Handbook of PEDIATRIC Neuropsychology

Andrew S. Davis
Editor

With compliments of Springer Publishing Company, LLC

SPRINGER PUBLISHING COMPANY

64 The Dystrophinopathies

Veronica J. Hinton

The dystrophinopathies (including Duchenne and Becker muscular dystrophies) are unrelentingly progressive neuromuscular diseases of childhood that cause an affected boy to become continuously weaker over years. Throughout the child's life, he and his family will have to adjust and cope with a chronic, progressive, and ultimately fatal, muscle disease. His mobility will be impaired, limiting him from running, jumping and riding a bike as a youngster, walking as an adolescent, and using his arms, fingers and diaphragm as a young man. His death will be premature, and his life may be colored with this knowledge. A diagnosis of dystrophinopathy brings with it a myriad of concerns and requires a multi-disciplined care team, one of whom may be the pediatric neuropsychologist. Although known primarily as "muscle diseases," less well-known complications of the dystrophinopathies are the effects on brain function which impact a child's development of cognitive, language, behavioral and academic skills. As such, the role of the pediatric neuropsychologist may be particularly resonant to the affected young child and his family, helping his early development and schooling.

BACKGROUND AND DESCRIPTION OF THE DYSTROPHINOPATHIES

In 1868, the French neurologist Guillaume-Benjamin-Amand Duchenne first described in detail 13 children with a severe neuromuscular disorder that came to be known as Duchenne's dystrophy (Duchenne, 1968). He noted that only boys were affected and described their physical characteristics and the progressive nature of the illness. Moreover, Duchenne observed that for some affected children "intellect was dull and speech was difficult" (p 630, Duchenne, 1968).

It is now well established that the dystrophinopathies are X-linked, developmental neuromuscular disorders that are associated with cognitive and behavioral limitations in some affected individuals. The dystrophinopathies are found across ethnic groups and about one third of the cases are spontaneous new mutations. Duchenne muscular dystrophy (DMD), the more severe form, is the most common neuromuscular disease of childhood, with prevalence rates ranging from 19 to 95 per million and an estimated overall prevalence of 63 per million (Emery, 1991). Children with DMD lose the ability to walk independently before age 12 and die before their third decade of life. Children with Becker muscular dystrophy (BMD) have a slower rate of progression. BMD is diagnosed when children with dystrophinopathy remain walking independently into their teens. Prevalence rates for BMD range from 12 to 27 per million (Emery, 1991).

In 1987, the gene that causes both DMD and BMD was identified (Koenig et al., 1987) and found to code for the protein dystrophin. The dystrophinopathies result when the gene is mutated and no (or dysfunctional) dystrophin made. In the absence of dystrophin, muscle cells break down with use. This presents clinically as progressive weakness. The weakness progresses at different rates in different individuals, but its course is constant—proximal muscles weaken before distal, legs weaken before arms, extensors weaken before flexors (McDonald, Abresch, Carter, Fowler, Johnson, & Kilmer, 1995a, 1995b). Over time, a seemingly healthy looking youngster with dystrophinopathy will lose the ability to walk, then lose arm and hand movement, and eventually lose respiratory and cardiac function. The gene also codes for dystrophin isoforms that normally localize to the central nervous system and are missing in affected children. The absence of the dystrophins normally localized in the cerebral cortex and cerebellum likely accounts for the cognitive and behavioral deficits associated with the disorder (Anderson, Head, Rae, & Morley, 2002; Cyrulnik & Hinton, 2008). It is this aspect of the underlying pathology that is of greatest interest for the pediatric neuropsychologist. Although the exact function of the brain dystrophins is unknown, it appears likely that the proteins contribute to the optimal brain structure necessary for development of language and immediate verbal memory skills.

Unfortunately, there is currently no cure for the dystrophinopathies and medical treatment is aimed at slowing the disease progression and improving the quality of life for those affected. Medical management is complex and multifaceted. It includes care for neuromuscular, orthopedic, rehabilitative, nutritional, respiratory,

Copyright Springer Publishing Company, LLC

cardiac, gastrointestinal, palliative, cognitive and behavioral aspects of the disease (e.g., Bushby & Straub, 2005).

THE ROLE OF THE PEDIATRIC NEUROPSYCHOLOGIST

The devastating physical toll of the dystrophinopathies is well known. In contrast, the associated cognitive and behavioral abnormalities are less familiar to most clinicians. Nonetheless, the cognitive and behavioral attributes of the dystrophinopathies impact the affected individual's functioning in far ranging ways. For the pediatric neuropsychologist, identifying associated cognitive and behavioral abnormalities early and providing appropriate interventions contributes substantially to an affected child's quality of life. The pediatric neuropsychologist can potentially change a struggling and frustrated child coping with a chronic illness into a competent and well-adjusted one.

CLINICAL PRESENTATION

Initially, a boy with DMD will appear to be developing normally. At age two to three, he may have slight motor impairments and be perceived as being somewhat clumsy. His calf muscles will likely be overdeveloped or hypertrophic. He will have difficulty keeping up with his peers on the playground. He will be unable to jump from a standing position, have difficulty climbing stairs and will begin to have frequent falls. As the boy's muscles continue to weaken, he will have greater difficulty walking. Specifically, as his quadriceps weaken, he will compensate by shifting his weight onto the balls of his feet, and push his abdomen forward and shoulders back for stability. If he is asked to raise himself from a sitting position on the floor, he may do so by a typical sequence of movements. This involves him first raising his rear in the air and then, using his arms as supports, "walking" his hands up his legs to get into a standing position, a movement known as the Gower's maneuver. By age 12, he will tire easily and use a wheelchair for extended mobility. Over the next few years he will lose significant skeletal muscle strength, and will need assistance in all activities that require his legs and trunk and arms. Additionally, he will develop multifocal joint contractures and scoliosis that may be painful. He will still be able to move his fingers, so he can operate his motorized wheelchair and use a computer, as long as his arms are properly supported. As he continues to age into his late teens, he may develop heart problems due to weakness in the myocardium. Additionally, as the muscles around his lungs weaken, he will lose the ability to cough independently and clear his lungs, putting him at increased risk for developing pneumonia. Without ventilator support, his death will occur before he reaches 30, usually due to respiratory or cardiac failure resulting from extreme muscle weakness.

The cognitive presentation and course is more variable across affected individuals than the physical presentation. For the majority of affected children, there may be no associated cognitive or behavioral concerns; yet each affected child has an increased risk for language, behavior and learning disabilities when compared to his unaffected peers. An affected infant may show delayed learning of language and motor skills, such that performance on standard measures of infant development may indicate generalized delayed development. Language delays may continue and at times may be the observation that first brings the child to medical attention. Many children may also have concomitant behavior concerns including poor social and attention skills along with stereotyped behaviors. Anecdotal reports from parents who noted "something" was wrong but were not considering a muscle diseases are commonplace. At early school age, the boy may come to the attention of his teachers due to difficulty in adjusting to the classroom setting and distractible behavior. When learning to read, the boy affected with dystrophinopathy may struggle with associating phonemes with letters and decoding, and many meet criteria for developmental dyslexia. Without appropriate interventions for reading disability, a boy may face ongoing academic declines as a consequence of his limited reading. Yet it is important to emphasize that unlike the physical characteristics of the dystrophinopathies, there is no evidence of underlying progressive decline in cognitive skills over time. Rather, academic failures may result from inability to keep up with the reading requirements if reading basics are never mastered. Another possible contribution to academic failure may be inappropriate academic placement. It is not uncommon for an affected boy to be enrolled in a special education classroom because of his physical limitations, even though his intellectual abilities may be average, thus depriving him of adequate educational opportunities. As the affected child loses muscle function, he may struggle with feelings of loss and inadequacy and may have difficulty coping with his physical limitations, which may in turn impact on his ability to participate at school and maintain friendships. Major transitions, such as beginning to use a wheelchair, may be particularly problematic. Similarly, the introspective turmoil of adolescence may be exacerbated by his illness and treatment. His hampered mobility will make engaging in many activities with his peers problematic and he runs the risk of becoming socially isolated. As his peers make long-term plans to attend college and pursue a career, he may feel limited about what opportunities exist for him. Likewise, as his peers grow more independent, his increasing dependence on adaptive equipment and caretakers may heighten his sense of vulnerability. Yet all of these cognitive and behavioral concerns that he may face can be improved and lessened with appropriate identification and intervention. As such, the pediatric

Copyright Springer Publishing Company, LLC

neuropsychologist can potentially provide essential support that ultimately will contribute to a much improved quality of life for the youngster with dystrophinopathy.

It is also crucial to note that a diagnosis of dystrophinopathy will impact more than just the affected individual. His diagnosis will affect his family in multiple ways. How a family functions contributes to every member's well-being. For a chronically ill or developmentally disabled child, how his parents and family adjust to the diagnosis will, in turn, affect his own adjustment. Managing healthcare, adapting home and school environments, and providing opportunities for a physically disabled child requires time, effort, and considerable financial expense. The repercussions of the diagnosis will affect the roles and relationships within the family, along with lifestyle choices and goals. As such, the pediatric neuropsychologist may play a crucial role in helping the family as a whole adjust to the child's illness.

NEUROPSYCHOLOGY: DISENTANGLING RESEARCH FINDINGS FROM CONFOUNDS

For all children, interpretation of neuropsychological tests results must be considered within the context of environment (including the child's home, school and immediate environments), family factors (including genetic, relational and socioeconomic) and child factors (including age, mood, and health). For the child with dystrophinopathies, numerous potential confounds may impact on his performance, from underlying etiology to adjustment issues to physical limitations.

In general, the distribution of IQ scores among affected boys appears to be shifted down about one standard deviation from the population mean. The most comprehensive evaluation of intellectual function in DMD comes from two meta analytic studies conducted by Cotton and colleagues (Cotton, Voudouris, & Greenwood, 2001; Cotton, Voudouris, & Greenwood, 2005). By combining data from 32 published papers examining IQ among a total of 1146 individuals with dystrophinopathy, the authors found that mean full scale IQ value was 80.2 with a standard deviation of 19.3 (Cotton et al., 2001). IQ scores were shifted down from the normative population, but the frequency distribution did not differ significantly. Thus, as a result of this downward shift, 35% of the children in the dystrophinopathy sample had IQ scores in the mentally retarded range (or scores less than 70). Moreover, when the available data examining Verbal versus Performance IQ were collapsed across studies in a sample of 878 individuals affected with dystrophinopathy, the mean group difference indicated that verbal scores were mildly, but significantly, lower than performance scores (Cotton et al., 2001). Given the motor and speed demands on many performance (but not verbal) subtests, the finding of higher performance scores among a motor-impaired group is suggestive of even greater verbal-performance discrepancies than are reported.

Because the dystrophinopathies are relatively rare disorders, there are limited data available. The above described meta-analyses were based on a range of studies of varying samples of children who were available and willing to participate in studies and there are no population-based studies of cognitive performance among children with dystrophinopathies. It is possible that these convenience samples may be skewed and over-represent those with cognitive deficits (as they are most likely to come to clinical attention). Across studies, the methods used to examine cognition and behavior in dystrophinopathy have varied, and many have small samples with inadequate or no comparison groups. Given the variability in the disease presentation, multiple confounds may hamper the research in cognition. Physical disability, overall level of intellectual function, environmental background and age variables may all influence results. Nonetheless, some findings appear to be consistent across studies. Overall, most studies have found that individuals with dystrophinopathy have compromised verbal and reading skills and limited immediate verbal memory.

To control for the potentially confounding effects of physical impairment, a number of studies have compared test performance of children with dystrophinopathy to those with spinal muscular atrophy (SMA), a different neuromuscular disorder. Results have demonstrated that the children with dystrophinopathy have poorer verbal, immediate memory and reading skills than their SMA peers (Billard et al., 1992; Billard, Gillet, Barthez, Hommet, & Bertrand, 1998; Ogasawara, 1989; Whelan, 1987). Specific findings included lowered scores on digit span, arithmetic, similarities, word repetition, supraspan and reading tests. Other areas, including many measures of basic language skill and nonverbal abilities, were not different between the two groups, highlighting the selective nature of the cognitive profile (Billard et al., 1992; Whelan, 1987).

To control for environmental background, we have compared performance of children with dystrophinopathy to that of their unaffected siblings. These results also showed poorer verbal, immediate memory and academic skills (Hinton, De Vivo, Nereo, Goldstein, & Stern, 2001; Hinton, DeVivo, Fee, Goldstein, & Stern, 2004; Hinton, Kim, Fee, Goldstein, & DeVivo, in submission). Specifically, children with DMD did poorly on digit span, comprehension, story memory and token test when compared to their sibling controls, in addition to having lower reading and arithmetic skills. The main finding, however, was that most cognitive areas remained strong. Performance on tests of basic receptive vocabulary, naming, category fluency and factual knowledge did not differ between the groups, clearly demonstrating that many basic language skills are not compromised. Likewise, problem solving, abstraction, categorization and set shifting were also good; children with DMD performed

Copyright Springer Publishing Company, LLC

similarly to their siblings on a range of higher order tests of executive function. Similarly, there was no evidence of visual spatial impairment among the boys with dystrophinopathy, based on performance on a selection of puzzle completion tests that did not require manual dexterity, but did require mental manipulations and/or familiarity with spatial features. There was also no evidence of impaired visual memory for details or learning and recall of spatial location.

Since the range of intellectual level in the dystrophinopathies is great, and among children with dystrophinopathy there are as many as 35% who have pronounced cognitive deficits (Cotton et al., 2001), performance on measures of selective cognitive skills may be biased somewhat by those who are able to comply with the testing. Even among those children who are not mentally retarded, IQ may have significant influence. To try and control for this, researchers have compared the children with dystrophinopathy to IQ-matched and age-matched normal children. On neuropsychological test batteries, the group with dystrophinopathies generally performed more poorly than the comparison group on measures of memory (Cotton, Crowe, & Voudouris, 1998; Wicksell, Kihlgren, Melin, & Eeg-Olofsson, 2004). The most striking finding of these comparisons, however, was the number of measures the two groups performed equivalently on, including measures of vocabulary, non verbal reasoning and a variety of visual-spatial measures.

To determine whether individual strengths and weaknesses were similar across intellectual level, we examined boys with dystrophinopathies by individually rank ordering their performance on standardized subtests and compared the relative rankings across individuals. The results demonstrated that boys with dystrophinopathies have a selective cognitive profile such that subtests that tap verbal immediate recall (e.g., digit span and story memory) are consistently lowest, regardless of general intellectual function (Hinton, De Vivo, Nereo, Goldstein, & Stern, 2000). Additionally, when data are examined covarying for the effects of IQ, the findings of poor performance on digit span and story memory were confirmed (Hinton et al., 2001). We hypothesized that for all children with DMD some skills are selectively compromised, but these reduced abilities may be detrimental only to those children of overall lower cognitive function.

The influence of age on selective cognitive skills in dystrophinopathies is of interest. Although age is definitively associated with physical progression of the disease, there is no evidence of intellectual decline over time. Limited longitudinal data have shown no significant loss of skills over time (Hinton, unpublished data; McDonald et al., 1995a, 1995b).

Interestingly, although there is no evidence of progressive decline of intellectual ability over time, there are data to support the idea that some cognitive skills selectively increase with age. Most studies have grouped children with dystrophinopathies over wide age spans out of necessity due to a limited number of participants. Yet comparison of children at different developmental stages may be misleading. When younger children have been systematically compared to older children, the results have suggested that over time language skills may improve. Analysis of cross-sectional data across age groups from 32 published studies indicated increases in Verbal, but not Performance, IQ scores with age among boys with dystrophinopathies (Cotton et al., 2005). Comparison of younger versus older affected children on a battery of tests showed the younger group to have more generalized impairments (Cyrulnik, Fee, De Vivo, Goldstein, & Hinton, 2007; Sollee, Latham, Kindlon, & Bresnan, 1985). Further, there is evidence to suggest that early language delays may be commonplace and may, at times, be even more pronounced than motor difficulties in the young child (Cyrulnik et al., 2007; Kaplan, Osborne & Elias, 1986; Smith, Sibert & Harper, 1990). Reports of children who have been referred for language delays and later found to have dystrophinopathies have been published (Kaplan, Osborne & Elias, 1986), and we know of numerous anecdotal accounts of children with early language and behavioral concerns that predated any clear evidence of motor loss (Hinton, Nereo, Fee, & Cyrulnik, 2006).

Thus, across studies, even when controlling for effects of physical involvement, environmental background, IQ and age, the cognitive profile in the dystrophinopathies is defined by multiple strengths and selective deficits in language (particularly phonological processing) and immediate verbal memory skills. Moreover, contrary to the physical presentation that declines with age, the cognitive profile may show selective improvements in verbal skills over time.

NEUROPSYCHOLOGY: ACADEMIC ACHIEVEMENT

It is also the case that children with dystrophinopathies are at increased risk for having academic difficulties (Billard et al., 1992; Hendriksen & Vles, 2006; Hinton et al., 2004; Leibowitz & Dubowitz, 1981; Worden & Vignos, 1962). This may be due, in part, to the hardships associated with physical disability and "fitting in," yet is also clearly related to the underlying cognitive deficits.

Most research has focused on reading skills and the findings across studies have suggested that about half the children with dystrophinopathies present with a form of developmental dyslexia. Leibowitz and Dubowitz (1981) tested 42 boys on reading tests and found the group had a mean standard score that was almost identical to their VIQ mean score. Yet they noted that the reading scores were very skewed, such that half of their sample did very poorly on the reading test. Dorman, Hurley and D'Avignon (1988) tested 15 boys with dystrophinopathies on reading tests and also demonstrated limited reading skills in about half of the children. Similarly, Billard

Copyright Springer Publishing Company, LLC

et al. (1992) demonstrated that among a group of 24 older boys with dystrophinopathies, about half of the children with dystrophinopathies had severe reading disabilities, while none of the comparison group of children affected with affected spinal muscular atrophy did. Likewise, Hendriksen and Vles (2006) examined 25 children with dystrophinopathies and found 40% of them to be reading disabled. In more detailed examinations of the components of reading it is evident that phonological processing is particularly impaired in dystrophinopathies. Children have reduced phonetic word attack skills and make their greatest number of errors when reading nonwords (Billard et al., 1998; Dorman et al., 1988).

We have demonstrated that for both reading and math skills, boys with DMD have lower scores than their siblings on achievement tests (Hinton et al., 2004). Similarly to the other published studies, there was variability across individual performance, yet the mean scores were about one standard deviation lower than that of their siblings. Additionally, when individual achievement scores were compared to the nonverbal IQ scores from the same individuals, the children with dystrophinopathies had significantly discrepant scores (with academic scores being lower) while the unaffected siblings' academic and IQ scores were comparable. Examination of what contributed to the lower academic achievement test scores showed that age, physical disability, and behavior ratings did not significantly influence the outcome, while performance on tests of intellectual ability and Digit Span did. Thus, we proposed that limited verbal span associated with dystrophinopathies impacts negatively on academic achievement in both reading and math.

NEUROPSYCHOLOGY: BEHAVIOR

Research examining behavior in children with DMD has indicated a few general areas which are susceptible to pathology: internalizing/depressive disorders, attention deficits and social problems. Similar to the other phenotypic characteristics of DMD, there is a range in presentation and the behaviors observed in DMD are associated with numerous factors including age, disease progression, intellectual level and environmental background.

Early data collected using parent questionnaires has documented children with dystrophinopathies have depressive signs that increased with age and less well-characterized antisocial tendencies (Fitzpatrick, Barry, & Garvey, 1986; Leibowitz & Dubowitz, 1981; Thompson, Zeman, Fanurik, & Sirotkin-Roses, 1992). These studies showed that as children matured and became more physically disabled, parental ratings of depression and anxiety among the youths increased.

Harper (1983) investigated personality profiles of adolescents with dystrophinopathies and compared them to those of children with other physical impairments. Both groups showed tendencies for increased social inhibitions and depressive symptoms. Physical disability and adjustment status were not linearly associated, but more rapid declines in the dystrophinopathy group were associated with behaviors suggestive of increased stress. A later study replicated the finding that adolescents with dystrophinopathies have significant adjustment difficulties (Reid & Renwick, 2001). Specifically, they found adolescents with dystrophinopathies had poorer psychosocial adjustment than their healthy peers and that their adjustment was significantly associated with the level of stress reported by the family.

In a large-scale survey of parents across the United States and the Netherlands, Hendriksen and Vles (2008) reported that among 351 children with dystrophinopathies, rates of associated psychiatric disorders were notably high. According to the parent ratings, 11.7% of the boys with dystrophinopathies had a comorbid diagnosis of ADHD, 3.1% had autism spectrum disorder, and 4.8% had obsessive-compulsive disorder.

We examined parent ratings of behavior in a sample of 181 boys with dystrophinopathies who were between 6 and 17 years old at the time of assessment, and compared them to parental ratings from both unaffected siblings and children with cerebral palsy (Hinton et al., 2006). Parent ratings on the *Child Behavior Checklist* demonstrated that children with DMD were more likely to fall in the "clinically significant" range (as defined by being more common than 96% of the normative population) on the Social Problems scale than either comparison group. About a third of the boys were reported to have significant Social Problems (e.g., being immature, having poor peer relationships) and about a quarter reportedly had significant problems with being withdrawn and having poor attention. Of note is that the younger children were more likely to have increased Social Problems and the older children were more likely to have increased depression and anxiety (Hinton et al., unpublished data). We hypothesize that the social difficulties may be related to underlying etiology and associated with compromised verbal skills, while the depressive behaviors are likely a reactive response to the disease progression.

A few case studies describing children with dystrophinopathies and autism have been published (Komoto, Usui, Otsuki, & Terao, 1984; Zwaigenbaum & Tarnopolsky, 2003). Further, the number of autism spectrum disorders reported in a Massachusetts muscular dystrophy clinic was found to be considerably more common than expected among the general population(Wu, Kuban, Allred, Shapiro, & Darras, 2005). They reported a prevalence of 6/158 in their clinic compared to 1.6/1,000 in the general population. Likewise, in a survey of 82 caregiver of children with DMD/BMD in the United Kingdom, 9/82 had a diagnosis of autism spectrum disorders (Darke, Bushby, Le Couteur, & McConachie, 2006) We too have observed multiple cases of children with dystrophinopathies and autism spectrum disorders, with rates as high as 13% of the children participating in our studies meeting criteria (as reported in Poysky, 2007; Hinton et al.).

Copyright Springer Publishing Company, LLC

Although most children with dystrophinopathies clearly are not autistic, the tendencies of being withdrawn and having poor peer relations may be mild behaviors on the spectrum.

NEUROPSYCHOLOGY: BEHAVIORAL AND COGNITIVE EVIDENCE-BASED INTERVENTIONS

One published study examined intervention to decrease social isolation among individuals affected with the dystrophinopathies (Soutter et al., 2004). The researchers provided 74 families with a son with dystrophinopathy with a personal computer and e-mail and Internet connectivity, as part of the Golden Freeway project initiated in northern England to ameliorate the isolation experienced by families with a child with a life-limiting illness. The use of the computer and parental perceptions were recorded. Results indicated that social isolation was felt to have decreased and boys with dystrophinopathies enjoyed using the computers, and did so both for helping with their schoolwork and for entertainment.

There are no published studies investigating systematic interventions for the cognitive aspects of the dystrophinopathies. As such, recommendations for treatment must be based on individual assessment and application of interventions found to be beneficial for others with comparable difficulties are recommended. The published research delineates the areas of cognition and behavior that are at increased risk for being compromised in children with dystrophinopathies. Specifically, clinicians need to be aware that the child with dystrophinopathy may be at particular risk for language delays, learning disabilities (particularly developmental dyslexia) and behavioral anomalies consistent with attention deficits and autism spectrum disorders. Once the diagnosis is established in any child with dystrophinopathy, standard evidence-based interventions for the diagnosed cognitive and/or behavioral concerns should be initiated.

DYSTROPHINOPATHIES AND BRAIN FUNCTION

The role of dystrophin on brain function is offers an intriguing explanation for the observed cognitive and behavioral abnormalities associated with the dystrophinopathies (Anderson et al., 2002; Cyrulnik & Hinton, 2008; Mehler, 2000). Normally, dystrophin isoforms localize in the brain to circumscribed cerebral and cerebellar cortical regions (Boyce, Beggs, Feener, & Kunkel, 1991; Gorecki, Lukasiuk, Szklarczyk, & Kaczmarek, 1998; Gorecki et al., 1992; Kimura et al., 1997; Lederfein et al., 1992; Lidov, Byers, Watkins, & Kunkel, 1990; Tian et al., 1996; Uchino, Teramoto, Naoe, Miike et al., 1994; Uchino, Teramoto, Naoe, Yoshioka et al., 1994). These isoforms are absent in autopsied brains of individuals affected with dystrophinopathies as well as in the brains of the *mdx* mouse (a knock-out mouse model for dystrophinopathy).

In addition to being localized to specific brain areas, the brain-dystrophins have been localized to specific cell types. Dystrophins have been clearly identified in pyramidal, stellate and Purkinje cells (Tian et al., 1996; Uchino, Teramoto, Naoe, Yoshioka et al., 1994) and appear to be concentrated primarily in the post synaptic region (Jancsik & Hajos, 1998; Lidov et al., 1990). Further, brain dystrophins are also involved in developmental processes of the central nervous system. Transcripts have been found transiently during embryonic and fetal stages (Gorecki et al., 1998; Jones, Kim, & North, 1998; Rodius et al., 1997; Tian et al., 1996; Ueda et al., 1995).

Brain dystrophins have also been localized to specific GABAergic synapses, and it hypothesized that dystrophin in the brain functions to help anchor some neuronal post-synaptic receptor clusters. Reduced numbers of $GABA_A$ alpha 1 and 2 receptor subunit clusters have been found in *mdx* mouse cerebellum, hippocampus and amygdala. Further, when compared to littermate controls, the *mdx* mice have functional changes observed on post-synaptic currents (Anderson, Head, & Morley, 2003, 2004; Graciotti, Minelli, Minciacchi, Procopio, & Fulgenzi, 2008; Kueh, Head, & Morley, 2008; Vaillend & Billard, 2002; Vaillend, Rampon, Davis, & Laroche, 2002; Vaillend, Ungerer, & Billard, 1999). In *mdx* cerebellar Purkinje cells, the overall decreased number of $GABA_A$ receptor clusters at inhibitory synapses is associated with lowered amplitude and frequency of spontaneous miniature inhibitory postsynaptic currents (mIPSCs) (Anderson et al., 2002, 2003, 2004; Kueh et al., 2008). Likewise, in *mdx* amygdala, the reduced number of GABA receptors in the basolateral nucleus pyramidal neurons is associated with reduced frequency of norepinephrine-induced GABAergic inhibitory synaptic currents (Sekiguchi et al., 2009). While in the *mdx* hippocampal CA1 neurons, there is increase in frequency of miniature spontaneous inhibitory post-synaptic currents (Graciotti et al., 2008), believed to be due to the altered GABA functions that activate NMDA receptors (Vaillend & Billard, 2002; Vaillend et al., 1999).

The observed effects on *mdx* mouse behavior include impaired retention of learned tasks after long delays and enhancement of fear-motivated defensive behaviors, yet exploratory behaviors and rate of learning tasks were not impaired (Sekiguchi et al., 2009; Vaillend, Rendon, Misslin, & Ungerer, 1995). Thus, when compared to littermate controls, mice lacking dystrophin behave differently in specific ways, much as most boys with dystrophinopathies show specific cognitive and behavioral abnormalities.

Human functional studies of the brain in boys affected with dystrophinopathies are limited, but suggest central nervous system dysfunction secondary to dystrophin deficiency. Abnormal EEG findings have been demonstrated in about half of all DMD patients(Uchino, Teramoto, Naoe, Yoshioka et al., 1994). Flourodeoxyglucose positron emission tomography studies demonstrated cerebellar

Copyright Springer Publishing Company, LLC

hypometabolism and variable involvement of the associative cortical areas (Lee et al., 2002). Metabolic abnormalities have also been demonstrated in the brains of patients with dystrophinopathies; phosphorous-31 magnetic resonance spectroscopy of brain indicated a significantly increased ratio of inorganic phosphate to ATP (Koenig, Monaco, & Kunkel, 1988; Tracey et al., 1995).

For individuals with dystrophinopathies, the absence of dystrophin products from the brain is associated with cognitive and behavioral abnormalities. The presentation of the cognitive and behavioral deficits varies according to developmental level, socioeconomic status, family adjustment and educational opportunity. Nonetheless, lowered intellectual function preferentially affecting verbal skills has been consistently observed for the group (Cotton et al., 2005), as has increased risk for academic difficulties (Billard et al., 1992, 1998; Dorman et al., 1988; Hendriksen & Vles, 2006; Hinton et al., 2004) and behavioral problems (Darke et al., 2006; Hendriksen & Vles, 2008; Hinton et al., 2006; Poysky, 2007)

DYSTROPHINOPATHIES AND STRESS

The dystrophinopathies are both chronic and terminal. They involve specialized and time-consuming care, even when the terminal phase lies years in the future (Gravelle, 1997). As such, the diagnosis may be expected to have effects on the family similar to both chronic and terminal illnesses. The dystrophinopathies poses stressors in terms of daily care requirements, such as negotiating wheelchair transportation and meeting recommended physical therapy requirements. In addition, as with other complex chronic illnesses, many psychological adjustments become necessary, such as facing separation and loss, experiencing and expressing emotions (including anger, guilt, sadness, loss of control, resentment of increased demands) and changing values, expectations, roles and responsibilities (Copeland, 1988).

In a study comparing ratings of parents of boys with Duchenne muscular dystrophy to ratings of parents of children with other complex chronic conditions parents of boys with dystrophinopathies reported higher levels of stress than parents of children with cystic fibrosis or renal disease. All groups of children with a chronic disease reported more stress than parents of healthy controls, and in patterns consistent with the care requirements of their child's disease (Holroyd & Guthrie, 1986).

In a study examining stress in 36 families with adolescents with dystrophinopathies, familial stress was found to be associated with both psychosocial adjustment and intellectual function of the teen boys with DMD and not associated with sociodemographic variables (Reid & Renwick, 2001). The authors concluded that the effects of the dystrophinopathies extend well beyond the affected individual, and they recommended a holistic approach offering support for the whole family.

We also have examined parenting stress in 112 families with a son affected with dystrophinopathies (Nereo, Fee, & Hinton, 2003) and compared it to stress reported in mothers of children with cerebral palsy and normative data. The results indicated that the mothers of boys with dystrophinopathies report increased levels of stress relative to the normative sample, but the degree of the increase is comparable to that reported in mothers of children with cerebral palsy. The groups differed, however, in that among the group with dystrophinopathies, but not the cerebral palsy group, the high ratings of stress were found to be associated with increased behavior problems in the children. Thus, as expected, parents of children with physical disabilities (either dystrophinopathies or cerebral palsy) rate themselves as being more stressed than parents of able-bodied children. Yet surprisingly for the parents of the children with dystrophinopathies it is the children's behavior, rather than their physical limitations, that is most strongly related to the parents' perceived high stress levels,

These findings highlight the importance of a family's adjustment to a child diagnosed with the dystrophinopathies. How families adjust and cope to illness and developmental disability in general has been repeatedly documented to be associated with improved psychological well-being (Copeland, 1988). In the dystrophinopathies where the phenotype impacts on physical, intellectual and behavioral attributes and involves substantial personal and financial burden associated with care giving, the role of stress and adjustment on the family is particularly salient.

QUALITY OF LIFE IN OLDER INDIVIDUALS WITH DYSTROPHINOPATHIES

As individuals with dystrophinopathy age, they become less independent physically. With treatment designed to prolong life, many become adults who are dependent on mechanical ventilation. Two studies examining these individuals have found the majority have positive affect and most self-report good quality of life (Bach, Campagnolo, & Hoeman, 1991; Rahbek et al., 2005). Moreover, the affected individuals rate their own life satisfaction and affect as considerably higher than health care professionals judge them to be. Among 82 ventilator-assisted young men with dystrophinopathies in the United States, only 12.5% expressed dissatisfaction with their lives (compared to rate of 7% in the general population), despite being unable to engage in activities that others their age do (Bach et al., 1991). Similarly, when 65 Danish young adults with dystrophinopathies were surveyed, the majority responded that their quality of life was excellent, even while reporting lack of educational opportunity and a love life (Rahbek et al., 2005). These studies confirm the need to provide the older individuals with

Copyright Springer Publishing Company, LLC

dystrophinopathies as many opportunities as possible to lead an involved and satisfying life, as well as highlight the difficulty families and professionals may have in judging another's quality of life.

SPECIAL CONSIDERATIONS FOR THE PEDIATRIC NEUROPSYCHOLOGIST

When evaluating a child with dystrophinopathies, a number of factors should be considered. First, given that verbal skills are more likely compromised than nonverbal skills among these children, and given the fact that many tests rely heavily on verbal instructions and responses, a nonverbal measure of intellectual function is recommended. In this way, a general level of function that is not confounded by verbal limitations can be obtained. This is particularly important with younger children who may be less accustomed to the testing setting.

Additionally, language tests should be given that are broken into basic components. That is, data indicate that children with dystrophinopathies have difficulty processing phonemic information and lengthy strings of verbal material, yet have appropriate receptive vocabulary skills. Thus, a thorough language battery that examines individual contributions of language may be helpful in determining the exact nature of a child's cognitive profile. A measure of basic phonemic awareness and phonemic memory may be particularly valuable in detailing underlying deficits.

Other critical areas to assess include executive, academic and behavior domains. Tests of attention and executive functions should be offered in both verbal and nonverbal modalities to determine whether the overriding executive functions or the nature of the material (whether verbal or visual) is compromised. Test of academic achievement are necessary to determine whether the child is performing at the level expected. Particular focus should be given to a child's educational placement and whether it is appropriate for his needs.

Behavioral scales examining social functioning as well as possible signs of pathological attention, obsessive or depressive problems should be administered to parents, teachers and the affected child.

When working with older children, attention should be given to their physical limitations. Muscle fatigue is a common concern for the older child, and writing may be particularly difficult. Timed tests that involve manipulation of objects or writing may be compromised by slow motor speed. Further, as children's arms begin to weaken, support for their forearm should be offered. For many children, use of an adaptive keyboard with forearm support is an excellent intervention when writing becomes too difficult.

Additionally, care should be given to determining how the family as a whole is functioning. Examination of parent and sibling coping skills, adjustment and interpersonal relationships is necessary to ensure every family member's well-being.

SUMMARY

A diagnosis of dystrophinopathy brings with it an array of complications and adjustments that require input from multiple integrated specialties. Medical, adaptive, neuropsychological, behavioral and educational interventions are all necessary to ensure the best possible quality of life for those living with the dystrophinopathies. The genetic etiology of the dystrophinopathies and its resultant phenotype of progressive muscle weakness are well characterized, but a cure has yet to be found. In contrast to the severe physical manifestations of the dystrophinopathies, the cognitive and behavioral problems seem relatively mild and as such, may not get the full attention they merit. Nonetheless, to the individuals and families struggling with educational difficulties, these prove to be very stressful.

When evaluating a child with dystrophinopathy, the pediatric neuropsychologist needs to be aware that he is at increased risk of having lowered IQ, delayed language, compromised social skills, attention deficits, and poor academic achievement. Further, the neuropsychologist should consider that the neuropsychological profile associated with the dystrophinopathies is relatively selective, and affected individuals have weak immediate verbal memory and phonological processing skills with stronger visuospatial, declarative memory, and abstraction skills. The neuropsychologist also must consider that unlike the muscle aspects of the disease that are severe and get progressively worse with time, the neuropsychological aspects may be most pronounced in the younger child and lessen with time. With medical attention focused on the seriousness of the physical aspects of the disease, the neuropsychological ramifications often escape clinical attention. Yet the pediatric neuropsychologist can make crucial contributions to the child's care and well-being by highlighting areas that may be problematic and offering recommendations for treatment. By working closely the child, his family, his health care team and his school, the pediatric neuropsychologist can play a unique and valuable role in optimizing the quality of life for all individuals affected by the dystrophinopathies.

ACKNOWLEDGMENTS

The author is extremely grateful to all the families and clinicians with whom he worked, and who him taught him so much. This work was supported partially by grants from the National Institute of Neurological Disorders and Stroke (R01 NS047918–06A2) and the Muscular Dystrophy Association.

Copyright Springer Publishing Company, LLC

REFERENCES

Anderson, J. E., Head, S. I., & Morley, J. W. (2003). Altered inhibitory input to Purkinje cells of dystrophin-deficient mice. *Brain Research, 982*(2), 280–283.

Anderson, J. L., Head, S. I., & Morley, J. W. (2004). Long term depression is reduced in cerebellar Purkinje cells of dystrophin-deficient mdx mice. *Brain Research, 1019*(1–2), 289–292.

Anderson, J. L., Head, S. I., Rae, C., & Morley, J. W. (2002). Brain function in Duchenne muscular dystrophy. *Brain, 125*(Pt. 1), 4–13.

Bach, J. R., Campagnolo, D. I., & Hoeman, S. (1991). Life satisfaction of individuals with Duchenne muscular dystrophy using long-term mechanical ventilatory support. *American journal of physical medicine & rehabilitation , 70*(3), 129–135.

Billard, C., Gillet, P., Barthez, M., Hommet, C., & Bertrand, P. (1998). Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. *Developmental Medicine and Child Neurology, 40*(1), 12–20.

Billard, C., Gillet, P., Signoret, J. L., Uicaut, E., Bertrand, P., Fardeau, M., et al. (1992). Cognitive functions in Duchenne muscular dystrophy: A reappraisal and comparison with spinal muscular atrophy. *Neuromuscular Disorders, 2*(5–6), 371–378.

Boyce, F. M., Beggs, A. H., Feener, C., & Kunkel, L. M. (1991). Dystrophin is transcribed in brain from a distant upstream promoter. *Proceedings of the National Academy of Sciences of the United States of America, 88*(4), 1276–1280.

Bushby, K., & Straub, V. (2005). Nonmolecular treatment for muscular dystrophies. *Current Opinion in Neurology, 18*(5), 511–518.

Copeland, D. R. (1988). Stress management for chronic disease. In M. L. Russell (Ed.), *Stress and the patient's family* (pp. 30–48). New York: Pergamon.

Cotton, S., Crowe, S. F., & Voudouris, N. (1998). Neuropsychological profile of Duchenne muscular dystrophy. *Child Neuropsychology, 4*, 110–117.

Cotton, S., Voudouris, N. J., & Greenwood, K. M. (2001). Intelligence and Duchenne muscular dystrophy: Full-scale, verbal, and performance intelligence quotients. *Developmental Medicine and Child Neurology, 43*(7), 497–501.

Cotton, S. M., Voudouris, N. J., & Greenwood, K. M. (2005). Association between intellectual functioning and age in children and young adults with Duchenne muscular dystrophy: Further results from a meta-analysis. *Developmental Medicine and Child Neurology, 47*(4), 257–265.

Cyrulnik, S. E., & Hinton, V. J. (2008). Duchenne muscular dystrophy: A cerebellar disorder? *Neuroscience and Biobehavioral Reviews, 32*(3), 486–496.

Cyrulnik, S. E., Fee, R. J., De Vivo, D. C., Goldstein, E., & Hinton V. J. (2007). Delayed developmental language milestones in children with Duchenne's muscular dystrophy. J Pediatr. May; 150(5), 474–8.

Darke, J., Bushby, K., Le Couteur, A., & McConachie, H. (2006). Survey of behaviour problems in children with neuromuscular diseases. *European Journal of Paediatric Neurology, 10*(3), 129–134.

Dorman, C., Hurley, A. D., & D'Avignon, J. (1988). Language and learning disorders of older boys with Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology, 30*(3), 316–327.

Duchenne, G. B. (1968). Studies on pseudohypertrophic muscular paralysis or myosclerotic paralysis. *Archives of Neurology, 6*, 629–636.

Emery, A. E. (1991). Population frequencies of inherited neuromuscular diseases—A world survey. *Neuromuscular Disorders, 1*(1), 19–29.

Fitzpatrick, C., Barry, C., & Garvey, C. (1986). Psychiatric disorder among boys with Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology, 28*(5), 589–595.

Gorecki, D. C., Lukasiuk, K., Szklarczyk, A., & Kaczmarek, L. (1998). Kainate-evoked changes in dystrophin messenger RNA levels in the rat hippocampus. *Neuroscience, 84*(2), 467–477.

Gorecki, D. C., Monaco, A. P., Derry, J. M., Walker, A. P., Barnard, E. A., & Barnard, P. J. (1992). Expression of four alternative dystrophin transcripts in brain regions regulated by different promoters. *Human Molecular Genetics, 1*(7), 505–510.

Graciotti, L., Minelli, A., Minciacchi, D., Procopio, A., & Fulgenzi, G. (2008). GABAergic miniature spontaneous activity is increased in the CA1 hippocampal region of dystrophic mdx mice. *Neuromuscular Disorders, 18*(3), 220–226.

Gravelle, A. M. (1997). Caring for a child with a progressive illness during the complex chronic phase: Parents' experience of facing adversity. *Journal of Advanced Nursing, 25*(4), 738–745.

Harper, D. C. (1983). Personality correlates and degree of impairment in male adolescents with progressive and nonprogressive physical disorders. *Journal of Clinical Psychology,* Nov; *39*(6), 859–867.

Hendriksen, J. G., & Vles, J. S. (2006). Are males with Duchenne muscular dystrophy at risk for reading disabilities? *Pediatric Neurology, 34*(4), 296–300.

Hendriksen, J. G., & Vles, J. S. (2008). Neuropsychiatric disorders in males with Duchenne muscular dystrophy: Frequency rate of Attention-Deficit Hyperactivity Disorder (ADHD), autism spectrum disorder, and obsessive—Compulsive disorder. *Journal of Child Neurology, 23*(5), 477–481.

Hinton, V. J., Cyrulnik, S. E., Fee, R. J., Batchelder, A., Kiefel, J. M., Goldstein, E. M., et al. (in press, 2009) Association of autism spectrum disorders with dystrophinopathies. *Pediatric Neurology, 41*(5), 338–346.

Hinton, V. J., De Vivo, D. C., Nereo, N. E., Goldstein, E., & Stern, Y. (2000). Poor verbal working memory across intellectual level in boys with Duchenne dystrophy. *Neurology, 54*(11), 2127–2132.

Hinton, V. J., De Vivo, D. C., Nereo, N. E., Goldstein, E., & Stern, Y. (2001). Selective deficits in verbal working memory associated with a known genetic etiology: The neuropsychological profile of Duchenne muscular dystrophy. *Journal of the International Neuropsychological Society, 7*(1), 45–54.

Hinton, V. J., DeVivo, D. C., Fee, R. J., Goldstein, E., & Stern, Y. (2004). Investigation of poor academic achievement in children with Duchenne muscular dystrophy. *Learning Disabilites Research & Practice, 19*, 146–154.

Hinton, V. J., Kim, S. Y., Fee, R., Goldstein, E., & DeVivo, D. C. Cognitive and behavioral gains over time in Duchenne muscular dystrophy. Manuscript submitted for publication.

Hinton, V. J., Nereo, N. E., Fee, R. J., & Cyrulnik, S. E. (2006). Social behavior problems in boys with Duchenne muscular dystrophy. *Journal of Developmental and Behavioral Pediatrics, 27*(6), 470–476.

Holroyd, J., & Guthrie, D. (1986). Family stress with chronic childhood illness: Cystic fibrosis, neuromuscular disease, and renal disease. *Journal of Clinical Psychology, 42*(4), 552–561.

Jancsik, V., & Hajos, F. (1998). Differential distribution of dystrophin in postsynaptic densities of spine synapses. *Neuroreport, 9*(10), 2249–2251.

Jones, K. J., Kim, S. S., & North, K. N. (1998). Abnormalities of dystrophin, the sarcoglycans, and laminin alpha 2 in the muscular dystrophies. *Journal of Medical Genetics, 35*(5), 379–386.

Kaplan, L. C., Osborne, P., & Elias, E. (1986). The diagnosis of muscular dystrophy in patients referred for language delay. *Journal of Child Psychology Psychiatry,* Jul; *27*(4), 545–549.

Kimura, S., Abe, K., Suzuki, M., Ogawa, M., Yoshioka, K., Yamamura, K., et al. (1997). 2.1 kb 5′-flanking region of the brain type dystrophin gene directs the expression of lacZ in the cerebral cortex, but not in the hippocampus. *Journal of the Neurological Sciences, 147*(1), 13–20.

Koenig, M., Hoffman, E. P., Bertelson, C. J., Monaco, A. P., Feener, C., & Kunkel, L. M. (1987). Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. *Cell, 50*(3), 509–517.

Koenig, M., Monaco, A. P., & Kunkel, L. M. (1988). The complete sequence of dystrophin predicts a rod-shaped cytoskeletal protein. *Cell, 53*(2), 219–226.

Komoto, J., Usui, S., Otsuki, S., & Terao, A. (1984). Infantile autism and Duchenne muscular dystrophy. *Journal of Autism and Developmental Disorders, 14*(2), 191–195.

Copyright Springer Publishing Company, LLC

Kueh, S. L., Head, S. I., & Morley, J. W. (2008). GABA(A) receptor expression and inhibitory post-synaptic currents in cerebellar Purkinje cells in dystrophin-deficient mdx mice. *Clinical and Experimental Pharmacology & Physiology, 35*(2), 207–210.

Lederfein, D., Levy, Z., Augier, N., Mornet, D., Morris, G., Fuchs, O., et al. (1992). A 71-kilodalton protein is a major product of the Duchenne muscular dystrophy gene in brain and other non-muscle tissues. *Proceedings of the National Academy of Sciences of the United States of America, 89*(12), 5346–5350.

Lee, J. S., Pfund, Z., Juhasz, C., Behen, M. E., Muzik, O., Chugani, D. C., et al. (2002). Altered regional brain glucose metabolism in Duchenne muscular dystrophy: A pet study. *Muscle Nerve, 26*(4), 506–512.

Leibowitz, D., & Dubowitz, V. (1981). Intellect and behaviour in Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology, 23*(5), 577–590.

Lidov, H. G., Byers, T. J., Watkins, S. C., & Kunkel, L. M. (1990). Localization of dystrophin to postsynaptic regions of central nervous system cortical neurons. *Nature, 348*(6303), 725–728.

McDonald, C. M., Abresch, R. T., Carter, G. T., Fowler, W. M., Jr., Johnson, E. R., & Kilmer, D. D. (1995a). Profiles of neuromuscular diseases. Becker's muscular dystrophy. *American Journal of Physical Medicine & Rehabilitation, 74*(Suppl. 5), S93–S103.

McDonald, C. M., Abresch, R. T., Carter, G. T., Fowler, W. M., Jr., Johnson, E. R., Kilmer, D. D., et al. (1995b). Profiles of neuromuscular diseases. Duchenne muscular dystrophy. *American Journal of Physical Medicine & Rehabilitation, 74*(Suppl. 5), S70–S92.

Mehler, M. F. (2000). Brain dystrophin, neurogenetics and mental retardation. *Brain Research Reviews, 32*(1), 277–307.

Nereo, N. E., Fee, R. J., & Hinton, V. J. (2003). Parental stress in mothers of boys with Duchenne muscular dystrophy. *Journal of Pediatric Psychology, 28*(7), 473–484.

Ogasawara, A. (1989). Downward shift in IQ in persons with Duchenne muscular dystrophy compared to those with spinal muscular atrophy. *American Journal of Mental Retardation, 93*(5), 544–547.

Poysky, J. (2007). Behavior patterns in Duchenne muscular dystrophy: Report on the parent project muscular dystrophy behavior workshop 8–9 of December 2006, Philadelphia, USA. *Neuromuscular Disorders, 17*(11–12), 986–994.

Rahbek, J., Werge, B., Madsen, A., Marquardt, J., Steffensen, B. F., & Jeppesen, J. (2005). Adultlife with Duchenne muscular dystrophy: observations among an emerging andunforeseen patient population. *Pediatric Rehabiliation,* Jan-Mar; *8*(1), 17–28.

Reid, D. T., & Renwick, R. M. (2001). Relating familial stress to the psychosocial adjustment of adolescents with Duchenne muscular dystrophy. *International Journal Of rehabilitation Research, 24*(2), 83–93.

Rodius, F., Claudepierre, T., Rosas-Vargas, H., Cisneros, B., Montanez, C., Dreyfus, H., et al. (1997). Dystrophins in developing retina: Dp260 expression correlates with synaptic maturation. *Neuroreport, 8*(9–10), 2383–2387.

Sekiguchi, M., Zushida, K., Yoshida, M., Maekawa, M., Kamichi, S., Sahara, Y., et al. (2009). A deficit of brain dystrophin impairs specific amygdala GABAergic transmission and enhances defensive behaviour in mice. *Brain, 132*(Pt. 1), 124–135.

Smith, R. A., Sibert, J. R., & Harper, P. S. (1990). Early development of boys with Duchenne muscular dystrophy. *Developmental Medicine Child Neurology, 32*, 519–527.

Sollee, N. D., Latham, E. E., Kindlon, D. J., & Bresnan, M. J. (1985). Neuropsychological impairment in Duchenne muscular dystrophy. *Journal of Clinical and Experimental Neuropsychology, 7*(5), 486–496.

Soutter, J., Hamilton, N., Russell, P., Russell, C., Bushby, K., Sloper, P., et al. (2004). The golden freeway: A preliminary evaluation of a pilot study advancing information technology as a social intervention for boys with Duchenne muscular dystrophy and their families. *Health & Social Care in the Community, 12*(1), 25–33.

Thompson, R. J., Jr., Zeman, J. L., Fanurik, D., & Sirotkin-Roses, M. (1992). The role of parent stress and coping and family functioning in parent and child adjustment to Duchenne muscular dystrophy. *Journal of Clinical Psychology, 48*(1), 11–19.

Tian, M., Jacobson, C., Gee, S. H., Campbell, K. P., Carbonetto, S., & Jucker, M. (1996). Dystroglycan in the cerebellum is a laminin alpha 2-chain binding protein at the glial-vascular interface and is expressed in Purkinje cells. *European Journal of Neuroscience, 8*(12), 2739–2747.

Tracey, I., Scott, R. B., Thompson, C. H., Dunn, J. F., Barnes, P. R., Styles, P., et al. (1995). Brain abnormalities in Duchenne muscular dystrophy: Phosphorus-31 magnetic resonance spectroscopy and neuropsychological study. *Lancet, 345*(8960), 1260–1264.

Uchino, M., Teramoto, H., Naoe, H., Miike, T., Yoshioka, K., & Ando, M. (1994). Dystrophin and dystrophin-related protein in the central nervous system of normal controls and Duchenne muscular dystrophy. *Acta Neuropathologica (Berlin), 87*(2), 129–134.

Uchino, M., Teramoto, H., Naoe, H., Yoshioka, K., Miike, T., & Ando, M. (1994). Localisation and characterisation of dystrophin in the central nervous system of controls and patients with Duchenne muscular dystrophy. *Journal of Neurology, Neurosurgery, and Psychiatry, 57*(4), 426–429.

Ueda, H., Kobayashi, T., Mitsui, K., Tsurugi, K., Tsukahara, S., & Ohno, S. (1995). Dystrophin localization at presynapse in rat retina revealed by immunoelectron microscopy. *Investigative Ophthalmology & Visual Science, 36*(11), 2318–2322.

Vaillend, C., & Billard, J. M. (2002). Facilitated CA1 hippocampal synaptic plasticity in dystrophin-deficient mice: Role for GABAA receptors? *Hippocampus, 12*(6), 713–717.

Vaillend, C., Rampon, C., Davis, S., & Laroche, S. (2002). Gene control of synaptic plasticity and memory formation: Implications for diseases and therapeutic strategies. *Current Molecular Medicine, 2*(7), 613–628.

Vaillend, C., Rendon, A., Misslin, R., & Ungerer, A. (1995). Influence of dystrophin-gene mutation on mdx mouse behavior. I. Retention deficits at long delays in spontaneous alternation and bar-pressing tasks. *Behavior Genetics, 25*(6), 569–579.

Vaillend, C., Ungerer, A., & Billard, J. M. (1999). Facilitated NMDA receptor-mediated synaptic plasticity in the hippocampal CA1 area of dystrophin-deficient mice. *Synapse, 33*(1), 59–70.

Whelan, T. B. (1987). Neuropsychological performance of children with Duchenne muscular dystrophy and spinal muscle atrophy. *Developmental Medicine and Child Neurology, 29*(2), 212–220.

Wicksell, R. K., Kihlgren, M., Melin, L., & Eeg-Olofsson, O. (2004). Specific cognitive deficits are common in children with Duchenne muscular dystrophy. *Developmental Medicine and Child Neurology, 46*(3), 154–159.

Worden, D. K., & Vignos, P. J., Jr. (1962). Intellectual function in childhood progressive muscular dystrophy. *Pediatrics, 29*, 968–977.

Wu, J. Y., Kuban, K. C., Allred, E., Shapiro, F., & Darras, B. T. (2005). Association of Duchenne muscular dystrophy with autism spectrum disorder. *Journal of Child Neurology, 20*(10), 790–795.

Zwaigenbaum, L., & Tarnopolsky, M. (2003). Two children with muscular dystrophies ascertained due to referral for diagnosis of autism. *Journal of Autism and Developmental Disorders, 33*(2), 193–199.

Copyright Springer Publishing Company, LLC