Neurogenetic Developmental Disorders

Variation of Manifestation in Childhood

edited by

Michèle M. M. Mazzocco
and Judith L. Ross

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The MIT Press
Cambridge, Massachusetts
London, England

For information about special quantity discounts, please email special_sales@mitpress.mit.edu

This book was set in Times New Roman on 3B2 by Asco Typesetters, Hong Kong.
Printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

Neurogenetic developmental disorders : variation of manifestation in childhood /
Michèle M. M. Mazzocco and Judith L. Ross, editors.
p. ; cm. — (Issues in clinical and cognitive neuropsychology)
Includes bibliographical references and index.
ISBN 978-0-262-13480-4 (hc : alk. paper)
1. Developmental disabilities—Genetic aspects. 2. Chromosome abnormalities. 3. Neurogenetics.
4. Pediatric neuropsychology. I. Mazzocco, Michèle M. M. II. Ross, Judith L. III. Series.
[DNLM: 1. Genetic Diseases, Inborn—diagnosis. 2. Child. 3. Genetic Counseling—methods.
4. Heredodegenerative Disorders, Nervous System—diagnosis. 5. Sex Chromosome Disorders—
diagnosis. WS 200 N494 2007]

RJ506.D47N486 2007
619.92'8588—dc22 2006046910

10 9 8 7 6 5 4 3 2 1

4 Duchenne Muscular Dystrophy

Veronica J. Hinton and Edward M. Goldstein

Duchenne muscular dystrophy is a devastating neurogenetic developmental disorder that occurs in about 1 in 3,500 male births (Emery, 1991). Duchenne is known primarily as a disease of muscle with an unforgivingly predictable course that is both progressive and fatal. Yet it affects far more than just muscles. Cognitive and behavioral characteristics are also associated with the disease, although their presentation is more variable than that of the physical characteristics. Children with Duchenne appear normal at birth and become weaker with age, and most die before their third decade. 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 et al., 1995). Duchenne also causes cognitive difficulties including mental retardation, yet the majority of affected boys are of normal intellectual level (Cotton et al., 2001). Further, Duchenne is associated with some behavioral characteristics, including limited social skills and depression (Hinton, Nereo, et al., 2006). Some behaviors are likely due to the underlying etiology, while others may be reactive responses to the condition. Duchenne impacts on more than just the affected individual; the diagnosis causes changes in families and family members' roles. Duchenne brings with it physical, emotional, and financial burdens. A child diagnosed with Duchenne will require multiple interventions on multiple levels, and the needs of the child will change with time.

The combination of symptoms, along with the progressive nature of the disease, makes characterizing the phenotype particularly problematic. In this chapter we will review what is known of Duchenne in the school-age child; we will review basic mechanisms, describe physical presentation and medical management of Duchenne, and give a particular emphasis to the cognitive and behavioral presentation. Four cases illustrating the combined impact of Duchenne on physical, cognitive, behavioral, and family status will be described, and potential interventions will be discussed at the chapter's end.

Duchenne and Becker Muscular Dystrophy

Duchenne 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, and affects all ethnic groups (Emery, 1991, 1992). It is X linked, and boys are primarily affected. Although there are cases of affected girls, they are very rare (Emery, 1992). Duchenne runs in families where women are carriers and have affected sons; yet about one third of all cases are spontaneous, new mutations. Duchenne is due to a mutated gene that inhibits the production of the protein dystrophin that normally is found in muscle and brain. Becker muscular dystrophy, a milder form of the disease with later onset and slower progression, has a lower incidence than Duchenne. In Becker muscular dystrophy, an abnormal dystrophin molecule is made that does not function in muscle as efficiently as the normal protein. Prevalence rates for Becker muscular dystrophy range from 12 to 27 per million (Emery, 1991).

Positive diagnosis for Duchenne is based on the following criteria: (a) male; (b) onset of weakness before age 5; (c) initial proximal muscle weakness; (d) muscle hypertrophy, most prominent in the calves; (e) elevated creatine kinase activity of at least 10 times above the upper limit of normal; and either (f) positive histopathological confirmation by muscle biopsy or (g) molecular characterization of a mutation within the gene for dystrophin.

History

In 1868, the French neurologist Guillaume-Benjamin-Amand Duchenne published detailed observations in 13 children with a progressive neuromuscular disorder (Duchenne, 1868). He referred to it as pseudohypertrophic dystrophy, due to the overdevelopment of calf muscles in boys with the disease. Duchenne was not the first to describe the illness, but his detailed report examining the signs and symptoms of the disease caused it to become known as Duchenne's muscular dystrophy. Duchenne noted that the disease ran in families and affected boys, and he deduced that it was inherited. Further, he noted that the boys with the disease were "mentally dull." The specific cause of the disease, however, was unknown, and the cognitive limitations were often thought to be associated with disability, but not disease specific.

Gene

In 1986, the gene for Duchenne muscular dystrophy was discovered on the short arm of the X chromosome at position Xp21 (Monaco et al., 1986). It was the first gene to be discovered using positional cloning techniques. The gene is the largest

in the human genome, at greater than 2.5 Mb in length, and has a high proclivity for mutation (Beggs & Kunkel, 1990; Calvert et al., 1996; Drenckhahn et al., 1996; Hyser et al., 1987; Koenig et al., 1987; Wilton et al., 1998). One third of boys with Duchenne are the result of spontaneous mutations in the dystrophin gene, with the patient's mother maintaining a normal X chromosomal constitution. Deletion of genetic material in the dystrophin gene is detected by conventional polymerase chain reaction/gel electrophoresis technologies in about two thirds of boys with Duchenne. These deletions may occur at any point along the dystrophin gene, though there are two "hot spots" within the gene where the bulk of these mutations occur. In the remaining one third of affected males this testing is negative, due to the presence of point mutations or small deletions/insertions of genetic material (Mendell et al., 2001). The development of techniques to rapidly sequence the dystrophin gene now permits the detection of mutations in these patients for diagnostic purposes (Flanigan et al., 2003). Duchenne is associated with mutations that disrupt essential functional domains of the dystrophin molecule, or mutations that shift the reading frame of DNA transcription, resulting in a truncated, unstable, and nonfunctional dystrophin (Muntoni et al., 2003).

Dystrophin

A year after the discovery of the gene, its protein product, dystrophin, was identified (Hoffman et al., 1987). Dystrophin is a 427 kDa protein that is absent in the muscles of boys with Duchenne (Hoffman et al., 1987; Hoffman & Wang, 1993; Koenig et al., 1988). The gene also codes for other protein products that localize to other tissue types, including the brain (Boyce et al., 1991; Gorecki et al., 1992; Lederfein et al., 1992; Uchino et al., 1994a). Different internal promoters in the gene and posttranscriptional splicing regulate expression of the products. Three products are full-length 427 kDa molecules, and four are shorter with molecular weights of 260 kDa, 140 kDa, 116 kDa, and 71–78 kDa, respectively. Dp427, Dp140, Dp116, and Dp71 have been localized to brain tissue, and their absence in boys with Duchenne has been invoked as the reason for cognitive dysfunction in the context of their muscle disease (Felisari et al., 2000).

In muscles, dystrophin is localized to the sarcolemma in a glycoprotein complex. It serves to stabilize the plasma membrane during muscle contractions. In boys with Duchenne, dystrophin is missing, while in Becker muscular dystrophy an abnormal dystrophin molecule is made. With muscle use, tears develop in the cellular membrane and calcium ions enter into the cells, disrupting the intracellular homeostasis and causing the cells to break down. As a result, skeletal muscle fibers continually deteriorate and regenerate until they can no longer repair themselves and the muscle

Table 4.1
Duchenne muscular dystrophy affects multiple systems in the body that result in a range of disabilities requiring treatment

System/Organ	Impairment	Disability	Treatment
Skeletal muscle	Strength and endurance	Motor performance Mobility Fatigue	Corticosteroids Physical therapy
Bone and joint	Joint contractures Spine deformity	Function Pain and deformity	Physical therapy—stretching, Orthotics, surgery
Lungs	Pulmonary function	Restrictive lung disease Fatigue	Positive airway pressure, Cough assist, Nocturnal ventilation
Heart	Cardiomyopathy Conduction defects	Cardiopulmonary adaptations Fatigue	Pharmacologic intervention
Brain	Intellectual capacity Behavioral issues	Cognitive deficits Psychosocial adjustment Stress	Educational support, individual counseling, family therapy, Social support

fibers undergo irreversible degradation with replacement by fat and connective tissue. For the child with Duchenne, this presents as progressive weakness that is fatal. For the child with Becker muscular dystrophy, onset is later and disease progression is slower.

Physical Presentation

Natural history studies have been conducted to characterize the course of the disease. The Clinical Investigation of Duchenne Dystrophy group followed more than 200 individuals affected with Duchenne for more than 10 years (Brooke et al., 1983; Hyser et al., 1987; Mendell et al., 1987). The group measured numerous physical characteristics with standardized measures and developed a scoring system to allow for accurate assessment of severity, so that effects of interventions could be effectively tested. The results confirmed that the disease impacts multiple systems and organs as described in table 4.1. Moreover, although the rate of progression varies among boys, the course is markedly similar and all children progress through the same stages of the illness.

Initially, a boy with Duchenne will appear to be developing normally (figure 4.1). At age 2 to 3, 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, will have difficulty climbing stairs, and will begin to have frequent falls. As the boy's muscles continue to weaken, he will have greater dif-

Figure 4.1
Youngsters with Duchenne muscular dystrophy are visually indistinguishable from other children. There are no dismorphic facial characteristics associated with the disorder. This boy walks but cannot jump or ride a bike like his peers.

ficulty 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 to steady himself. If he is asked to raise himself from a sitting position on the floor, he will generally 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 be dependant on a wheelchair for extended mobility (figures 4.2, 4.3). Over the next few years, he will lose significant skeletal muscle strength and will need assistance in all activities that require his legs, 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

Figure 4.2
Most children with Duchenne muscular dystrophy share the interests and activities of their peers. Although dependent on a wheelchair to get around, this boy lives a full and varied life. He is an avid baseball fan and enjoys sharing his enthusiasm for his team with his friends.

resulting from extreme muscle weakness. Duchenne is the most common inherited fatal childhood disorder.

Research supported by the National Institute on Disability and Rehabilitation further characterized the percentage of individuals with specific disease-related features (McDonald et al., 1995). Table 4.2 is adapted from their findings and shows changes in percentages of children affected with different symptoms over time.

Medical Management

There is currently no known cure for Duchenne, and treatment focuses on slowing the disease progression and improving the quality of life of those affected. Medical management involves multiple interventions to help ameliorate symptoms associated with different systems involved (table 4.1). Protracted corticosteroid therapy in order to slow the progression of muscle weakness is the primary treatment for Duchenne. In 2005, the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society published a review

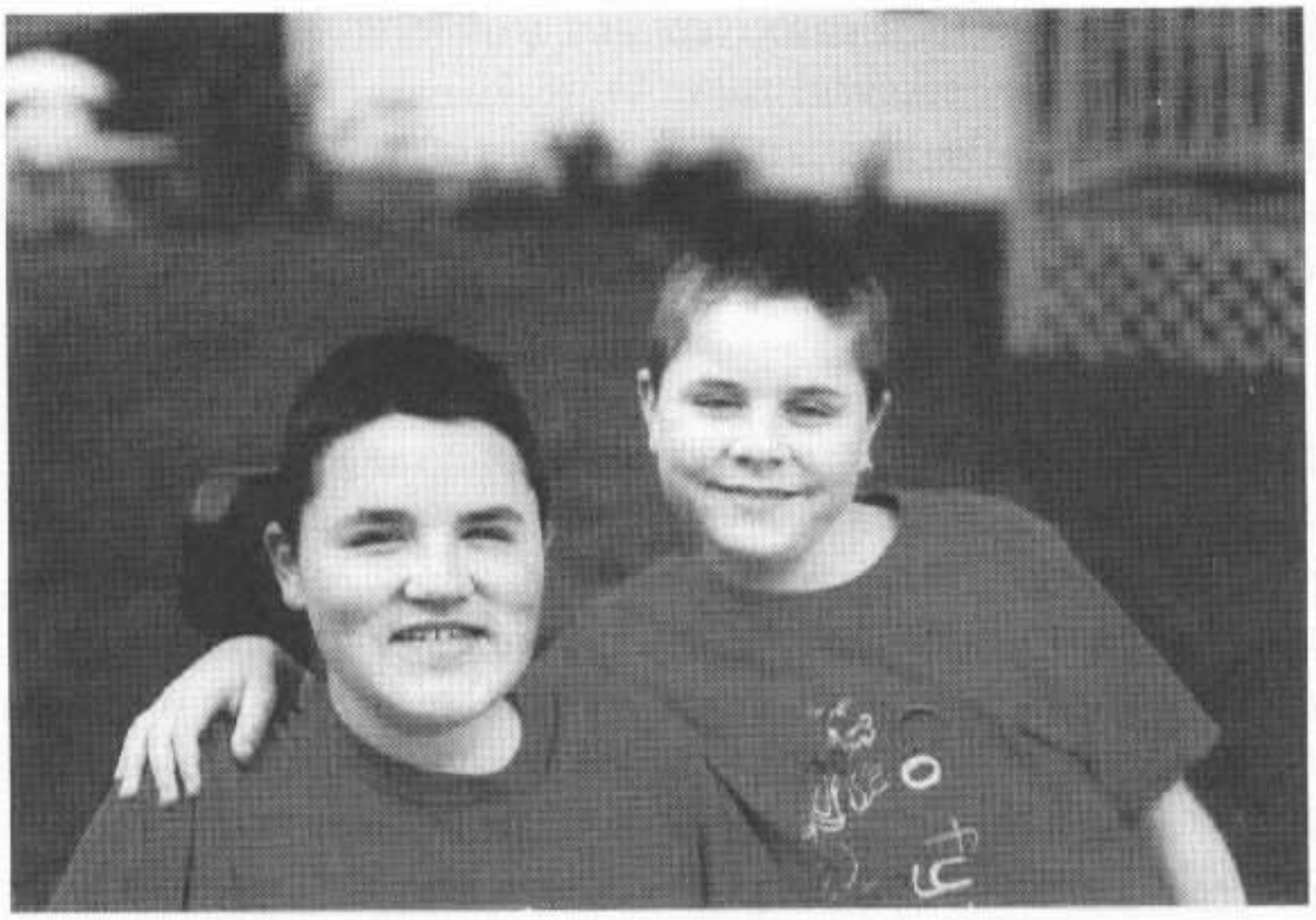

Figure 4.3
These brothers both have Duchenne muscular dystrophy. The older brother can no longer get around without the aid of a wheelchair, while his younger brother still walks independently. Both boys have the Cushingoid facial characteristics associated with long-term steroid use.

Table 4.2
The percentage of individuals affected with different physical symptoms of Duchenne muscular dystrophy varies according age

	Age (years)			
Impairment	<9	9–13	14–16	>16
Joint contractures (%)	18	68	97	100
Scoliosis (%)	15	50	70	90
Respiratory complications (%)	7	17	—	48
Cardiovascular complications (%)	—	9	24	67

Note: The above data show that as age increases, a greater percentage of affected boys will develop the listed impairments (McDonald et al., 1995).

of the relevant literature that confirmed that daily corticosteroid treatment with prednisone (0.75 or 1.5 mg/kg/day) increased muscle strength, performance, and pulmonary function and significantly decreased the progression of weakness (Moxley et al., 2005). In many boys with Duchenne, treatment with corticosteroids may also result in weight gain and development of Cushingoid facial appearance.

To maintain range of motion and optimize muscle strength and endurance, physical therapy consisting of a daily exercise program is also prescribed. Physical and occupational therapists assist with the mobilization of adaptive equipment to

optimize function for children and their caregivers and to minimize complications such as skin breakdown and musculoskeletal pain. As weakness progresses, affected boys develop contractures in both the arms and legs. Range of motion exercises are performed to minimize their development, along with the application of braces where appropriate. Most commonly, night splints are employed to stretch the Achilles tendon and reduce forefoot gait.

If a functionally disabling contracture develops despite these interventions, consideration may be given to orthopedic surgery to improve joint range of motion. Regrettably, with wheelchair dependence, multifocal contractures develop in all boys with Duchenne. Additionally, scoliosis develops in the majority of boys who are wheelchair dependent. Left untreated, scoliosis produces pain and difficulty with positioning and may compromise respiratory status. As such, most boys with Duchenne will undergo spine fusion surgery in their early teen to midteen years.

Additional measures to maximize respiratory function include immunizations to reduce the frequency and severity of infections, chest physical therapy, aerosol treatments, cough assist machines, and the use of positive pressure ventilation.

Like the respiratory muscles, the heart may also be weakened by Duchenne and cardiac function must be carefully monitored. Regular electrocardiograms and echocardiograms are performed looking for evidence of cardiomyopathy. If heart muscle fails, pharmacologic therapies are invoked to improve heart contractility and reduce the heart's workload.

Finally, dietary management is critical to maintaining good health in boys with Duchenne. In addition to treating frequent problems like constipation, dietary intake must be carefully monitored to avoid obesity. Dietary management is particularly important in the setting of steroid therapy. Calcium and vitamin D supplements are prescribed to maintain bone density, while caloric restriction is frequently necessary to prevent weight gain.

Dystrophin and the Brain

The discovery that the mutated gene in Duchenne codes for multiple protein products that localize to separate tissue types, including the brain, offers a potential explanation for the cognitive manifestation of the Duchenne phenotype (Anderson et al., 2002; Mehler, 2000). In the brain, dystrophin isoforms normally localize to circumscribed cerebral and cerebellar cortical regions (Boyce et al., 1991; Gorecki et al., 1992; Kimura et al., 1997; Lederfein et al., 1992; Gorecki et al., 1998; Lidov et al., 1990; Tian et al., 1996; Uchino et al., 1994a; Uchino et al., 1994b) and are absent in autopsied brains of individuals affected with Duchenne. Brain dystrophins have been localized to specific cell types in both neurons and glia. In neurons, dystrophins have

been clearly identified in pyramidal, stellate, and Purkinje cells (Tian et al., 1996; Uchino et al., 1994) and appear to be concentrated primarily in the postsynaptic region (Jancsik & Hajos, 1998; Lidov, Byers, Watkins, & Kunkel, 1990). Although the contribution of the dystrophin brain products to function is unknown, they have been hypothesized to play a structural role that aids in synaptic transmission (e.g., Jancsik & Hajos, 1998) and may modulate neuronal function (Gorecki et al., 1998; Kimura et al., 1997).

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 et al., 1998; Rodius et al., 1997; Ueda et al., 1995; Tian et al., 1996). Neuroradiologic studies reveal no obvious structural anomalies, although older patients may exhibit some cerebral atrophy (Echenne et al., 1998). Functional studies are limited but suggest central nervous system dysfunction secondary to dystrophin deficiency. Abnormal EEG findings have been demonstrated in about half of all patients with Duchenne (Uchino et al., 1994b). Flourodeoxyglucose positron emission tomography studies demonstrated cerebellar 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 Duchenne; phosphorous-31 magnetic resonance spectroscopy of brain indicated a significantly increased ratio of inorganic phosphate to ATP (Koenig et al., 1988; Tracey et al., 1995). For the child with Duchenne, this is associated with lowered intellectual function preferentially affecting verbal skills and an increased incidence of mental retardation (Cotton et al., 2001).

IQ Scores

In general, the distribution of IQ scores among affected boys appears to be shifted down about 1 *SD* from the population mean. No epidemiological studies have been done to document the presentation of language or intellectual deficits among children diagnosed with Duchenne, so estimates of ranges of impairment are based on samples of children who are available and willing to participate in studies and may well overrepresent those with cognitive deficits. Table 4.3 presents information on the percentage of children affected with specific cognitive and behavioral characteristics derived from potentially biased convenience samples, rather than population based studies.

A meta-analysis of 32 published papers examining IQ among a total of 1,146 individuals with Duchenne found the mean full scale IQ value was 80.2 with a standard deviation of 19.3 (Cotton et al., 2001). Scores were shifted down from the normative population, but the frequency distribution did not differ significantly. Thus, as a

Table 4.3
The percentage of individuals with Duchenne muscular dystrophy who have significant cognitive and/or behavioral difficulties

Source	Diagnosis	% Found	% Expected in General Population
Emery, 1992	Mental retardation	19	2
Cotton, Voudouris, & Greenwood, 2001		35	2
Wu, Kuban, Allred, Shapiro, & Darras, 2005	Autism	3.8	0.2
Hinton, Batchelder, Cyrulnik, Fee, & Kiefel, 2006		13	0.2

Note: Data are from convenience samples, rather than a population survey, so numbers presented may be biased.

result of this downward shift, 35% of the children with Duchenne had IQ scores in the "mentally retarded" range (or scores less than 70). Most children, however, had normal intellectual level.

As a group, boys with Duchenne have significantly lower Verbal IQ scores than Performance IQ scores. When available data were collapsed across studies in a sample of 878 individuals affected with Duchenne, the mean group difference between the two scales was five points, which was statistically significant (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.

Specific Cognitive Skills

The methods used to examine cognitive skills associated with Duchenne have differed across studies, 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 Duchenne 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 Duchenne to those with spinal muscular atrophy (SMA), a different neuromuscular disorder. Results have demonstrated that the children with Duchenne have poorer verbal, immediate memory, and reading skills than their SMA peers (Billard et al., 1992; Billard et al., 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 Duchenne to that of their unaffected siblings. These results also showed poorer verbal, immediate memory, and academic skills (Hinton et al., 2001; Hinton et al., 2004; Hinton et al., in press). Specifically, children with Duchenne 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 Duchenne performed 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 Duchenne, 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 among children with Duchenne is great, with as many as 35% manifesting 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 testing. Even among those children who do not have mental retardation, IQ may have significant influence. To control for this, researchers have compared children with Duchenne to IQ-matched and age-matched children without Duchenne. On neuropsychological test batteries, the group with Duchenne generally performed more poorly than the comparison group on measures of memory (Cotton et al., 1998; Wicksell et al., 2004). The most striking finding of these comparisons, however, was the number of measures the two groups performed equivalently on, including measures of vocabulary, nonverbal reasoning, and a variety of visualspatial measures.

To determine whether individual strengths and weaknesses were similar across intellectual level, we examined boys with Duchenne by individually rank ordering their performance on standardized subtests and compared the relative rankings across individuals. The results demonstrated that boys with Duchenne 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

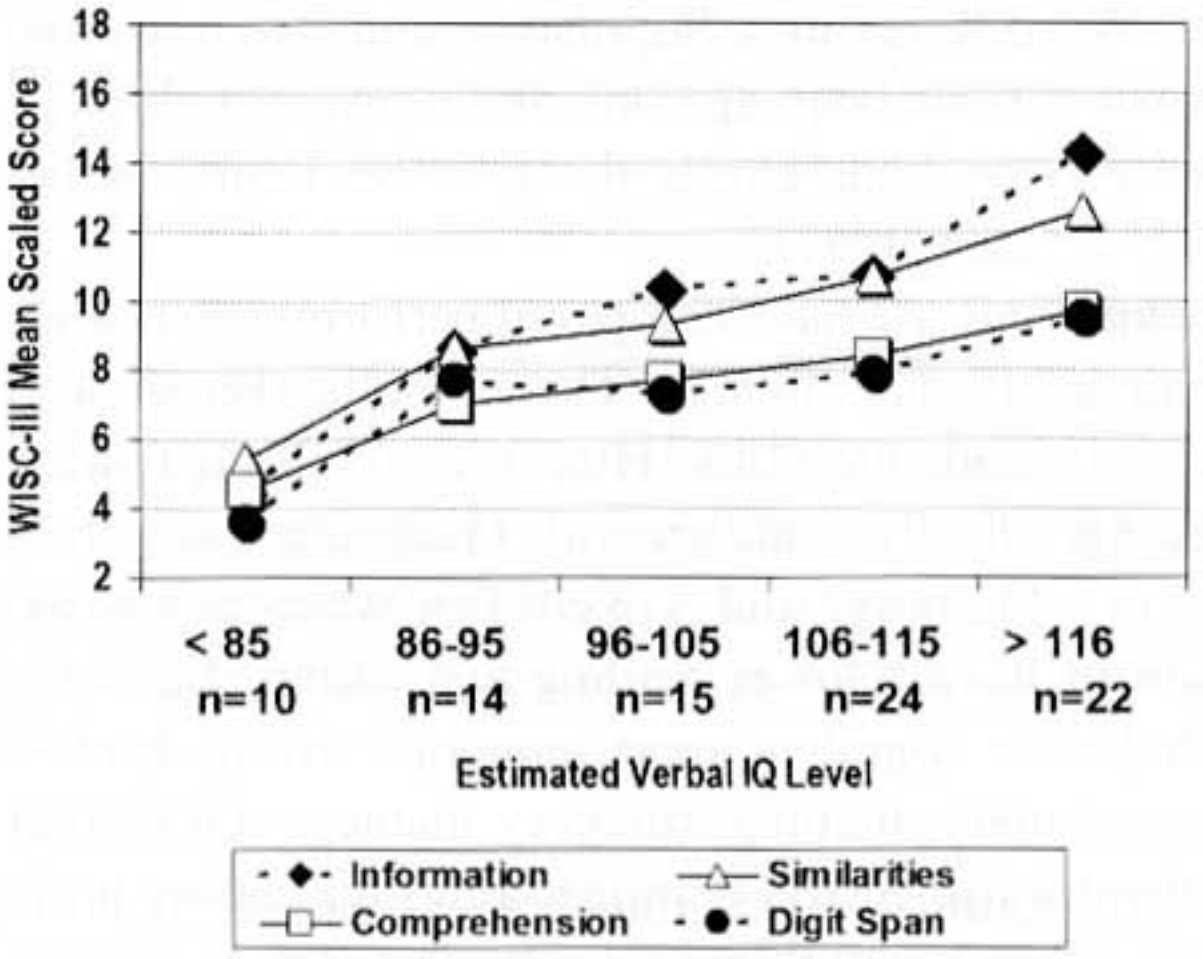

Figure 4.4
Children with Duchenne muscular dystrophy show relative weakness on Digit Span and Comprehension subtests, regardless of overall intellectual level. Participants (ages 6 to 16 years) are grouped according to their estimated Verbal IQ (as determined by performance on the Peabody Picture Vocabulary Test), and mean scaled scores on four subtests of the Wechlser Intelligence Scale for Children—III (WISC–III) are plotted. Note that scores on Digit Span and Comprehension are lowest across the IQ groups.

(Hinton et al., 2000). Plotting the data across IQ levels also shows that some scores are preferentially lower over the range of IQ (figures 4.4 and 4.5). 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 Duchenne 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 Duchenne 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 (McDonald et al., 1995; Prosser et al., 1969). Moreover, there has been no evidence to indicate that more severely disabled individuals have more pronounced intellectual deficits (Glaub & Mechler, 1987; Leibowitz & Dubowitz, 1981; Zellweger & Hanson, 1967).

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 Duchenne 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

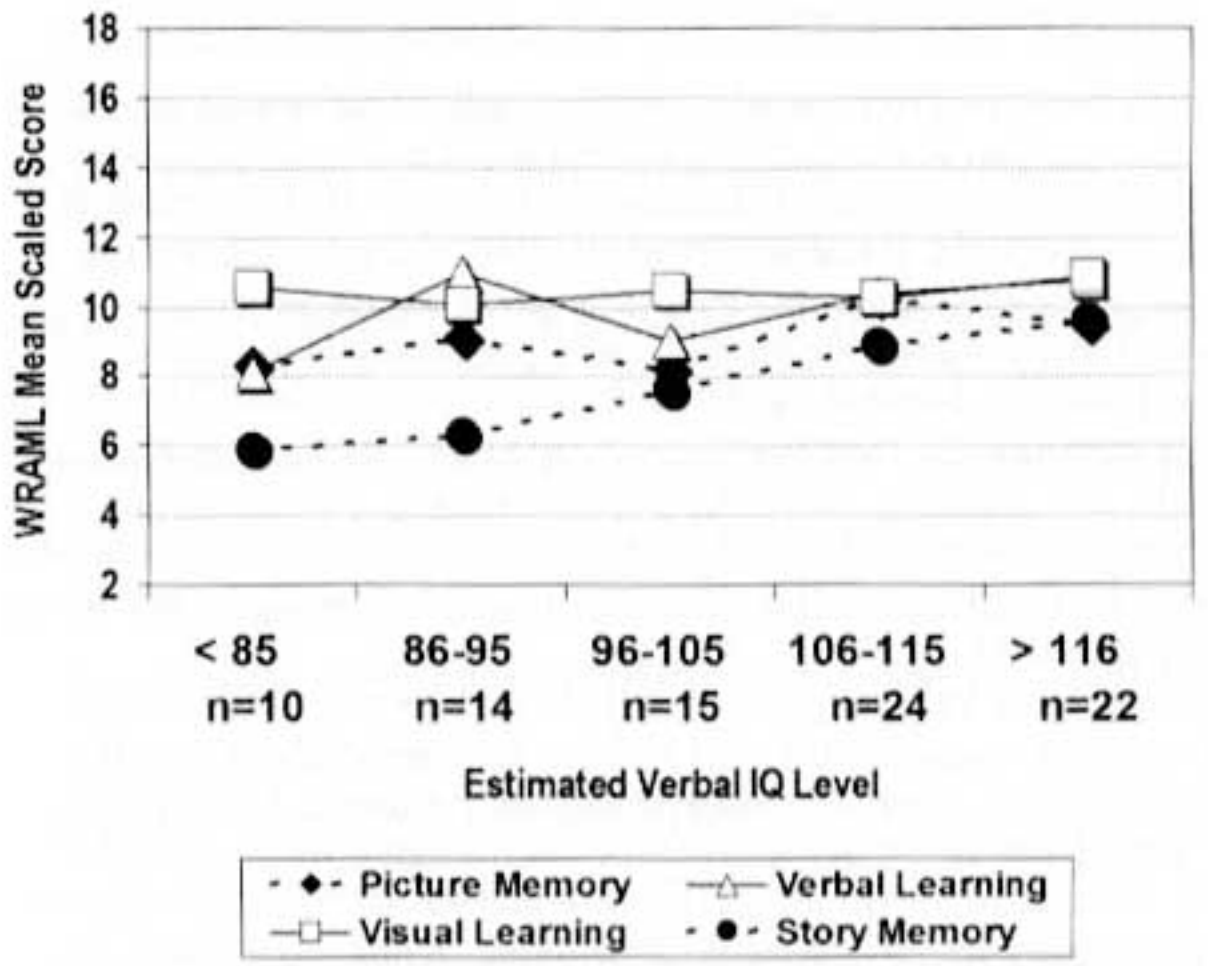

Figure 4.5
Children with Duchenne muscular dystrophy show relative weakness on Story Memory, irrespective of general intellectual level. Participants (ages 6 to 16 years) are grouped according to their estimated Verbal IQ (as determined by performance on the Peabody Picture Vocabulary Test), and mean scaled scores on four subtests of the Wide Range Assessment of Memory and Learning (WRAML) are plotted. Note that scores on Story Memory are lowest across the IQ groups.

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 Duchenne (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 (Hinton et al., in submission; Sollee et al., 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., in press; Kaplan et al., 1986; Smith et al., 1990). Reports of children who have been referred for language delays and later found to have Duchenne have been published (Kaplan et al., 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, Batchelder, et al., 2006).

Thus, across studies, even when controlling for effects of physical involvement, environmental background, IQ, and age, the cognitive profile in Duchenne is defined by multiple strengths and deficits in language 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.

Case 4.1: Kane Kane, age 5, first came to medical attention when he said only single words at age 3. At that time, his pediatrician told his parents that Kane had unspecified developmental delay and recommended speech therapy. Kane's vocabulary has expanded dramatically since then. He names pictures of common items and speaks in sentences of about three words. For example, Kane says, "I want juice" and "ride in car." Kane has dark curls and large eyes. His parents have taken him to numerous developmental specialists who have concentrated on Kane's poor language and suggested different programs to augment his language development.

Kane looks physically fit and has large calf muscles that look like those of an athlete. Yet Kane tires easily when walking, and he has difficulty climbing stairs. At a recent visit to a pediatric neurologist, the physician noted Kane's enlarged calves and had blood taken to screen for creatine phosphokinase levels. The results showed levels of more than 10 times normal. Standard genetic testing was equivocal; no mutations were identified.

Kane attends nursery school. He does not "join in" the group activities and spends his free time playing with the train set. Kane takes all the engines and parks them next to each other. He becomes upset if the arrangement is disturbed or a classmate takes an engine. At home, Kane plays with his own trains similarly. He has special places on his shelves for each engine to go, and he enjoys arranging them.

Kane is an only child who lives with his parents. When he is introduced, Kane says, "ride in car." On standardized tests, Kane is generally not compliant. For single-word comprehension, he scores in the "impaired" range. On drawing tests, he scribbles but does not copy the items asked of him. When asked to solve a puzzle, Kane moves the pieces but shows no attempt to put them together, then gets up and says "ride in car!" When asked simple questions such as "How old are you?" or "What do you like to do?" Kane either does not respond or says, "ride in car."

Academic Skills

Children with Duchenne face considerable obstacles in maintaining a "normal" school life, including all the hardships associated with physical disability and "fitting in." Research suggests that they are at increased risk for poor academic achievement. Determining whether this is due to underlying cognitive deficits or adjustment issues is complex.

An early study by Worden and Vignos (1962) found that among boys with Duchenne, scores on academic achievement tests in reading and mathematics were about 1 *SD* lower than the general population. They reported that although the evaluation of 38 boys with Duchenne indicated decreased performance, it was commensurate with their IQ. The authors concluded that the boys with Duchenne were achieving as expected given their intellectual ability, and there was no evidence to indicate they had selective learning disabilities (Worden & Vignos, 1962).

Other researchers have focused solely on reading skills and have suggested that about half the children with Duchenne present with a form of developmental dyslexia. Liebowitz and Dubowitz (1981) tested 42 boys on reading tests and found the group had a mean standard score that was almost identical to their Verbal IQ mean score. Yet they note that the reading scores were very skewed, such that half of their

sample did very poorly on the reading test. Dorman et al. (1988) tested 15 boys with Duchenne on reading tests and also demonstrated limited reading skills in about half of the children. Similarly, Billard et al. (1992) demonstrated that among a group of 24 older boys with Duchenne, about half of the children with Duchenne had severe reading disabilities, while none of the comparison group of children affected with a different neuromuscular disorder, spinal muscular atrophy, did. Further, the mean standard score on the Reading Index of the Duchenne group was about 1 *SD* lower than that of children with spinal muscular atrophy. Thus, across studies, children with Duchenne present with reading difficulties, yet group mean scores on reading tests are not substantially different from mean IQ scores.

In more detailed examinations of the components of reading, both Dorman and Billard report that phonological processing is particularly impaired in children with Duchenne. In Dorman's sample, the children with Duchenne had significantly reduced phonetic word attack skills (Dorman et al., 1988). Billard demonstrated the overall error rate was highest for the Duchenne group when reading nonwords, also implicating poor phonological processing skills (Billard et al., 1998). Billard's analyses compared boys with Duchenne to either children with spinal muscular atrophy or normal controls who were matched on age and socioeconomic level. They found the children with Duchenne had a reading age of about 2 years behind the comparison children, and they discussed possible contributions to the poor reading skills among the children with Duchenne. They noted that poor attention, difficulty with graphophonological conversion, reduction in short-term memory, a deficit on the level of speech production, or psychoaffective and cultural processes might each limit reading ability in the Duchenne group, and after careful consideration of each they concluded, "A deficit in graphophonological process seems to be the principal explanation of the reading disability" (Billard et al., 1998).

We have demonstrated that across academic areas, boys with Duchenne had lower scores than their siblings on achievement tests. Similarly to the other published studies, the children in our sample performed within normal limits, yet their mean scores were about 1 *SD* lower than that of their siblings. 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. We hypothesized that a "core" deficit of limited verbal span (as evidenced by decreased digit recall on Digit Span) was the reason behind the lower academic skills (Hinton et al., 2004).

Case 4.2: Louis Louis, age 7, is a sandy-haired little boy who was diagnosed with Duchenne when he was 4 years old, after his mother told the pediatrician he was having difficulty climbing stairs. The doctor examined Louis and had him sit on the floor and rise, and he observed Louis's Gower's maneuver, alerting him to the possible diagnosis of Duchenne. The pediatrician took blood samples from Louis and his two brothers and had them analyzed for possible mutations consistent with Duchenne. Both Louis and his infant brother were found to have large deletions spanning exons 49 through 63 in the dystrophin gene. Subsequent analysis of their mother showed that she too had the deletion and was therefore a carrier.

When Louis walks, his unusual posture is apparent; he has a broad gait and arched back, and he sticks his abdomen forward. When introduced, he shakes hands and briefly smiles. When queried about school and what he likes to do, Louis says, "School is okay," and he likes "to play fetch with my dog, Benji."

Louis repeated kindergarten and is now in the first grade. Currently, his teacher complains that he has attention problems. Louis has learned his alphabet but struggles with learning to sound out basic words. He has one friend who he seeks out during activity time. Louis sits near the other boy and they each play, yet there is little interaction between them.

Louis lives with his mother and two brothers. His parents separated 2 years before; his mother states that it was due, in part, to her husband's unwillingness to accept that anything was wrong with Louis and the baby. His mother describes Louis as "a good kid, but maddening at times" because he ignores her and does what he pleases. She oversees his daily stretching exercises and tries to get Louis to wear lower leg splints that keep his feet flexed and Achilles tendons stretched, but she says he is resistant to wearing them and she does not battle him over it. She reports that Louis does not "mind" her, and she often gets frustrated with him. She notes that his 9-year-old brother was always respectful and did as he was asked. She'd like Louis to behave more like him.

Louis's full scale IQ is in the "low average" range. Louis does well—at his appropriate age level—on tests of receptive vocabulary and naming. On more complex tests of language comprehension and expression, however, his limitations are evident. When asked a complex question, Louis repeats back the last few words instead of answering. When asked to make up a sentence about a picture, he names the picture and looks at the examiner. Similarly, when asked to point to a picture that best describes a sentence he has heard, he points to each choice and names something in the picture. He scores in the "borderline" range on tests of language. On nonverbal measures, his scores generally fall in the "low average" range.

Behavior

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

Data collected using parent questionnaires has documented children with Duchenne have depressive signs that increased with age and less well-characterized antisocial tendencies (Fitzpatrick et al., 1986; Leibowitz & Dubowitz, 1981; Thompson et al., 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) directly investigated personality profiles of adolescents with Duchenne 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 Duchenne group were associated with behaviors suggestive of increased stress. A later study replicated the finding that adolescents with Duchenne have significant adjustment difficulties (Reid & Renwick, 2001). Specifically, they found adolescents with Duchenne had poorer psychosocial adjustment than their healthy peers and that their adjustment was significantly associated with the level of stress reported by the family.

We examined parent ratings of behavior in a sample of 181 boys with Duchenne 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, Nereo, et al., 2006). Parent ratings on the Child Behavior Checklist demonstrated that children with Duchenne 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., manuscript in submission). 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 Duchenne and autism have been published (Komoto et al., 1984; Zwaigenbaum & Tarnopolsky, 2003). Further, a recent screen by Wu and colleagues (2005) found that autism spectrum disorders in a Massachusetts muscular dystrophy clinic were considerably more common than expected among the general population. They reported a prevalence of 6/158 in their clinic compared to 1.6 in 1,000 in the general population. We too have observed multiple cases of children with Duchenne and autism spectrum disorders, with rates as high as 13% of the children participating in our studies meeting criteria (Hinton, Batchelder, et al., 2006). Although most children with Duchenne clearly are not autistic, the tendencies of being withdrawn and having poor peer relations may be mild behaviors on the spectrum.

Case 4.3: Muhhamad Muhhamad, age 11, lives with his mother, father, and younger brother. Muhhamad was diagnosed with Duchenne at age 6 years, after his mother grew increasingly concerned about how often Muhhamad fell and was unable to keep up with his peers. Muhhamad was found to have elevated creatine kinase levels but a negative DNA test, so a muscle biopsy was performed. The results indicated that there was no positive staining for dystrophin in the muscle tissue examined, confirming the diagnosis of Duchenne. Muhhamad's parents have stated they do not agree with the diagnosis and refuse to accept that Muhhamad's motor difficulties will be fatal. They have no known family history of Duchenne but report on a number of relatives who had significant illnesses of various types who improved or "beat" the illness with time and proper diet. Muhhamad's parents have chosen to pursue physical therapy and orthopedic interventions for Muhhamad but have declined to give Muhhamad steroid medications because they are concerned that the side effects are too unpleasant and the benefits too uncertain. They also believe that a diet high in protein and low in fat will help Muhhamad and are careful about monitoring his food intake.

Muhhamad attends the sixth grade in a small school where he receives physical therapy two times a week. His school performance is average, and his teachers describe him a quiet and proud boy who keeps to himself. At home and at school Muhhamad uses long-leg braces and walks, but it is increasingly difficult for him and he gets fatigued. He has limited flexibility in his ankles, and they are painfully tight. Whenever he needs to go any distance, Muhhamad uses a wheelchair, but he does so reluctantly. At home, he sleeps in a room on the second floor, and Muhhamad relies on a family member to carry him up the stairs each night.

Muhhamad's family speaks Arabic at home. Muhhamad's manner is somewhat withdrawn, and he answers that he "is fine" and has "no problems" when asked. When asked how he likes to spend his time, he answers, "Draw." His younger brother asks "when will Muhhamad get well?" and states that their parents have said that Muhhamad will soon improve. During his evaluation, Muhhamad applies himself but rarely looks at the examiner. He does not initiate conversation but always answers any questions asked of him.

Muhhamad scores in the "average" range on IQ tests, yet there is scatter among his subtest scores and Digit Span and Arithmetic are notably low, while his Block Design and Picture Completion are impressively high. On most memory tests he also scores in the "average" range and demonstrates good long-term recall for both verbal and visual information. The exception to this is when he is read a story and asked to retell it. Muhhamad responds by stating some of the details in the story, but he does not give a cohesive narration. Further, on tests of reading comprehension and mathematics he struggles, but he tries everything asked of him and never states that he does not know an answer. His scores on academic achievement tests fall in the "borderline" range. His reading scores are particularly low; when asked to read words he was unfamiliar with, Muhhamad states words that begin with the same letter, but he shows no skill at decoding the word phonetically. On tests of reading comprehension, Muhhamad shows little understanding of more complex passages.

Stress

Duchenne, which is both chronic and terminal, may be characterized as a "complex chronic condition" in that it involves specialized and time-consuming care, even when the terminal phase lies years in the future (Gravelle, 1997). As such, it may be expected to have effects on the family similar to those of both chronic and terminal illnesses. Duchenne 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 psycho-

logical 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 to ratings of parents of children with other "complex chronic conditions," parents of boys with Duchenne 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 children, 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 and Duchenne, familial stress was found to be associated with both psychosocial adjustment and intellectual function of the teen boys with Duchenne and not associated with sociodemographic variables (Reid & Renwick, 2001). The authors concluded that the effects of Duchenne 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 Duchenne (Nereo et al., 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 Duchenne 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. Among the Duchenne group, there were high ratings of stress related to the difficult parent–child interaction, and these were associated with increased report of behavioral concerns in the children more than with physical disability.

Thus, with Duchenne, the family's adjustment to the disorder is also an important feature of the impact of the illness. How families adjust to and cope with illness and developmental disability in general has been repeatedly documented to be associated with improved psychological well-being (Copeland, 1988 see also chapter 12, this volume). In Duchenne, where the phenotype impacts on physical, intellectual, and behavioral attributes and involves substantial personal and financial burden associated with care giving, family's stress levels and adjustment are particularly salient.

Case 4.4: Ned Ned, age 16 years, is a heavy teenager who states that he is self-conscious about his "chipmunk cheeks." Ned has taken prednisone since he was 7 years old, and his face has the typical Cushingoid characteristics. Ned used to be slim, but since he became wheelchair dependent at age 11, he has gained a significant amount of weight. Ned is friendly and polite and answers all questions asked of him. When asked to describe his interests, he readily discusses movies he has seen and describes favorites articulately and animatedly.

Ned originally received the diagnosis of Duchenne when he was 4 years old, and he tired easily and struggled on stairs or when running. His mother had had a brother who died of Duchenne, and she was the one to report her suspicions to Ned's physician. Ned was found to have elevated creatine kinase levels. Even with his mother's positive family history and strong suspicions, Ned's parents hoped the diagnosis was incorrect, so they chose to have Ned have muscle biopsy to be certain of the diagnosis. The results confirmed that Ned had no dystrophin in the muscle sample, and he was definitively diagnosed with Duchenne.

Ned's school performance is good. Ned has a small group of male friends who share his interests for movies and computer games. He attends a public school and is in the 11th grade. He feels shy and awkward around girls. He plans to go to college and hopes to study law to become a civil rights lawyer. Ned's school has ensured that he has handicap accessible facilities. Ned has a bulky motorized wheelchair, which he operates with proficiency, and he is able to move from classroom to classroom with his peers. Ned uses an adaptive keyboard for taking notes. He eats lunch with his 15-year-old sister, who helps him as needed. Ned has adaptive utensils and can feed himself, but it can be quite messy and he can no longer raise a glass to his lips. Ned relies on an aide to help with toileting. He is uncomfortable asking for such help and often holds his urine until he gets home at the end of the school day.

Ned lives at home with his parents and sister. At home, his mother helps him with many of his self-care needs, including dressing, washing, toileting, and turning him at night. She also monitors his nighttime ventilation, ensuring that he gets adequate pulmonary assistance during his sleep. The house has been adapted for his wheelchair; there is a ramp out front and the family had renovations to make all the doorways on the ground floor wider. The ground floor family room has been converted to a bedroom for Ned and the bathroom has a Hoyer lift to help with transferring him to the toilet or bath.

On an IQ test, Ned scores in the "high average" range. He is particularly adept at solving puzzles and reasoning tasks, and his knowledge of factual information is impressive. His academic achievement skills are a little lower than expected given his IQ, yet still well within normal limits. On tests of reading fluency he is slower than expected, and he has mild difficulty decoding nonsense words.

Quality of Life in Older Individuals with Duchenne

As individuals with Duchenne 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 (Rahbek et al., 2005; Bach et al., 1991). 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 Duchenne in the United States, only 12.5% expressed dissatisfaction with their lives (compared to a 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 Duchenne 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 Duchenne with as many opportunities as possible to lead an involved and satisfying life, as well as high-

light the difficulty families and professionals may have in judging another's quality of life.

Behavioral and Cognitive Interventions

One published study examined intervention to decrease social isolation among individuals affected with Duchenne (Soutter et al., 2004). The researchers provided 74 families with a son with Duchenne 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 that boys with Duchenne 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 Duchenne. 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 Duchenne. The cases presented earlier illustrate the spectrum of involvement. Potential interventions and hypothetical outcomes follow.

Case 4.1: Kane Kane's family is told of his probable diagnosis of Duchenne. At first, Kane's parents deny this possibility, as his primary problems appear to delayed language development. Moreover, the initial DNA test shows no evidence of mutation. A subsequent DNA test, screening the entire gene's length for possible mutations, is positive. Subsequent analysis of his mother does not show evidence of a similar mutation.

To help with adjustment to the overwhelming news of their son's diagnosis of Duchenne, Kane's parents are urged to attend supportive therapy. They do so and also read up on all aspects of the disease. After initially refusing to accept that the diagnosis was even possible in a son who looked so physically fit, Kane's parents start him on early treatment with corticosteroids and daily physical therapy. They meet individual families with children who are also diagnosed with Duchenne and became actively involved in parent advocacy and educational organizations.

Kane's parents learn that his behaviors are not commonplace among children with Duchenne, and they have him evaluated further. After interviews with his parents and observation of Kane in both his natural and a controlled setting, Kane receives a diagnosis of autism spectrum disorder in addition to Duchenne. Kane's poor reciprocal social interactions, limited communication, and a restricted range of interests all contribute to the diagnosis. Behavioral interventions, including applied behavior analysis and inclusion in a specialized preschool program, are initiated to help ameliorate the behaviors that are associated with autism spectrum disorder and that are of the greatest immediate concern for his family.

Case 4.2: Louis Louis and his younger brother had previously been diagnosed with Duchenne. Their mother was actively involved in the physical care of the boys but had been unaware that any cognitive or behavioral problems might co-occur with the disease. After a thorough neuropsychological evaluation, Louis is diagnosed with specific language impairment. Speech therapy and extra resource room help at school aimed at increasing Louis's familiarity with and discrimination of basic phonemes are initiated to help him improve his language skills. Louis's mother and teachers are advised of his limited auditory processing abilities, and they modify their interactions with him by speaking in shorter, more concise statements and repeating their verbal commands when he appears not to understand. At-home early reading and rhyming games (including computer games) are encouraged. Supportive family therapy is recommended to try to shift the focus away from Louis as "the problem" who caused the family to break apart and, instead, help everyone to adjust and cope with the diagnosis and the changing family dynamics. Additionally, increased focus on Louis's limited language comprehension helps remove the negative emphasis on Louis's behavior as willful disrespect. Instead, Louis's "maddening" behavior becomes more understandable as a disability that he struggles with, and he is understood to merit support with his struggles. In turn, relationships within the family improve considerably. With the reduction of stressful interaction, Louis becomes more compliant with physical therapy and wearing his night splints.

Case 4.3: Muhhamad A social worker with fluent knowledge of Arabic is recruited to help with Muhhamad's care. She speaks with his parents to describe Muhhamad's condition, relates medical information and advice from Muhhamad's treating physicians, and helps the family make adjustments to help Muhhamad cope. The family has known of Muhhamad's diagnosis of Duchenne for more than 5 years but have repeatedly stated, "Muhhamad is strong. He will get better." The social worker helps them face what he is going through. She recommends that Muhhamad's parents meet other parents of children with Duchenne and educates them as to the adaptive changes they must make to their home to help Muhhamad as he transitions to a wheelchair. She emphasizes the need for his increased physical therapy and compliance with treatment. She attempts to encourage them to speak with others in their community about Muhhamad and his illness to remove any stigma that they (and Muhhamad) might be feeling.

After a diagnostic interview with a clinical psychologist, Muhhamad is diagnosed with adjustment disorder and depression. Antidepressant medication and individual supportive therapy are initiated with positive results. Muhhamad becomes more animated, outgoing, and able to discuss his fears related to his physical decline and increasing need for assistance. Increasing Muhhamad's involvement in social activities outside of his home is also recommended. Muhhamad enrolls in a formal drawing class and finds that he enjoys it and is able to express himself more readily through drawing than speech. After a thorough neuropsychological evaluation, Muhhamad is also diagnosed with developmental dyslexia. Reading interventions to help Muhhamad increase his overall fluency and proficiency are offered at his school.

Case 4.4: Ned Open discussions about Ned's future and how best to facilitate his autonomy at a time while he is growing steadily less independent physically are encouraged. Ned begins individual counseling, and he and his family attend family therapy sessions. In individual counseling, Ned discusses feelings of being unattractive, desires for sexual experiences, and a need to be treated like a young man capable of making his own decisions—all issues considered perfectly normal for any 16-year-old youth. In the family sessions, focus is given to each individual's needs, as well as the whole family. Ned's mother is encouraged to devote more time to her interests by increasing the involvement of at-home health care workers. Ned's parents are recommended to take some time for themselves to focus on their relationship as partners and lovers rather than solely caregivers and parents. Ned's sister is supported to develop her own identity, separate and distinct from that of solely Ned's healthy sister. Additionally, carrier screening is recommended for his sister, so she can be aware of her status to help her with future family planning. Ned's plans for attending college and pursuing a career of his interest are reinforced. Together, they work out logistics of how to maintain a good quality of life for each family member.

Summary

A diagnosis of Duchenne brings with it an array of complications and adjustments that require input from multiple integrated specialties. Medical, neuropsychological, behavioral, and educational interventions are all necessary to ensure the best possible quality of life for those living with Duchenne. The genetic etiology of Duchenne 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 Duchenne, the cognitive and behavioral phenotypes seem relatively mild and, as such, have not been adequately studied. Families struggling with their child's educational difficulties feel the daily impact of these issues. Research characterizing the cognitive and behavioral phenotypes of Duchenne offers insight as to what specific domains may be involved. However, no intervention studies have been conducted to determine whether—and how—the neuropsychological aspects of the disease can be ameliorated. The disease provides a model for better known behavioral diagnoses such as developmental dyslexia and autism spectrum disorders, yet although Duchenne is associated with these disorders, most individuals with Duchenne do not have them. Continued characterization of the neuropsychological profile and investigation of ways to help children deal with their limitations are necessary to improve the quality of life for all individuals affected by Duchenne. Through its association with behavioral diagnoses such as developmental dyslexia and autism spectrum disorders, Duchenne provides a model for the study of the relationship between the molecular biology of dystrophin and cognitive development.

Acknowledgments

This work was supported in part by a National Institute of Neurological Disorders and Stroke grant to Veronica J. Hinton. We are most grateful to all the families we have worked with.

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978-0-262-13480-4