



Neuro UpdateSM

DUCHENNE MUSCULAR DYSTROPHY: AN OVERVIEW

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Duchenne muscular dystrophy (DMD) is the most common, fatal heritable disorder of childhood, occurring with a frequency of one in 3,500 live male births. The first, well-documented description of DMD was made by British physician Edward Meryon in 1852.

He described a family of four affected boys, the oldest of whom “. . . ascended the stairs with the greatest difficulty . . . By the age of 11 he could not stand or walk . . . at the age of 16 he died.” At autopsy, Meryon described a muscle in which, “The striped elementary primitive fibers were completely destroyed . . .”¹ Despite this seminal description, DMD bears the name of the French neurologist Guillaume Benjamin Armand Duchenne. In his treatise of 1861 about hypertrophic paraplegia of infancy, he expanded the clinical description of DMD and included drawings of affected boys. By 1868, Duchenne elaborated further on the pathologic changes in dystrophic muscle, obtained from patients via harpoon (needle) biopsy.² The clinical features of DMD were consolidated by British neurologist Sir William Richard Gowers in 1886.³ He described a disease in which asymptomatic mothers pass the disease to their affected sons, intimating at the subsequent understanding of X-linked recessive inheritance.

Boys with DMD appear developmentally normal until 18 to 36 months of age, when calf hypertrophy, delays in walking, toe walking, waddling gait and difficulty with stair climbing are noted. Between ages 3 and 5, boys with DMD are noted to be slow runners by comparison to their peers and have difficulty jumping. A Gowers' Maneuver (see Figure 1) implies evolving axial weakness, which also is associated with frequent falls and exaggerated lumbar lordosis. Contracture formation begins at the heel cords and steadily evolves thereafter. At ages 7 to 9, there is a loss of stair-climbing ability, followed by a complete loss of ambulation by age 11, with associated wheel-chair dependency. Weakness progresses through the teen years, along with muscle wasting, multifocal joint contracture and scoliosis. Without ventilator support, death ensues around ages 18 to 22 primarily from respiratory failure and, to a lesser degree, from associated cardiomyopathy.

For nearly 100 years following Gowers' review article in 1886, the understanding of DMD changed little. During the first half of the 20th century, the disorder's association with markedly elevated serum creatine phosphokinase (CPK) levels was delineated, as was the clinical genetics of X-linked recessive inheritance. Finally, in the mid 1980s, positional cloning techniques revealed precisely where the gene for DMD was located, and the gene product dystrophin was characterized.

In a matter of years, the role of dystrophin in stabilizing the sarcolemma was delineated, as was its place in force generation by contributing to the protein assemblage that links actin/myosin contractile elements inside the muscle cell to the basement membrane outside the muscle cell (see Figure 2). The molecular basis for DMD was finally evident. A genetic mutation results in an absence of dystrophin and produces fragility and loss of muscle cells, which clinically manifests as progressive weakness and disability. This was a major victory for molecular biology and prompted renewed interest in DMD. DNA-based testing for DMD rapidly replaced muscle biopsy as the test of choice, and permitted

carrier testing in the patient's mother (particularly important in that one-third of all DMD cases are the result of de novo mutations that are not associated with increased risk of the disease in other family members).

A more aggressive approach to patient management was adopted, including the use of steroids to slow the progression of weakness in DMD. In addition to improving quality of life, these treatments were directed at optimizing health in anticipation of potentially curative therapeutic interventions. Potential cures for DMD have developed rapidly during the past two decades.

Clinical trials currently are under way to assess the safety and efficacy of techniques, such as viral vector therapy, exon skipping and stem cell therapies, which share the common objective of replacing a damaged gene with one that produces a functional dystrophin molecule. As these developments unfolded, the need for specialized treatment centers for patients with DMD was evident. In this context, a collaboration was established between the Muscular Dystrophy Association (MDA) and Scottish Rite

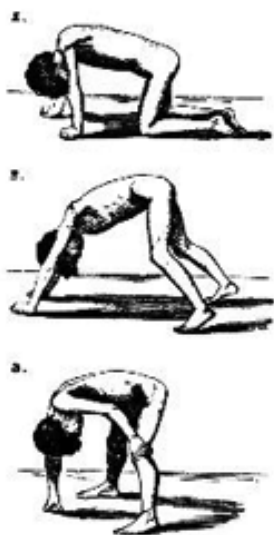


Figure 1
Gowers' Maneuver: Hip girdle weakness in a boy with Duchenne muscular dystrophy compels the adjunctive use of his arms for purposes of rising from the floor.

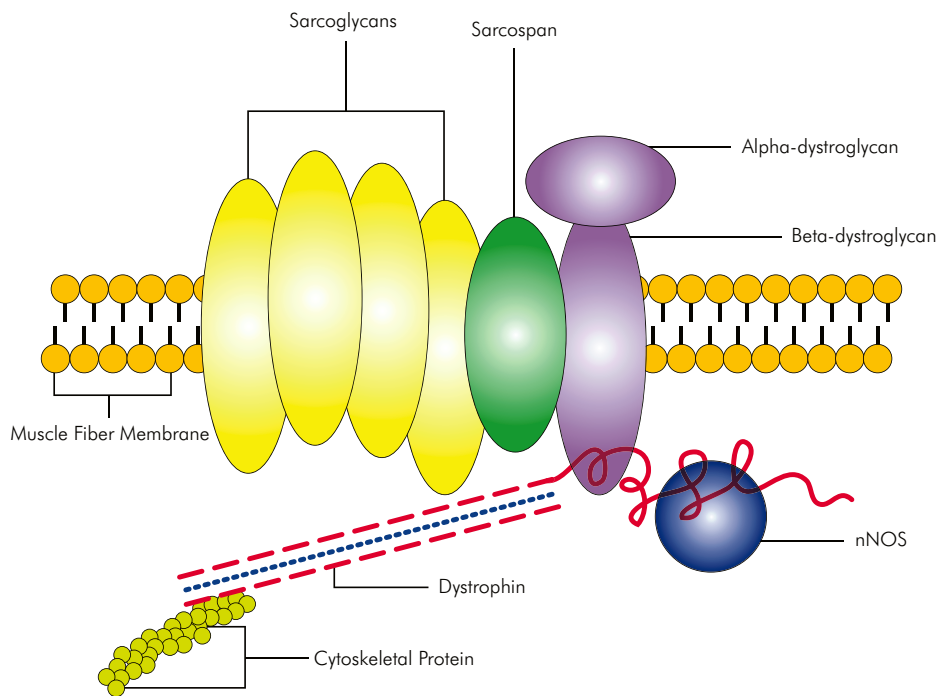


Figure 2
Dystrophin links the cytoskeletal protein actin to the dystroglycan/sarcoglycan complex embedded in the sarcolemma. In so doing, dystrophin is an essential component of muscle cell force generation and membrane stability. (Graphic courtesy of the Muscular Dystrophy Association)

Children's Medical Center in 1992. The resulting clinic continues to provide services as the MDA Clinic at Children's Healthcare of Atlanta at Scottish Rite.

The clinic is designed to provide one-stop clinical services essential to boys with DMD and other children with different types of neuromuscular disease. The clinic involves a team of specialists, including neurologists, orthopaedists, physiatrists, geneticists, physical and occupational therapists, adaptive equipment specialists, social workers, MDA health service coordinators and a nurse specialist, who oversees the clinic. In addition to these specialists, the clinic offers services, such as X-ray, electrocardiograms, echocardiograms and pulmonary function tests.

The clinic team is devoted to maximizing patient health and optimizing quality of life by providing the best possible supportive care and adaptive equipment for our patients, while awaiting the development of a cure for disorders like DMD. Beyond the clinic, the team is involved in MDA-sponsored support groups, and has provided physician and nursing coverage for the MDA Summer Camp program since 1993. The clinic team also is involved in several research initiatives, including a collaborative, multicenter program examining the cognitive impact of DMD.

Duchenne noted that boys with DMD were "mentally dull," by comparison to their peers. Despite this long identified association between DMD and cognitive disabilities, a century lapsed before research regarding this relationship was undertaken. A meta-analysis of 32 papers about cognition in DMD was published in 2001, which revealed a mean drop in full scale IQ of boys with DMD by approximately one standard deviation. (Cotton, et al.) Statistically, this placed one-third of boys studied with DMD in the mentally retarded range.

Furthermore, despite the expected drop in performance IQ scores associated with DMD-related weaknesses, boys with DMD had verbal IQ scores significantly lower than their performance IQs. A plausible explanation for this cognitive dysfunction was tendered by basic science literature, which identified multiple isoforms of the protein dystrophin. Isoforms refer to proteins derived from the same gene, which are different in structure on the basis of differential promoter sites or changes in posttranscriptional modification of RNA. The 427 kDa isoform of dystrophin is

absent from the muscles of boys with DMD. Additionally, there is a deficiency of at least four additional isoforms of this protein that have been localized to the brain. These dystrophin molecules have been identified in the cerebral and cerebellar cortex of normal brains, and are present in both neurons and glial cells. These brain-related dystrophins are believed to have a role in regulating prenatal brain development, synapse formation and neuronal maintenance throughout life.

This evolving interface between basic neuroscience and the cognitive symptom complex of boys with DMD captured the interest of Veronica Hinton, Ph.D. Dr. Hinton is an Associate Professor of Clinical Neuropsychology at Columbia University in New York. In the 1990s, she initiated a series of studies about cognitive dysfunction in DMD. These studies utilized a healthy sibling control group in an effort to separate hereditary aspects of cognition and the potential impact of the child's environment from those aspects of these boys' cognitive profile that were uniquely secondary to dystrophin deficiency.

In an effort to increase the size of her eligible study population, Dr. Hinton advertised for collaborators. The Atlanta-based population of patients with DMD proved a good fit for her studies, and now, the MDA Clinic at Children's has been working with Dr. Hinton for more than 10 years. These collaborative research endeavors were expanded and intensified when pediatric neuropsychologist, Jacqueline Kiefel, Ph.D., an associate of Dr. Hinton, joined the Children's Neuropsychology team and began to evaluate our DMD patients in 2001.

These collaborative research protocols have produced substantive results, and greatly increased our understanding of the cognitive issues associated with DMD. In a study published in 2000, 6- to 16-year-old boys with DMD were noted to perform poorly on measures of digit span, verbal comprehension and story memory (see Figures 3 and 4). These cognitive issues were present regardless of the subject's overall level of cognitive function, and were unique from the cognitive profile of a sibling control group.⁴ As such, this study delineated a specific change in cognitive function, affecting the working verbal memory in boys with DMD. This is noteworthy for several reasons.

First, an improved understanding of a unified cognitive profile in our DMD population permits preemptive intervention for a group of boys with a longstanding history of academic difficulties. Further, this well-delineated change in cognitive function is linked to a specific gene, with a clearly defined gene product (dystrophin), which has been localized and functionally characterized throughout the brain. These studies of cognitive function in DMD provide a window through which changes in genotype can be correlated with variations in cognitive phenotype. This pathway from gene to cognition is much clearer for DMD than for other hereditary developmental disorders. In keeping with these findings, Dr. Hinton has attracted a growing circle of molecular biology and molecular genetic specialists, with an interest in the ontogeny of human cognition.

The demonstration of a common deficit in working verbal memory in our school-age DMD population prompted additional studies about cognitive dysfunction in younger children. These studies revealed more generalized cognitive dysfunction involving delays in the development of receptive and expressive language, memory skills, visuo-spatial skills, fine-motor performance and sustained attention. Collectively, these boys were found to have adaptive functional levels that were significantly delayed by comparison to their sibling controls.^{5,6} In contrast to their motor performance, boys with DMD sustained stable improvements in many domains of their cognitive function, yet they continued to have poor academic performance by comparison to their sibling controls. Correcting for other factors that impact school performance, such as physical disability and deficits in executive function, the only cognitive disability that substantively degraded the academic performance of the boys with DMD was their diminished working verbal memory.⁷

Ongoing clinical concerns regarding elements of autism spectrum disorders (ASD) in our patients with DMD also prompted investigations of the development of their social skills. These studies revealed poor recognition of facial affect. This is consistent with aberrancy of social learning.⁸ Data is currently being analyzed from expanded studies of socialization in our DMD population to better delineate the frequency and severity of ASD in these patients. A well delineated relationship between the absence of dystrophin and ASD would prompt more aggressive evaluation of young boys with DMD to ensure that preemptive social skills training is provided early in life. Additionally, if dystrophin gene mutations are strongly associated with ASDs, this provides neuroscientists with an important window into the molecular ontogeny of human social behavior.

The MDA Clinic at Children's has provided advanced clinical care for children with neuromuscular disorders for more than 15 years, in addition to participating in research initiatives, which will lead the way to understanding the developmental neurobiology of cognition. The next phase of the clinic's development involves the cultivation of an alliance between the Children's Neurosciences program, Emory University School of Medicine and the Georgia Institute of Technology. This alliance will facilitate the free flow of information and ideas between the MDA Clinic at Children's and the basic science labs, which will foster the development of the genetic therapies that will cure DMD and other childhood neuromuscular diseases.

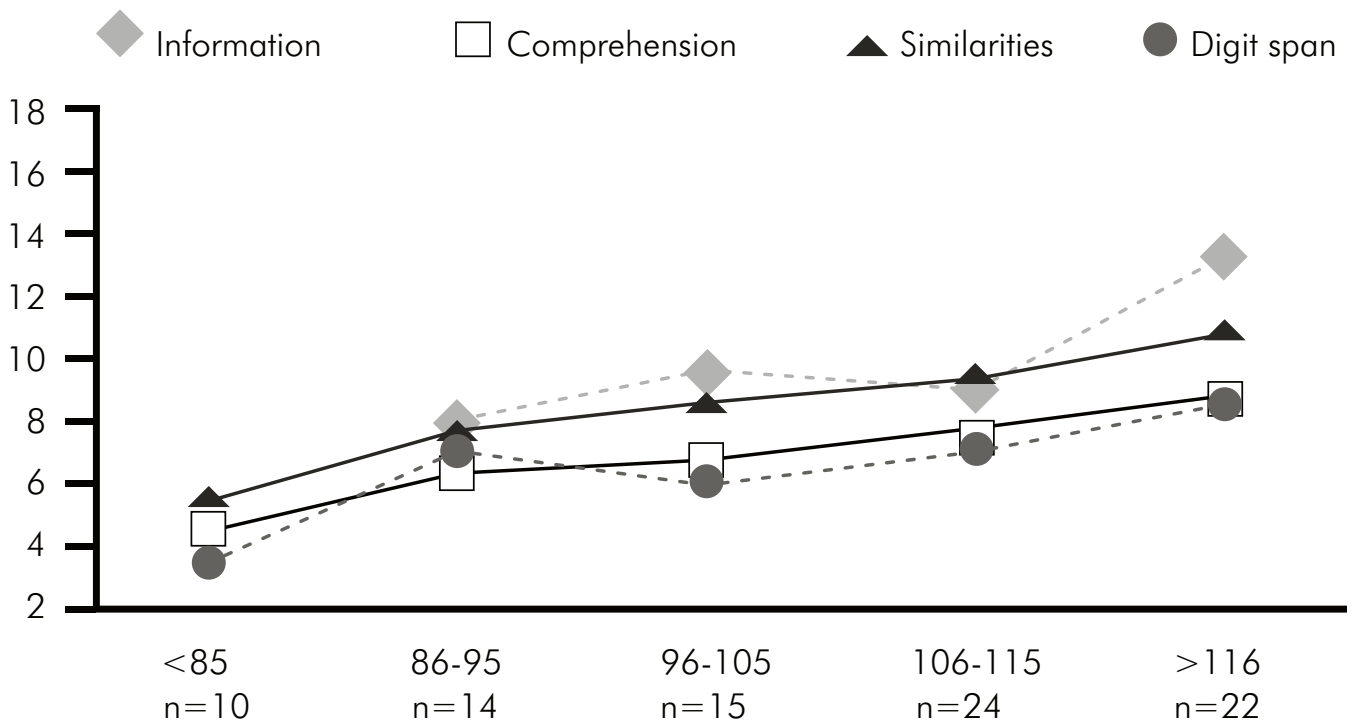


Figure 3
 Plot of the Duchenne muscular dystrophy group's mean scaled scores for the four Wechsler Intelligence Scale for Children-III verbal subtests across IQ levels. Note that the digit span and comprehension scores are lower than the scores for information and similarities across the IQ range.

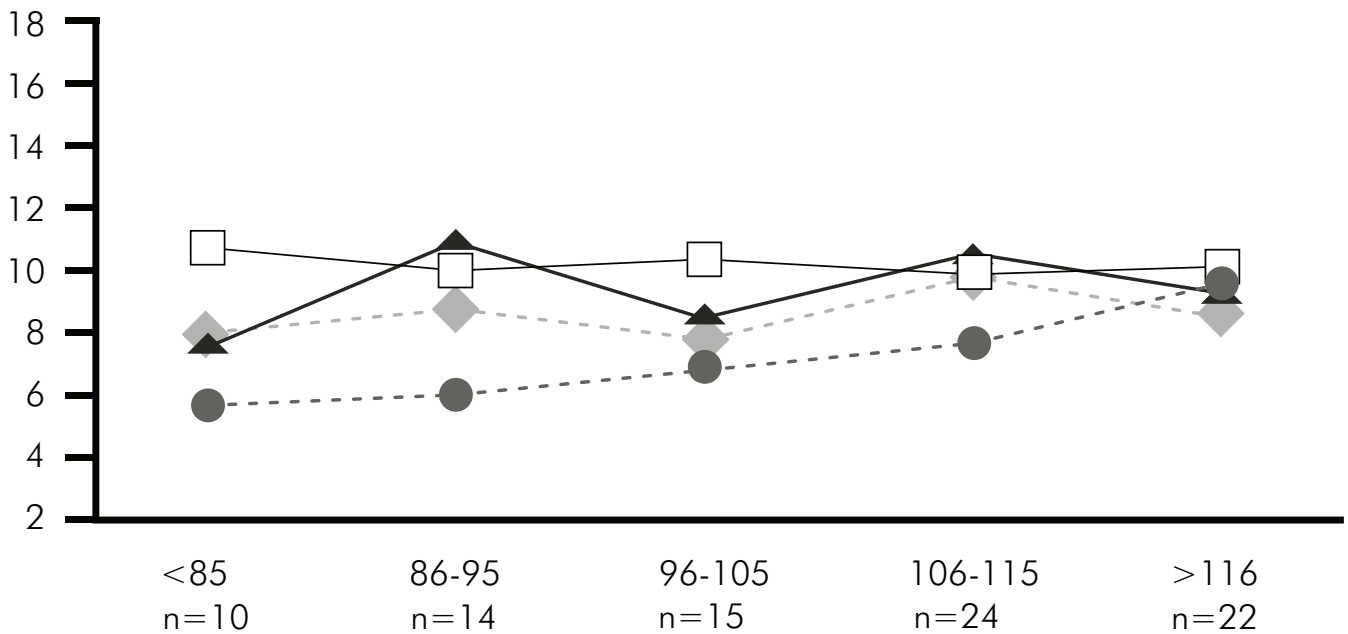


Figure 4
 Plot of the Duchenne muscular dystrophy group's mean scaled scores for the four Wide Range Assessment of Memory and Learning subtests across IQ levels. Note that the story memory scores are lower than the scores of the other memory tests across the IQ range.

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