qualitative abnormalities in reciprocal social interactions and communication, along with restricted or repetitive behaviors) occur at

a much higher than chance frequency in a number of neurodevelopmental disorders [1]. Recent evidence also indicates an association between autistic spectrum disorders and dystrophinopathy, (including Duchenne and Becker muscular dystrophies) that is not evident among other pediatric neuromuscular disorders. A review of 158 patients in a Boston neuromuscular clinic indicated that about 4% of their patients with dystrophinopathies exhibited autism spectrum disorders [2]. In a survey of the parents of 351 children with dystrophinopathies from the Netherlands and United States, 11 reported a son with a diagnosis of autistic spectrum disorders (or 3.1%) [3]. A similar survey from the northern United Kingdom revealed that 5% of patients with dystrophinopathies had also received a diagnosis of autistic spectrum disorders [4]. Moreover, the United Kingdom study reported that a surprising 37% of patients with Becker muscular dystrophy manifested associated autism spectrum disorders. These numbers suggest a strong association between dystrophinopathies and autism spectrum disorders, and add to the few previously described case studies of children with both dystrophinopathy and autism [5,6].

Although most children with dystrophinopathies are clearly not autistic, many may exhibit mild behaviors on the spectrum. When compared with either the general population or children with other neuromuscular disorders, parents of children with dystrophinopathies rate the presence of behaviors associated with the autism spectrum (e.g., social problems and communication difficulties) significantly more frequently than expected. Our survey examining parental ratings of behavior in a sample of 181 boys with dystrophinopathies from the United States demonstrated that about a third exhibited significant social problems [7]. Likewise, in the United Kingdom survey described above, about one third of the parents of 45 boys with

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dystrophinopathies indicated unexpectedly high levels of social and communication difficulties [4].

On direct testing, evidence suggests a pattern of cognitive deficits reminiscent of that seen in pervasive developmental disorders, or a mild version of autistic spectrum disorders. Children with dystrophinopathies tend to exhibit stronger nonverbal than verbal skills [8-11], early language delays [12-14], deficits in their narrative speech [15], and academic difficulties [16-20]. Few data have directly examined social skills, in part because these are generally not as readily assessed. However, we examined children with dystrophinopathies on a matching-to-sample task, and discovered that boys of normal intellectual function were accurate at matching objects and faces, yet manifested mild difficulty matching affect, a finding that was previously observed among children with pervasive developmental disorders [21].

An examination of parent ratings of stress levels among 127 families with a child with dystrophinopathies indicated that the child's behavior (as measured by the total behavior scale on the Child Behavior Checklist [22]) contributed significantly to parents' reports of increased stress [23]. Moreover, the data showed that a child's behavior contributed more to parental stress levels than did measures of a child's physical disability, estimated intelligence quotient, and demographic characteristics of the family. Although these data did not specifically examine autistic-spectrum behaviors, they highlight that the impact of a child's behavior appears to have a greater negative consequence on parental functioning than either his physical or intellectual disability.

Taken together, these data suggest that a sizeable number of children diagnosed with dystrophinopathies may possess compromised social and communication skills, and that the presentation of these behaviors may have significant consequences for a family. The present study was undertaken to examine these characteristics in greater depth among a sample of children with dystrophinopathies. Parents of children participating in a neuropsychologic study of dystrophinopathies were surveyed for evidence of potential autistic spectrum disorders in their children, using the Social Communication Questionnaire [24]. Those who scored above a set cut-point were then administered the Autism Diagnostic Interview-Revised [25], the current "gold standard" for diagnosis of autistic spectrum disorders. Post hoc analyses of the Parenting Stress Index-Short Form [26] were used to examine the contribution of a diagnosis of autistic spectrum disorder to parental stress ratings.

The study objectives were to: (1) determine the number of children who met the criteria for autistic spectrum disorder among our sample, (2) describe the presentation of these behaviors, (3) seek similarities across patients that may be consistent with a dystrophinopathy-associated phenotype, and (4) examine the impact of a diagnosis of autistic spectrum disorder on parental stress within this sample.

Methods

Participants

Eighty-five boys with dystrophinopathies were studied. Children were recruited to participate in one of two ongoing neuropsychologic studies of dystrophinopathies. A newsletter describing the studies was distributed through private physicians associated with the Muscular Dystrophy Association and the Parent Project Muscular Dystrophy. Children were ascertained across a number of states in the United States, including New York, New Jersey, Georgia, Ohio, Missouri, Virginia, Maryland, and Connecticut. Families with a child diagnosed with dystrophinopathy who were interested in participating responded directly to the research coordinator.

All participants with dystrophinopathy were boys between 6-16 years of age who were otherwise in good health, spoke English, and were willing to participate. Where possible, one healthy sibling without dystrophinopathy was recruited for each proband. Selection criteria included age between 6-16 years, age within 5 years of the proband's age, good general health, English as primary language, and willingness to participate. Where more than one control participant was available, preference was given first to males and then to closeness of age. A total of 51 siblings met these criteria and participated. Twenty-three control participants were male, and 28 were female. All sibling pairs were from separate families.

Procedure

The present study was approved by the New York Presbyterian Hospital's Institutional Review Board. Before data collection, parents of all child participants provided written, informed consent, and all participants gave verbal assent.

Children were tested either at New York Presbyterian Hospital or in a quiet room at home. For children who lived outside the clinic's immediate area, research assistants traveled to their homes for the evaluation. Parents completed questionnaires while their children were being tested.

Parental questionnaires were scored, and for those whose responses suggested that their child exhibited an autistic spectrum disorder, interviews were scheduled with the principal investigator. Because of geographic constraints, the majority of interviews were conducted over the telephone, although two were performed in person. In all but one case, the child's mother was interviewed, because mothers deemed themselves the best informants about their children.

Measures

All children and their mothers received an estimate of language comprehension. Participants were individually administered the Peabody Picture Vocabulary Test-III, an untimed test of receptive vocabulary [27]. The Peabody Picture Vocabulary Test-III is appropriate for use across a wide age range and range of intellectual function, and does not involve any significant motor response that might confound performances among physically disabled children. Raw scores are converted to age-referenced standard scores, with a mean of 100 and standard deviation of 15. Children also received the Raven's Coloured Matrices, a nonverbal measure of intellectual function [28]. Other neuropsychologic tests were administered according to the study in which each child participated. Those data will be detailed elsewhere.

Parents completed the Social Communication Questionnaire [24], a 40-item questionnaire designed to screen for autistic spectrum disorder. Questions about a child's social interactions, communication skills, and presence of stereotyped behaviors are answered in a "yes" or "no" format. Scores of ≥ 15 are accepted as the standard cut-point for possible autistic spectrum disorders. The Social Communication Questionnaire demonstrates good psychometric properties, with a sensitivity of 0.92 and a specificity of 0.62 [29]. To catch a broader number of participants who may exhibit signs of autistic spectrum disorders, we set the cut-point at 12 for inclusion in the follow-up interview.

The Autism Diagnostic Interview-Revised was administered by a trained and certified interviewer (V.J.H.) [25]. The Autism Diagnostic Interview-Revised is a standardized, investigator-based interview based on the Diagnostic and Statistical Manual of Mental Disorders-IV [30] and International Classification of Diseases [31] criteria for autism. The interview is designed to probe for detailed descriptions of a target child's behavior. Parents respond to up to 93 questions about their child's behavior in four circumscribed domains: (1) qualitative impairments in reciprocal social interactions; (2) qualitative impairments in communication abilities; (3) restricted, repetitive, or stereotyped behavior; and (4) the appearance of behavioral concerns before 3 years of age. Parents are encouraged to describe clear examples of a child's behavior at his current age and when he was 4-5 years old. Interviews generally range from 2-3 hours' duration. Items are rated on a scale of 0-3, depending on the severity of a behavior. Tallies are made of the points within each domain of interest, and standard cut-points are used for each domain to determine whether behaviors are indicative of significant impairment. A diagnostic algorithm is determined by parents' responses about a child's behavior during his 4-5-year-old time-point on 42 of the interview items.

Parents also completed questionnaires about their child's development and demographic characteristics and the Parenting Stress Index-Short Form [26]. The Parenting Stress Index is a self-report measure developed from the perspective that the stress a parent experiences is a function of the characteristics of both the child and the parent, as well as their unique style of interaction. It contains 36 items in three subscales: parental distress (emotional distress in the parenting role), parent-child dysfunctional interaction (problematic parent-child interactions), and difficult child (problematic child behaviors or demands). A total raw score of >90 indicates elevated stress, because it falls above the 90th percentile in the normative group. In addition, a defensive responding scale is computed, based on items commonly endorsed by all parents, to determine whether a respondent's answers should be considered valid. A score of <11 on the defensive responding scale is considered "defensive," and the Parenting Stress Interview-Short Form's validity is therefore questionable.

Analyses

Tallies were made of the number of children in each group who scored above the set cut-point for the Social Communication Questionnaire, and χ^2 analyses were run to determine between-group differences. We used *t* tests to examine between-group differences in terms of age and cognitive test scores. Autism Diagnostic Interview-Revised data were examined in two ways. Tallies of scores above set cut-points for each domain were made, and percentages were reported. In addition, recorded responses were described qualitatively, to explore consistencies across participants.

After determining which children met the criteria for autistic spectrum disorder, post hoc analyses were used to examine parental stress. Only data from parents whose scores were >11 on the defensive responding scale were analyzed. Scores from parents of children with dystrophinopathy and Social Communication Questionnaires scores that were <12 were compared with those from parents of children with dystrophinopathy and autistic spectrum disorder, applying a *t* test to the total score.

Results

Social Communication Questionnaire

Twenty-one children (or 25%) in the dystrophinopathies group, and no sibling control subjects, scored at or above the set cut-point of 12 on the Social Communication Questionnaire ($\chi^2 = 14.25, P < 0.01$). Table 1 describes their characteristics. Children ranged in age from 6-14 years and had receptive vocabularies that ranged from "borderline impaired" to "average," and their Social Communication Questionnaire scores ranged from 12-28. Four boys

Table 1. Characteristics of DMD/BMD sample, cut by score on SCQ

	SCQ ≥ 12 (n = 21)	SCQ <12 (n = 64)	Difference
Age range, in years	6-14	6-16	
	7.76 \pm 2.62*	8.05 \pm 2.16*	<i>t</i> = 0.5, ns
PPVT-III	40-115	72-140	
Standard score	90.05 \pm 21.77*	106.41 \pm 12.39*	<i>t</i> = 4.13, <i>P</i> < 0.01
Raven's CM	69-113	65-131	
Standard score	102. \pm 13.19*	101.55 \pm 13.11*	<i>t</i> = 0.12, ns
Maternal PPVT-III	70-125	76-119	
Standard score	102.56 \pm 14.52*	98.36 \pm 12.21*	<i>t</i> = 1.44, ns
% with BMD (vs DMD)	19%	10%	$\chi^2 = 1.3$, ns
Median income	\$60,000-99,999	\$60,000-99,999	$\chi^2 = 9.14$, ns

* Mean \pm S.D.

Abbreviations:
 BMD = Becker muscular dystrophy
 DMD = Duchenne muscular dystrophy
 ns = No significance
 PPVT-III = Peabody Picture Vocabulary Test III
 Raven's CM = Raven's Coloured Matrices
 SCQ = Social Communication Questionnaire

were diagnosed with Becker muscular dystrophy, and the remainder manifested Duchenne muscular dystrophy. Three mothers were adoptive parents. All parents were well-educated (years of education ranged from high school graduate to professional degree) and from middle to upper socioeconomic households (income range, \$29,999 to over \$150,000). Twenty were Caucasian, and one was of East Indian background.

Comparisons with the remainder of the sample indicated that the selected children had lower receptive vocabulary scores (*t* = 3.97, *P* < 0.01) than the children with dystrophinopathies whose Social Communication Questionnaire scores were <12. The groups did not differ regarding measures of nonverbal intelligence quotient, age, maternal vocabulary scores, or family socioeconomic level.

Autism Diagnostic Interview-Revised, Diagnostic Algorithm (Age 4-5 Years)

Of 21 participants who scored at ≥ 12 on the Social Communication Questionnaire, diagnostic interviews were completed with 19 mothers (Fig 1). Two guardians had insufficient experience with their child during the crucial 4-5-year time point to conduct a valid interview. One child had been adopted from a Russian orphanage at age 5 years, and another child had been adopted by his grandmother at age 7 years. One family could not be contacted to schedule an interview.

Table 2 lists how the 19 participants who completed the Autism Diagnostic Interview-Revised scored on each of the four domains. Thirteen children met all four criteria for a diagnosis of autistic spectrum disorder. Three additional children met three of the four criteria. Thus, based on the

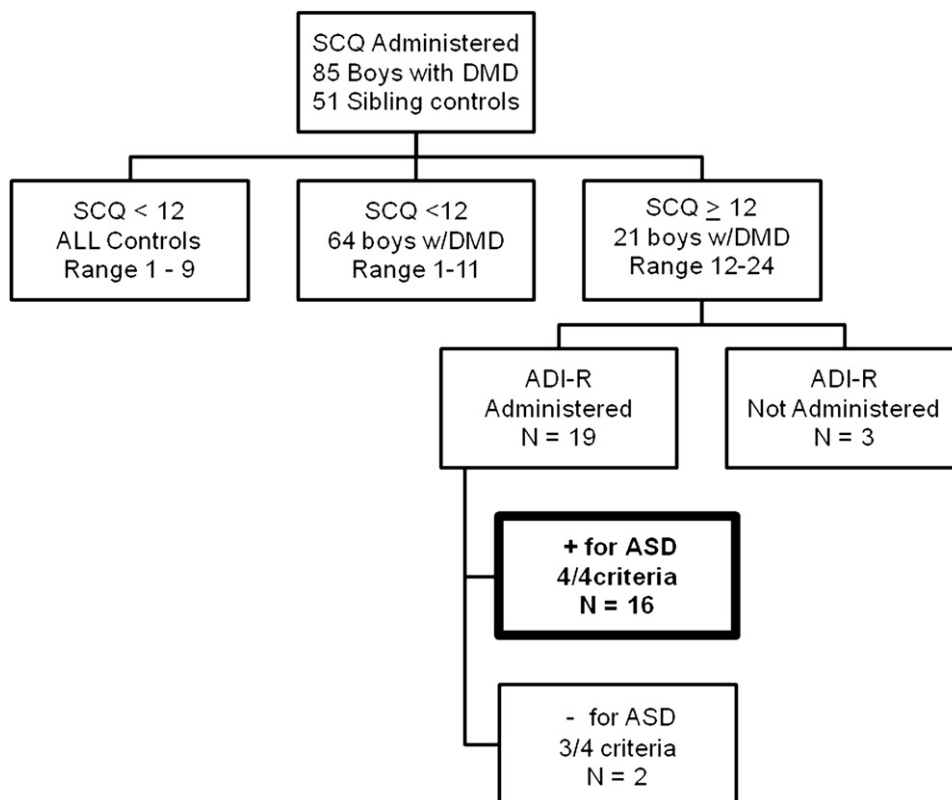


Figure 1. One hundred and thirty-six children (85 boys with dystrophinopathies, and 51 control subjects) were screened using the Social Communication Questionnaire. Of those, 21 boys with dystrophinopathy scored above the set cut-point, and 19 of those received the Autism Diagnostic Interview-Revised. A total of 16 boys with dystrophinopathy, and no control subjects, met full criteria for autistic spectrum disorder. DMD = dystrophinopathies; SCQ = Social Communication Questionnaire; ADI-R = Autism Diagnostic Interview-Revised; ASD = autistic spectrum disorder.

original number of 85 children with dystrophinopathies, the rates of autistic spectrum disorder among this sample ranged from 15-19%.

Table 3 presents specific characteristics of the Autism Diagnostic Interview responses for the 16 children who scored positive for autistic spectrum disorder.

Significant qualitative abnormalities in reciprocal social interactions were described in all 16 children. Overall, this was the domain where parents tended to report that their children had the greatest difficulties. Many respondents reported that their children rarely made eye contact or responded to social smiles. One mother described her son as “so focused on something he doesn’t notice anything else.” The majority of children demonstrated little interest

in other children, even when approached by another child, and did not join in group games. Most children did not offer to share. Many did not offer comfort if another was upset. Further, they were described as exhibiting inappropriate social responses that generally reflected an unawareness of the suitable behavior for a situation (such as a loud voice in a library), but not odd or unusual behaviors. In general, each child was described as keeping to himself and “doing his own thing,” with little or no awareness of others.

Significant qualitative abnormalities in communication were described in all 16 children. Difficulty with social conversation was the most prominent deficit reported. All the children were verbal and spoke in sentences, although the quality of their language was quite variable. Some were described as “talking all the time, but not saying anything to anyone.” All parents reported significant limitations in both social chatting and reciprocal conversational speech. Most children, however, were not described as using peculiar speech, with few reports of neologisms. Nonverbal means of communication were not reported to be as impaired as verbal communication. However, few children pointed and used gestures appropriately. Most children played with toys, yet their play repertoire was limited and lacked an imaginative quality. For example, a number of the boys were described as playing with toy cars in a manner that involved stacking the cars or lining them up or washing them, but with no obvious signs of pretending to drive the

Table 2. Number of 19 children with DMD or BMD who scored above cut-points

ADI-R Domain	Lifetime Rating	Current Age
Reciprocal social interaction	16	8
Communication	16	8
Restricted, repetitive behaviors	14	10
Apparent before age 3 years	17	17

Abbreviations:
 ADI-R = Autism Diagnostic Interview-Revised
 BMD = Becker muscular dystrophy
 DMD = Duchenne muscular dystrophy

Table 3. Percentages of 16 children with DMD or BMD receiving a score of 2 (definitely abnormal) on individual items on the ADI-R

Behavior	Lifetime Rating	Current Age
Direct gaze	56%	Not applicable
Social smiling	37%	12%
Range of facial expressions	19%	0%
Imaginative play with peers	62%	19%
Interest in children	62%	19%
Response to children	50%	0%
Group play with peers	69%	19%
Directing attention	56%	12%
Offering to share	81%	44%
Seeking to share enjoyment	19%	0%
Use of other's body to communicate	6%	0%
Offering comfort	62%	12%
Quality of social overtures	62%	0%
Inappropriate facial emotions	19%	6%
Appropriateness of social response	69%	31%
Pointing to express interest	25%	6%
Nodding	37%	12%
Head shaking	31%	6%
Conventional or instrumental gestures	56%	31%
Spontaneous imitation of actions	37%	6%
Imaginative play	37%	12%
Imitative social play	44%	0%
Social verbalization/chat	88%	19%
Reciprocal conversation	94%	25%
Stereotyped utterances	31%	6%
Inappropriate questions	25%	12%
Pronominal reversal	38%	6%
Neologisms	6%	0%
Unusual preoccupations	12%	12%
Circumscribed interests	25%	25%
Verbal rituals	44%	25%
Compulsions or rituals	31%	12%
Hand or finger mannerisms	12%	6%
Complex body mannerisms	12%	0%
Repetitive use of objects	31%	6%
Unusual sensory interests	6%	0%

Abbreviations:
ADI-R = Autism Diagnostic Interview-Revised.
BMD = Becker muscular dystrophy
DMD = Duchenne muscular dystrophy

cars or acting out stories with the cars. There were no reports of children playing with unusual objects or parts of objects in a very stereotyped, repetitive manner.

Restricted, repetitive, and stereotyped behaviors were evident in many of the children, but not all scored above the cut-point for this domain (13/16). Many children reportedly exhibited circumscribed interests. The choice of topics was not unusual, involving cars, the weather, and baseball statistics, for instance. Although these interests were described as intense, most were not compelling enough to constitute a definite autistic type of abnormality. Many children were also described as performing mild verbal rituals, generally reported as reciting an appropriate statement repetitively. For example, whenever one child saw a car, he cried over and over again, "Look at the car! Look at the car!" Only two parents reported unusual preoccupations

in their children. One was described as talking "incessantly about tornadoes," and the other was unusually focused on maps. Many reported difficulties with minor changes in their child's routines, yet more overt compulsions and rituals were not a predominant characteristic of the group. Few children were reported to exhibit odd finger or hand movements or complex body movements, and there was only one report of hand-flapping (and then only when the boy became very excited). All the children were described as being affectionate and cuddly with their mothers. Many of the boys disliked loud noises, but there were no other indications of unusual sensory defensiveness. There were no reports of any uncharacteristically high levels of skill in a circumscribed area or other savant qualities.

In all cases, parents reported awareness of some type of developmental delay before their child was 3 years old. Further, parents were aware of developmental delays before they ever received a diagnosis of muscular dystrophy. No parent reported any regression in development.

Autism Diagnostic Interview-Revised, Behavior at Current Age

Table 2 presents each participant's score at time of interview. Children's ages ranged from 6-14 years. Notable improvements are evident between the two time points, particularly in reciprocal social skills and communication domains. Moreover, larger gains were generally evident among older children and those with lower Social Communication Questionnaire scores. During interviews, all mothers described significant improvements in their children's behavior with time. Although substantial qualitative impairments persisted in some children, the scores of about half the children no longer fell above the cut-points, suggesting much milder manifestations of the behaviors. Some behaviors appeared to be particularly responsive to age. For example, parents reported a much improved quality of social overtures, indicating that with time, the children learned how to coordinate their gaze and language to gain another's attention appropriately. The boys also exhibited improved responses to other children, indicating awareness and openness to another child's approach.

Interestingly, although the domain of restricted, repetitive, and stereotyped behaviors contained fewer children with significant impairment during the 4-5-year-old period, those who did manifest impairments were resistant to change over time. Parents reported the fewest gains in this area, and a few suggested that these impairments had become more pronounced. For example, one mother described that her son was preoccupied with wiring to the point that whenever he entered a new home, he repeatedly asked to be told about the wiring.

Parenting Stress

Parenting stress scores from 12 parents whose child was diagnosed with autistic spectrum disorders were significantly

higher than those obtained from 55 parents of children with dystrophinopathies who scored <12 on the Social Communication Questionnaire, indicating increased levels of stress among families of children with autistic spectrum disorder. The mean total Parenting Stress Index score for the dystrophinopathy-autism group was 102 ± 22 S.D., well above the cut-point of 90 for "elevated stress." In contrast, parents of children with dystrophinopathy who did not have autism had a mean score of 82 ± 19 S.D.

Discussion

The observation that 15-19% of boys with dystrophinopathies met the criteria for the presence of autistic spectrum disorders, whereas none of their 51 siblings did, offers compelling evidence of an association between the disorders. Although the possibility of ascertainment bias exists in our sample, the finding of 16 cases among children with a relatively rare disorder (5.5 in 100,000) [32] is nonetheless striking. True population-based prevalence rates are likely lower, yet it is evident that individuals with a diagnosis of dystrophinopathies are at increased risk of autistic spectrum disorders. This is similar to findings in numerous other genetic neurodevelopmental disorders. Higher-than-expected rates of autistic spectrum disorders (ranging from 16-65%) were reported in individuals diagnosed with tuberous sclerosis, fragile X, Angelman, Prader-Willi, De Lange, Smith-Lemli Opitz, or velocardiofacial syndromes [1].

Interestingly, the majority of children in the dystrophinopathy group were of normal intellectual function, unlike the majority of those with the above-mentioned syndromes. Only one child of the 16 diagnosed with dystrophinopathies and autistic spectrum disorder scored <70 (the designated cut-point for mental retardation) on both cognitive measures. Moreover, the presentation of behavioral signs in the dystrophinopathy group was generally milder than that seen in many of the above-mentioned disorders. Although the 16 children with dystrophinopathy and autism manifested significant impairment of social interaction and communication, meeting the diagnostic criteria for pervasive developmental disorder according to the Diagnostic and Statistical Manual of Mental Disorders-IV and International Classification of Diseases-10 criteria [30,31], they could speak in multiword phrases, and their behavior was not as overtly "bizarre" as seen in some autistic individuals. Specifically, there were few or no stereotyped and repetitive movements, compulsive rituals, odd sensory aversions, or preoccupations with parts of objects. The children all showed signs of developmental delay before age 3 years, thus ruling out a diagnosis of Asperger's disorder. Further, there was no evidence of any loss of previously acquired skills (aside from the Duchenne muscular dystrophy-associated progressive weakness), ruling out childhood disintegrative disorder [30].

A limitation of this study was that the children did not take the Autism Diagnostic Observation Schedule, a standardized method of ascertaining autistic-like behaviors directly from the participant, known to contribute to rigor-

ous diagnostic validity [33,34]. We did not administer the Autism Diagnostic Observation Schedule because of geographic, methodological, time, and training constraints. A future study should examine the children's behavior more systematically. Although direct observation would have enhanced our descriptions of the children's behavior, our study is nonetheless the most comprehensive evaluation ever reported of autistic spectrum disorders in a large group of children with dystrophinopathies.

Interestingly, children with dystrophinopathies manifest a number of neurologic characteristics that are also evident among children with autism. Large head circumference was reported in both disorders [35-39], as was cerebellar involvement [36,40-44]. These data suggest the possibility of shared pathophysiologic mechanisms, and we previously reviewed the cerebellar evidence in depth [45]. However, given that the majority of children with dystrophinopathies do not exhibit autistic spectrum disorders, environmental factors are also likely to be influential, and the manifestation of the autistic spectrum disorder phenotype requires complex (and as yet, unknown) gene-environment interactions.

In Duchenne muscular dystrophy, the protein dystrophin that is normally localized to cerebellar Purkinje cells is absent, and an associated neurologic functional impact was demonstrated. In humans with Duchenne muscular dystrophy, significant cerebellar hypometabolism, evident on positron emission tomography scans [44], may contribute to associated language and social skill deficits. In a mouse model of Duchenne muscular dystrophy (the *mdx* mouse), the amplitude and frequency of spontaneous, miniature, inhibitory postsynaptic currents in cerebellar Purkinje cells were significantly lower than in littermate control mice [46], and synaptic plasticity is disrupted, as demonstrated by a substantial reduction in long-term depression [47]. Moreover, evidence that the brains of *mdx* mice are more susceptible to damage from hypoxia than are control mouse brains [48] may offer a potential gene-environment interaction model of why some, but not all, children with dystrophinopathy exhibit autistic spectrum disorders. If the developing dystrophin-deficient brain of a child with dystrophinopathy is at increased risk for incurring damage after routine environmental insults, then those with autistic spectrum disorders may have experienced adverse environmental events. Interestingly, two children in this sample with autistic spectrum disorders were adopted from Eastern European orphanages where early deprivation is commonplace. Although no definitive conclusions about mechanisms can be drawn from this large-scale, population-based study of children with dystrophinopathies, future prospective studies could examine whether significant associations exist between presentations of autistic spectrum disorders in children with dystrophinopathies and environmental factors.

The children with dystrophinopathies and autistic spectrum disorders demonstrated fewer autistic signs with age. About half the group exhibited significant improvement

in communication and social impairments, and about a third exhibited improvements in the restricted and repetitive behavior domain. Studies of adolescents and adults with autistic spectrum disorders also reported fewer behavioral characteristics in older individuals, compared with their Autistic Diagnostic Interview assessment at age 4-5 years, with the fewest changes evident in the restricted and repetitive domain [49,50]. In our sample, the interval between the age 4-5-year period and the assessment of current behavior ranged from 2-10 years, a period typified by substantive developmental progress in the area of autistic spectrum disorder symptomatology.

In dystrophinopathies, there is evidence for improvement in some language skills with age, and a number of reports documented more impaired skills among younger children [13,14,51,52]. Moreover, a recent study reported improvements in psychosocial adjustment among boys with dystrophinopathies with age [53]. We also revealed that social and attention deficits are reported less often in older children with dystrophinopathies, and this change was greater than that expected during normal development [21]. The improvements in the current sample of children with dystrophinopathies and autistic spectrum disorders were similar. Thus, the cognitive and behavioral phenotype associated with dystrophinopathies is dynamic: children make substantial gains with time, even those with the most severe manifestations of the phenotype.

Our data also support the hypothesis that a presentation of autistic spectrum disorders among children with dystrophinopathies has serious consequences, not only for the children, but for their parents and families as well. Previously, we reported that a child's behavior was a significant contributor to parental ratings of stress among families with dystrophinopathies [23]. The present analyses compared stress ratings in parents of children with dystrophinopathies diagnosed with autistic spectrum disorders, with those of parents whose sons with dystrophinopathies did not meet the criteria for autistic spectrum disorders. As expected, the parents of the autistic spectrum disorders group rated themselves as significantly more stressed than parents in the nonautism group. Thus, a diagnosis of autistic spectrum disorders has a wide-ranging impact on a family's overall quality of life. Clinicians need to be aware of the association between dystrophinopathies and autistic spectrum disorders, and to consider their presentation and impact on those affected and their families.

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References

- [1] Zafeiriou DI, Ververi A, Vargiami E. Childhood autism and associated comorbidities. *Brain Dev* 2007;29:257-72.
- [2] Wu JY, Kuban KC, Allred E, Shapiro F, Darras BT. Association of Duchenne muscular dystrophy with autism spectrum disorder. *J Child Neurol* 2005;20:790-5.
- [3] Hendriksen JG, Vles JS. Neuropsychiatric disorders in males with Duchenne muscular dystrophy: Frequency rate of attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, and obsessive-compulsive disorder. *J Child Neurol* 2008;23:477-81.
- [4] Darke J, Bushby K, Le Couteur A, McConachie H. Survey of behaviour problems in children with neuromuscular diseases. *Eur J Paediatr Neurol* 2006;10:129-34.
- [5] Komoto J, Usui S, Terao A. Infantile autism and Duchenne muscular dystrophy. *J Autism Dev Disord* 1984;14:191-5.
- [6] Zwaigenbaum L, Tarnopolsky M. Two children with muscular dystrophies ascertained due to referral for diagnosis of autism. *J Autism Dev Disord* 2003;33:193-9.
- [7] Hinton VJ, Nereo NE, Fee RJ, Cyrluk SE. Social behavior problems in boys with Duchenne muscular dystrophy. *J Dev Behav Pediatr* 2006;27:470-6.
- [8] Billard C, Gillet P, Signoret JL, et al. Cognitive functions in Duchenne muscular dystrophy: A reappraisal and comparison with spinal muscular atrophy. *Neuromuscul Disord* 1992;2:371-8.
- [9] Cotton S, Voudouris NJ, Greenwood KM. Intelligence and Duchenne muscular dystrophy: Full-scale, verbal, and performance intelligence quotients. *Dev Med Child Neurol* 2001;43:497-501.
- [10] Hinton VJ, De Vivo DC, Nereo NE, Goldstein E, Stern Y. Selective deficits in verbal working memory associated with a known genetic etiology: The neuropsychological profile of Duchenne muscular dystrophy. *J Int Neuropsychol Soc* 2001;7:45-54.
- [11] Whelan TB. Neuropsychological performance of children with Duchenne muscular dystrophy and spinal muscle atrophy. *Dev Med Child Neurol* 1987;29:212-20.
- [12] Cyrluk SE, Fee RJ, De Vivo DC, Goldstein E, Hinton VJ. Delayed developmental language milestones in children with Duchenne's muscular dystrophy. *J Pediatr* 2007;150:474-8.
- [13] Smith RA, Sibert JR, Harper PS. Early development of boys with Duchenne muscular dystrophy. *Dev Med Child Neurol* 1990;32:519-27.
- [14] Sollee ND, Latham EE, Kindlon DJ, Bresnan MJ. Neuropsychological impairment in Duchenne muscular dystrophy. *J Clin Exp Neuropsychol* 1985;7:486-96.
- [15] Marini A, Lorusso ML, D'Angelo MG, et al. Evaluation of narrative abilities in patients suffering from Duchenne Muscular Dystrophy. *Brain Lang* 2007;102:1-12.
- [16] Billard C, Gillet P, Barthez M, Hommet C, Bertrand P. Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. *Dev Med Child Neurol* 1998;40:12-20.
- [17] Dorman C, Hurley AD, D'Avignon J. Language and learning disorders of older boys with Duchenne muscular dystrophy. *Dev Med Child Neurol* 1988;30:316-27.
- [18] Hendriksen JG, Vles JS. Are males with Duchenne muscular dystrophy at risk for reading disabilities? *Pediatr Neurol* 2006;34:296-300.
- [19] Hinton VJ, DeVivo DC, Fee RJ, Goldstein E, Stern Y. Investigation of poor academic achievement in children with Duchenne muscular dystrophy. *Learn Disabil Res Pract* 2004;19:146-54.
- [20] Worden DK, Vignos PJ Jr. Intellectual function in childhood progressive muscular dystrophy. *Pediatrics* 1962;29:968-77.
- [21] Hinton VJ, Kim SY, Fee R, Goldstein E, DeVivo DC. Cognitive and behavioral gains over time in Duchenne muscular dystrophy (in preparation).
- [22] Achenbach TM. Manual for the Child Behavior Checklist/4-18 and 1991 profile. Burlington, VT: Department of Psychiatry, University of Vermont, 1991.
- [23] Nereo NE, Fee RJ, Hinton VJ. Parental stress in mothers of boys with Duchenne muscular dystrophy. *J Pediatr Psychol* 2003;28:473-84.
- [24] Rutter M, Bailey A, Lord C. The Social Communication Questionnaire (SCQ). Los Angeles: Western Psychological Services, 2003.
- [25] Le Couteur A, Lord C, Rutter M. Autism Diagnostic Interview-Revised. Los Angeles: Western Psychological Services, 2003.

- [26] **Abidin RA.** Parenting Stress Index-Short Form (PSI-SF): Professional manual. Odessa, FL: Psychological Assessment Resources, Inc., 1990.
- [27] **Dunn JF, Dunn LF.** Peabody Picture Vocabulary-III manual. Circle Pines: American Guidance Center 1997.
- [28] **Raven JC, Court JH, Raven J.** Coloured progressive matrices. Oxford: Oxford Psychologists Press, 1990.
- [29] **Witwer AN, Lecavalier L.** Autism screening tools: An evaluation of the Social Communication Questionnaire and the Developmental Behaviour Checklist-Autism Screening Algorithm. *J Intellect Dev Disabil* 2007;32:179-87.
- [30] **American Psychiatric Association.** Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1997.
- [31] **ICD-9-CM.** International classification of diseases, 9th revision, clinical modification, 3rd ed, vols 1, 2, and 3. Official authorized addendum effective October 1, 1990, HCFA. *J Am Med Rec Assoc* 1990;61(Suppl.): 1-35.
- [32] **Jeppesen J, Green A, Steffensen BF, Rahbek J.** The Duchenne muscular dystrophy population in Denmark, 1977-2001: Prevalence, incidence and survival in relation to the introduction of ventilator use. *Neuromuscul Disord* 2003;13:804-12.
- [33] **Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Pickles A.** Autism from 2 to 9 years of age. *Arch Gen Psychiatry* 2006;63:694-701.
- [34] **Risi S, Lord C, Gotham K, et al.** Combining information from multiple sources in the diagnosis of autism spectrum disorders. *J Am Acad Child Adolesc Psychiatry* 2006;45:1094-103.
- [35] **Appleton RE, Bushby K, Gardner-Medwin D, Welch J, Kelly PJ.** Head circumference and intellectual performance of patients with Duchenne muscular dystrophy. *Dev Med Child Neurol* 1991;33: 884-90.
- [36] **Courchesne E, Redcay E, Kennedy DP.** The autistic brain: Birth through adulthood. *Curr Opin Neurol* 2004;17:489-96.
- [37] **Lainhart JE, Bigler ED, Bocian M, et al.** Head circumference and height in autism: A study by the Collaborative Program of Excellence in Autism. *Am J Med Genet [A]* 2006;140:2257-74.
- [38] **Sacco R, Militerni R, Frolli A, et al.** Clinical, morphological, and biochemical correlates of head circumference in autism. *Biol Psychiatry* 2007;62:1038-47.
- [39] **Schmidt B, Watters GV, Rosenblatt B, Silver K.** Increased head circumference in patients with Duchenne muscular dystrophy. *Ann Neurol* 1985;17:620-1.
- [40] **Anderson JL, Head SI, Rae C, Morley JW.** Brain function in Duchenne muscular dystrophy. *Brain* 2002;125:4-13.
- [41] **Belmonte MK, Allen G, Beckel-Mitchener A, Boulanger LM, Carper RA, Webb SJ.** Autism and abnormal development of brain connectivity. *J Neurosci* 2004;24:9228-31.
- [42] **Bresolin N, Castelli E, Comi GP, et al.** Cognitive impairment in Duchenne muscular dystrophy. *Neuromuscul Disord* 1994; 4:359-69.
- [43] **Courchesne E.** Brain development in autism: Early overgrowth followed by premature arrest of growth. *Ment Retard Dev Disabil Res Rev* 2004;10:106-11.
- [44] **Lee JS, Pfund Z, Juhasz C, et al.** Altered regional brain glucose metabolism in Duchenne muscular dystrophy: A PET study. *Muscle Nerve* 2002;26:506-12.
- [45] **Cybulnik SE, Hinton VJ.** Duchenne muscular dystrophy: A cerebellar disorder? *Neurosci Biobehav Rev* 2008;32:486-96.
- [46] **Anderson JE, Head SI, Morley JW.** Altered inhibitory input to Purkinje cells of dystrophin-deficient mice. *Brain Res* 2003;982: 280-3.
- [47] **Anderson JL, Head SI, Morley JW.** Long term depression is reduced in cerebellar Purkinje cells of dystrophin-deficient *mdx* mice. *Brain Res* 2004;1019:289-92.
- [48] **Mehler MF.** Brain dystrophin, neurogenetics and mental retardation. *Brain Res Rev* 2000;32:277-307.
- [49] **Fecteau S, Mottron L, Berthiaume C, Burack JA.** Developmental changes of autistic symptoms. *Autism* 2003;7:255-68.
- [50] **Piven J, Harper J, Palmer P, Arndt S.** Course of behavioral change in autism: A retrospective study of high-IQ adolescents and adults. *J Am Acad Child Adolesc Psychiatry* 1996;35:523-9.
- [51] **Cotton SM, Voudouris NJ, Greenwood KM.** Association between intellectual functioning and age in children and young adults with Duchenne muscular dystrophy: Further results from a meta-analysis. *Dev Med Child Neurol* 2005;47:257-65.
- [52] **Cybulnik SE, Fee RJ, Batchelder A, Kiefel J, Goldstein E, Hinton VJ.** Cognitive and adaptive deficits in young children with Duchenne muscular dystrophy (DMD). *J Int Neuropsychol Soc* 2008;14: 853-61.
- [53] **Hendriksen JG, Poysky JT, Schrans DG, Schouten EG, Aldenkamp AP, Vles JS.** Psychosocial adjustment in males with Duchenne muscular dystrophy: Psychometric properties and clinical utility of a parent-report questionnaire. *J Pediatr Psychol* 2008;34: 69-78.