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Mental retardation in Duchenne muscular dystrophy

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Abstract

Objective: To survey the medical literature directed to the study of cognitive dysfunction in patients with Duchenne muscular dystrophy through description of the milestones of neurological development and psychometric tests for quantifying intelligence.

Sources: Non-systematic review of aspects of cognition in Duchenne muscular dystrophy in the major medical scientific bases: MEDLINE, LILACS, SciELO and Cochrane Library.

Summary of the findings: Patients with Duchenne muscular dystrophy exhibited delay in walking and language development, which correlated with lower scores on future intelligence tests. There is marked impairment in the verbal subtests.

Conclusions: Average IQ has standard deviation below the average of the population. The greater the cognitive impairment, the worse aspects related to morbidity and mortality in the disease will be.

J Pediatr (Rio J). 2012;88(1):6-16: Duchenne muscular dystrophy, mental retardation, delay milestones, neurological development delay.

Introduction

Duchenne muscular dystrophy (DMD) (Online Mendelian Inheritance in Man®, OMIM 310200) is a recessive hereditary disease, linked to the X chromosome, which affect skeletal muscles, heart and brain, with progressive evolution until death around the second decade, generally caused by cardiorespiratory events.[1]

DMD affects one in every 3,600 to 6,000 boys of live birth and it occurs as a result of mutations in the dystrophin gene (locus Xp21.2).[2] Around 1/3 of all new cases diagnosed arise from "new" mutations.[3,4] Dystrophin is a large structural protein (427 kDa) whose function is to connect the internal cytoskeleton of the skeletal fiber with the extracellular matrix proteins, stabilizing muscular contraction.[5] In DMD, the protein is absent or dysfunctional, thus resulting in imbalance in the integrity of the lipid bilayer of the membrane, with influx of calcium and cellular necrosis.[6,7]

The disease is manifested early in childhood with delay in motor behavior. Motor weakness is more pronounced in the lower members and is expressed through difficulty in running, climbing stairs, jumping, walking on the tips of one's feet and frequent falls. Paresis is progressive until loss of walking ability at around 11-12 years old.[8] Fibrosis of the heart muscle fibers occurs, resulting in dilated cardiomyopathy and disorders in rhythm and behavior after

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10 years of age.[9] Respiratory muscles are also affected, and after 10 years of age, development of restrictive ventilatory disorder is observed, with reduction of forced vital capacity from 8 to 12% a year.[9,10] Scoliosis is present in practically all patients and increases after loss of walking ability, significantly contributing to reduction of respiratory vital capacity.[11] Long bone fractures generally occur due to falls in 21-44% of the boys.[12-14]

In addition to motor delay, language delay is also observed. Mental retardation (MR) is a quite frequent aspect among boys with DMD, affecting around 30% of them. This prevalence is greater than that observed in the general population, in which MR rates of approximately 1% are observed. The average intelligence quotient (IQ) for patients with DMD is 85, in other words, below the IQ considered normal in the general population, which varies between 90 and 120. Generally, verbal IQ is more intensely affected than executive IQ. The seriousness of MR does not appear to be correlated with the intensity of muscle weakness. In addition to cognitive impairment, one also observes in this disease a greater frequency of psychiatric comorbidities, such as attention deficit disorder and hyperactivity.[15]

The present article seeks to survey the medical literature directed to the study of cognitive impairments in patients with DMD through description of the neurological development milestones and of the psychometric tests for quantification of intelligence. Thus, we intend to highlight the delay in acquisition of neurological skills, as well as lower intellectual performance in the psychometric tests in children who are carriers of this dystrophy, emphasizing the possible physiopathological explanations that determine greater probability of MR in a peripheral muscle type disease.

Methodology

A non-systematic review was undertaken regarding cognition aspects in DMD in the major medical scientific bases: MEDLINE, LILACS, Cochrane Library and SciELO, searching keywords like intelligence, cognition, brain functioning, central nervous system, psychometric tests, neurological development scales, global development delay and mental retardation in Duchenne muscular dystrophy in Portuguese and English respective terminology. Due to the relative scarcity of scientific publications on the theme, bibliographical research was not limited by date. Only periodicals published in English or Portuguese were selected and those that were listed as available in the journals/ magazines indexed to the CAPES periodical portal.

The intention was thus to describe the sequence of neurological development milestones and their cognitive aspects in children with DMD, establishing the discrepancies in the chronological ages for acquisition of motor, adaptive, personal-social and language skills. In addition, it will be possible to assess the differences of intellectual performance in the major psychometric tests applied to children with DMD when compared to healthy controls, as expected, given the greater prevalence of MR in this population.

Results

Neurological development in DMD

Motor delay in DMD is an event well known by neurologists. Less known is the delay in acquisition of language skills in these children. These are intriguing clinical observations because, *a priori*, changes in higher cortical functions would not be expected in a peripheral muscle type disease.

In Table 1, which may be found at the end of this article, are summarized the diverse observations regarding how the neurological development stages in children with DMD are processed.

Cognitive development in DMD

Cognitive deficit in dystrophy is a known clinical aspect, even referred to by Duchenne in 1868 in the first clinical description of the disease. Although many researchers in past decades (Gowers, 1879; Morrow & Cohen, 1954; Whalton & Natrass, 1954; Sherwin & McCully, 1961; and Lincoln & Staples, 1977) have refuted the hypothesis of MR being a clinical manifestation associated with dystrophy, there is currently overwhelming evidence corroborating the incorporation of this finding to the semiological scenario of the disease.[20]

Cotton et al.[21], Allen & Rodgin[22], Karagan[23], Leibowitz & Dubowitz[24] and Prosser et al.[25] observed that children with dystrophy exhibit a deficient intellectual profile. The average IQ in this group is less than the average in the general population, although the seriousness of this finding does not correlate with the intensity of muscle weakness or serum level of creatine phosphokinase.

In Table 2, we will be able to summarize the results of the diverse assessments and cognitive measures performed throughout the years on patients with dystrophy.

Discussion

Throughout history, the major focuses of research regarding the physiopathology of DMD were directed to the study of muscular-skeletal impairment. Even now, little is known about the psychocognitive manifestations of the disease and its etiopathogenic bases. Nevertheless, considering that an extensive share of children with DMD have MR, it is important to gather the results of scientific literature regarding this topic to better understand what deficits these are and the best strategy for dealing with them.

According to Haggerty, intelligence includes "sensation, perception, association, memory, imagination, discrimination, judgment and reasoning."[34,35] It is a challenge to discern the beginning of intelligence. It is believed that its development after birth begins in the nursing child with substitution of reflex and involuntary responses to the outside environment for more elaborate sensory motor skills. At the beginning of the past century, authors such as Bowlby (1951), Kirman (1953) and Bailey (1933) believed that the diagnosis of MR through neuropsychological tests could not be performed in children under 2 years of age. On the other hand, Gesell, in 1943, believed that practically all cases of cognitive deficiency could indeed be identified already in the first year of life, in the event that there was neurological delay. Global delay of the four behavioral areas of neurodevelopment (motor, adaptive, personal-social and language) is correlated with low scores on future intelligence tests[36]. In 1983, Kaminer verified that a large majority of children with MR began walking only at 17 months, thus corroborating the associative correlation between MR and neurological delay. Other studies, such as Matsuishi in 1984, also found the same associative correlation.[37,38]

The American Association of Mental Retardation (AAMR) defines MR as intellectual disability associated with two or more of the following adaptive skills: communication, independence at home, interaction with the community, caring for one's own health and safety, leisure, caring for one's own hygiene, self-direction, academic functions and work functions. These clinically diagnosed criteria of MR must be present before 18 years of age. To assess the level of intelligence, clinical criteria are necessary regarding adaptive behavior of the individual in relation to his environment and pyschometric criteria (through tests or scales).[39]

Intellectual functions are generally tested by means of IQ tests for children above 5 years of age. A score lower than 68 on the Stanford-Binet scale or below 70 on the Wechsler test defines the presence of intellectual impairment.[40] In 1968, the World Health Organization (WHO) introduced the four levels of MR, which are currently in effect in manual and statistical diagnosis of mental disorders (DSM-IV):

Profound MR: IQ below 20-25;

Serious MR: IQ from 20-25 and 35-40;

Moderate MR: IQ from 35-40 and 50-55;

Slight MR: IQ from 50-55 up to 70.

IQ considered as normal in the general population ranges from a score of 90 to 120. Graphic representation of the general IQ follows a normal or Gaussian distribution pattern; in other words, approximately 95% of the population has scores from 90 to 120, 2.5% below 90 (cognitive impairment) and 2.5% above 120 (cognitive superiority). Those whose acquired score is from 71 to 84 are called individuals with borderline IQ. From the functional point of view, individuals with slight and moderate MR would then be seen as "educable;" those with serious MR would be called "trainable;" and those with profound MR would be "dependents."[39]

In contrast with the high prevalence of MR among patients with DMD, it is estimated that in the general population these rates are from 1 to 3%, a bit more frequent in the male group, at a proportion between men and women of 1.3 and 1.9:1.[41]

Neurological delay in DMD

With follow-up of the cohort of 22 patients with DMD made by Parsons et al., motor and language delay was verified both through the Denver scales and the Griffiths scale.[18]

According to assessment of 130 patients with DMD made by Cyrulnik et al., children with dystrophy sat, crawled, stood and walked later when compared to healthy controls. Likewise, beginning of first words and construction of verbal sentences were observed at a later age. On the other hand, this same analysis did not show differences in ages for acquisition of bladder and bowel control between both groups. Another important finding was that children with DMD, and who had delay in speech, had worse performance on vocabulary tests when compared with those that did not have a history of delay in language. Comparative analysis between children with DMD with and without motor delay also showed differences; in other words, those that acquired walking skills in a later period exhibited less cognitive performance on reasoning tests. The etiopathological hypothesis raised by this group was that the same brain area responsible for learning and motor – cerebellum coordination also participates in cognitive abilities. In fact, studies with tomography through emission of positrons in patients with DMD reveal that the cerebellum – an area rich in dystrophin – has low energetic metabolism of glucose, a finding that partially sustains the previous hypothesis.[19]

Cognitive impairment in DMD

According to results from Prosser et al. During application of the Wechsler Intelligence Scale for Children, Wechsler Intelligence Scale for Adults and Stanford-Binet scale in children with DMD, a reduction of intellectuality was observed in this group, a non-progressive loss with the passage of years and without correlation to the seriousness or stage of the disease. Socio-economic conditions were not determinant for MR, because a normal IQ was observed in the healthy siblings of these patients. This group of scholars did not observe significant differences in the verbal and executive IQ scores.[25]

On the other hand, in 1974, Marsh & Munsat, upon studying 34 boys with DMD, found a lower score on verbal IQ when compared to executive IQ. Nevertheless, in spite of the verbal IQ deficit not being progressive with the

passage of years, executive IQ deteriorates to the extent that muscular weakness is accentuated, because most subtests depend on manual agility.[26]

According to the extensive meta-analysis performed by Cotton et al., 30% of the patients with DMD have MR, with the great majority (79%) being classified as slight. It was also observed that the deficit is greater for verbal mastery than for executive mastery, with the major difficulties being found for functions like naming, verbal fluency, expressive and receptive language, reading and verbal learning.[21]

Hinton et al., upon assessing 41 children with DMD, observed that there is worse performance in DMD in mathematical abilities, with attention and memory deficit. However, in tests of visual-spatial capacity, individuals with DMD had performance similar to that of their controls, indicating that the visual learning of these children is better than the verbal. In addition to Hinton, other authors had already described worse verbal IQ scores in children with DMD, such as Billard et al., in 1992; Ogasawara, in 1989; and Whelan, in 1987. It has been suggested that dystrophin may perform a stabilizing role in neurons, similar to their function in the muscle cell, thus contributing to the integrity of the synapses. Dystrophin is located in the dendrites and tends to aggregate in the postsynaptic densities, suggesting its possible role in interneuronal transmission.[27]

Wicksell et al. found statistically significant differences between memory scores (short and long term), learning and executive capacity in comparison of children with DMD and their respective controls.[28]

In 2004, Hinton et al. deepened analysis of academic abilities of individuals with dystrophy to test the suspicion that immediate verbal memory deficit would be the principal core of all the other school disabilities. The results obtained during analysis of 26 patients were similar to those found in 2001; in other words, worse performance in all academic areas in the affected group, especially mathematics. In fact, children with dystrophy had poor performance in all the tests which depended on listening to information or a sequence of commands to be executed. Thus, this led to the conclusion that limited immediate memory storage capacity is the central cause of academic disabilities. Dyslexia was not ascribed as the etiology of the literacy difficulties of these children, as other authors suggested in the past (Billard et al. in 1992, Dorman et al. in 1988). It is believed that the worse results in the framework of phonological decodification found in other studies are also derived from a greater deficiency, which is found in the immediate verbal memory.[29]

In 2007, this same group sought to assess the verbal and memory functions in dystrophy. After the performance of specific language tests, they concluded that the disease in a specific way affects language competencies: children with DMD have greater difficulties in tests of remembering sentences. For them, DMD does not globally affect all verbal abilities. Only immediate memory is found to be impaired, with the processes of consolidation and recovery of information intact.[30]

Cyrulnik et al., upon studying 20 children with DMD, observed that there was global delay in neurodevelopment, as well as deficit of attention/memory, receptive and expressive language, visual-spatial capacity and fine motor control, as well as in social abilities, approximately one standard deviation below that expected. [19] This same author had already described 1 year before that children with DMD that exhibit motor delay and delay in language milestones in the first years of life will have worse performance on intelligence tests after 4 years of age and greater cognitive deficit.[19]

While some authors like Hinton et al.[27] and Cyrulnik et al.[31] observed worse scores for verbal IQ if compared to executive IQ in DMD, the group of Donders & Taneja[32] found lower performance in both tests. Taneja et al. observed impairment of visual memory and non-verbal executive functions, just as Wicksell et al. in 2004.[28]

In 2009, the group of Wingeier et al. found the same IQ average in DMD as that already established in the literature, in other words, a score of 88 (borderline intelligence). In this analysis, around 24% of the sample fit into the assessment of slight MR (IQ < 70). Total loss or impairment of the Dp140 dystrophin isoform seems to be more strongly correlated with intellectual loss in boys with dystrophy.[33]

Conclusion

According to the proposed review, we observed that the IQ of patients with DMD is found to be around one standard deviation below the average considered as normal, and that the distribution of this score in the group also follows a normal or Gaussian pattern.[21]

Difficulties in the verbal subtests applied to patients with DMD are evident, as referred to by various authors: repeating the story (Billard et al., 1992; Hinton et al., 2000, 2001; Wicksell et al., 2004), repeating the sentence (Billard et al., 1992; Hinton et al., 2007), remembering digits (Billard et al., 1998; Hinton et al., 2000, 2001; Ogasawara, 1989; Wicksell et al., 2004) and digit scale (Anderson et al., 1988; Billard et al., 1998; Dorman et al., 1988; Hinton et al., 2000, 2001, 2004.; Sollee et al., 1985; Ogasawara, 1989; Whelan, 1987; Wicksell et al., 2004). These problems in verbal functions may be derived from failures in speech and language processing and reading, as many authors affirm. According to Cyrulnik et al., neurodevelopment and psychocognition impairment observed in dystrophy result from complete or partial absence of dystrophin in the central nervous system. This protein is found in the post-synaptic neuronal terminals of the cortex, hippocampus

and cerebellum, areas intensely involved with reasoning and learning.[42]

Nevertheless, we observed that in spite of the 143 years that have passed since the first clinical description of the disease made by Duchenne and of the extensive technical-scientific biological advances, currently many questions still remain to be answered regarding brain functioning in DMD.

There are few publications directed to the chronological sequencing of the neurological development milestones in dystrophy, for the purpose of establishing the average time for acquisition of each one of the specific behaviors. Krajewska, in 1977, observed that 58% of the patients with DMD acquired walking ability only at 19 months, on average.[16] It is known that children with DMD develop more slowly, as highlighted by Smith et al. in 1990[17], with delay not being only observed in motor skill, as would be expected in a peripheral muscle disease. Around 60% of the patients with DMD acquired walking ability only at 19 months, on average. Delay in language and personal-social abilities is the precursor of low intellectual performance and behavioral difficulties in the future.

Just as for other diseases that are affected by intellectual deficit, neuropediatricians lack psychometric assessment instruments with simple and practical applicability in day to day life to "quantify" the degree of this deficiency. The Gesell scale for assessment of neurological development is widely spread throughout the pediatrics scene and enjoys recognition and prestige in the area. Nevertheless, its use is restricted up to 5 years of age. As of school age, there is a lack of a cognitive assessment method for application in the medical appointment. The Wechsler and Stanford-Binet scales – in spite of being complete and extensive – are long and exclusive to the field of neuropsychology and, for that reason, are not used in routine medical semiology. Therefore, childhood neurology makes use of clinical definitions established by the WHO to diagnose and measure MR.

The observation that children with DMD that exhibit motor and language delay are precisely those that will develop diverse academic difficulties in the future in the most varied domains of cognition leads to the observation that the low intellectual performance of this group is not only due to motor disability and emotional disorders, but principally to early changes in the central nervous system. This reflects the need for creation of strategies for early pedagogical and speech and language stimulation for the group of children with DMD and neurological delay, because school difficulties will already be foreseen.

For teachers and educators, it is important to know that, contrary to the progressive nature of the muscular weakness, the intellectual deficit is not accentuated with the passage of time. Even those who are more limited from the motor skills point of view are capable of exercising their higher functions. As suggested by Hinton et al., some teaching strategies may be useful for minimizing the short term memory deficit in these patients, such as: use of direct and short phrases, dividing up of commands, repetition of information and use of visual resources in the pedagogical process.

In the same way, a lack of studies is observed with greater samples of patients directed at analysis of possible associations between the neurological delay and MR with a worse clinical evolution. According to Mochizuki et al., in 2008, in accordance with the analysis of 194 patients with DMD, 38% exhibited slight MR, and this group began walking in a later period (average of 18.6 months), lost walking ability earlier (average of 10.2 years), needed ventilatory support (average of 19.9 years old) and nutritional support (average of 24.5 years old) earlier and died earlier (25 years) than the group with DMD without RM. Therefore, the care and treatment for patients with DMD and MR must be more meticulous than that for those with DMD and without MR.[43]

If there is, in fact, a statistically significant correlation between MR and a worse prognosis in DMD, both in the aspects of morbidity and mortality, it is necessary that the diagnosis of cognitive deficit be made early. The objective of this detection in the initial phases is installing speech and language rehabilitation already in lactation and pre-school to improve the quality of life of the children and their families.

Table 1 - Development milestones in Duchenne muscular dystrophy

Authors	Methodology	Neuropsychological scales and tests	Results
Krajewska (1977)[16]	Retrospective descriptive observational 129 patients with DMD		58% of the patients with DMD. Delay in walking: average age for beginning of walking was 19 months.

DMD = Duchenne muscular dystrophy.

Table 1 - Development milestones in Duchenne muscular dystrophy (continuation)

Authors	Methodology	Neuropsychological scales and tests	Results
Smith et al. (1990)[17]	Prospective descriptive observational 33 patients with DMD (average of 3.4 years)	Griffiths Developmental Scales Reynell Language Scales British Picture Vocabulary Scales	Motor delay and progressive deterioration of strength through time in patients with DMD. Language delay in patients with DMD. Factors such as mother's intelligence, family environment and socio-cultural level did not influence delay in development.
Parsons et al. (2004)[18]	Quantitative and semiqualitative Cohort of 129,094 boys tested by neonatal screening exams in 8 years: 22 boys confirmed for DMD	Griffiths Developmental Scales Denver Development Screening Test	Patients with DMD exhibited the following results according to Denver criteria: Motor delay for: - sitting (average of 8 months) - 72%; - walking with support (average of 16 months) - 89%; - climbing stairs (average of 18 months) - 81%; - kicking a ball (average of 25 months) - 60%; - jumping (average of 18 months) - 57%. Language delay: - first words (average of 13 months) - 47%; - complete sentences (average of 29 months) - 53%. Patients with DMD exhibited the following results on the Griffiths scale: - 56% of the sample obtained a development score within the average; - 31% of the sample obtained a development score below the average; - 13% of the sample exhibited a development deficit.
Cyrulnik et al. (2007)[19]	Retrospective and prospective descriptive observational 130 patients with DMD (average: 9 years old) 59 healthy controls (average: 9.85 years old)	Manual for the Child Behavior Checklist Denver Development Screening Test Psychometric tests: - Peabody Picture - Vocabulary Test - Raven's Colored - Progressive Matrices	Patients with DMD ($p < 0.001$) Delay in motor behavior: - sitting (38%); - crawling (60%); - standing (56%); - walking (70%). Language delay: - beginning of first words (42%); - beginning of sentence formation (49%); - beginning of reading (94%). Absence of statistically significant differences for sphincter control ability. Patients with DMD and speech delay exhibited a greater cognitive deficit in the vocabulary test (p-value < 0.001). Patients with DMD and speech delay: score of 95. Patients with DMD without speech delay: score of 107.

DMD = Duchenne muscular dystrophy.

Table 2 - Intelligence scales in Duchenne muscular dystrophy

Authors	Methodology	Neuropsychological scales and tests	Results
Prosser et al. (1969)[25]	Prospective descriptive observational 47 patients with DMD 47 healthy controls	WISC WAIS Stanford-Binet Scale	Patients with DMD exhibited low IQ scores when compared to healthy controls. Average IQ: 85 (patients with DMD) *versus* 105 (healthy controls). 31% of the patients with DMD exhibited IQ below the average. IQ distribution among the DMD group and the control group: **IQ** / **Category** / **DMD (%)** / **Controls (%)** > 130 / Much higher / 0 / 2 120-129 / Higher / 0 / 7 110-119 / High normal / 6 / 16 90-109 / Average / 35 / 50 80-89 / Low normal / 29 / 16 70-79 / Borderline / 10 / 7 < 69 / Mental retardation / 21 / 2 The verbal and executive IQs were below the average in the same proportion in the group of patients with DMD. - Verbal IQ average: 87.1. - Executive IQ average: 88.0.
Marsh & Munsat (1974)[26]	Prospective descriptive observational 34 patients with DMD Group 1 (7.2 years old): lightly affected in execution of the ADLs Group 2 (10.85 years): moderately to seriously affected in execution of the ADLs 1,100 healthy controls (5-15 years old)	WISC	The group of patients with DMD exhibited an IQ score below the average when compared to the healthy controls. Group 1 - Verbal IQ: 85.3 (10 to 20 percentiles from the normal average for the age); - Executive IQ: 97.6 (40 to 50 percentiles from the normal average for the age); - Total IQ: 90.4 (25 percentile from the normal average for the age). Group 2 - Verbal IQ: 87.5 (20 percentile from the normal average for the age); - Executive IQ: 89.7 (25 percentile from the normal average for the age); - Total IQ: 87.4 (20 percentile from the normal average for the age). The verbal IQ score was around 12 points lower than the score on the executive IQ in the group of patients with DMD.
Cotton et al. (2001)[21]	Meta-analysis based on 32 studies developed from 1980 to 2000 1,224 patients with DMD (average of 12.6 years old)		The patients with DMD have a total average IQ below that found in the general population (p-value < 0.005). - Average IQ of the population: 100; - Average IQ of patients with DMD: 80.2.

DMD = Duchenne muscular dystrophy; WISC = Wechsler Intelligence Scale for Children; WAIS = Wechsler Intelligence Scale for Adults; IQ = intelligence quotient; ADL = Activities of Daily Living (food, clothing, hygiene, movement); CVLT-C = California Verbal Learning Test for children; CELF = Clinical Evaluation of Language Fundamentals; WASI = Wechsler Abbreviated Scale of Intelligence; CMS = Children's Memory Scale; D-KEFS = Delis-Kaplan Executive Function System; K-ABC = Kaufman Assessment Battery for Children; SON-R = Snijders-Oomen Non-verbal Intelligence Test for Children; WAIS-III = Wechsler Intelligence Scale for Adults; WISC-III = Wechsler Intelligence Scale for Children.

Table 2 - Intelligence scales in Duchenne muscular dystrophy (continuation)

Authors	Methodology	Neuropsychological scales and tests	Results
Cotton et al. (2001)[21]			34.8% of the patients with DMD have an IQ score < 70 and are considered as individuals with mental retardation. In this group are the following subcategories: - slight mental retardation (IQ 50-70): 79.3%; - moderate mental retardation (IQ 35-50): 19.3%; - serious mental retardation (IQ 20-35): 1.1%; - profound mental retardation (IQ < 20): 0.3%. The deficit in verbal intelligence is greater than the deficit in executive intelligence in the group of patients with DMD, however, without statistical significance. - Average verbal IQ: 80.4; - Average executive IQ: 85.4.
Hinton et al. (2001)[27]	Prospective descriptive observational 41 patients with DMD (6-16 years old) 41 healthy controls (6-16 years old)	Verbal capacity: - Wepman Auditory Discrimination Test - Boston Naming Test - Semantic Verbal Fluency - Token Test For Children - WISC-III Visual spatial capacity: - Ravens Colored Matrices - K-ABC - WISC-III - Woodcock-Johnson Cognitive Battery Attention and memory: - WRAML - WISC-III Abstract thinking: - WISC-III Academic performance: - comprehension - dictation - mathematics - Woodcock Johnson Cognitive Battery	Patients with DMD exhibited worse performance in the following skills: - attention and memory (p-value < 0.003); - abstract thinking (p-value < 0.003); - academic performance (p-value < 0.003).
Wicksell et al. (2004)[28]	Prospective descriptive observational 20 patients with DMD (average: 9 years old) 17 healthy controls (average: 9 years)	Block Span Digit Span Story Recall Rey Auditory Verbal Learning Test Rey Complex Figure Test Spatial Learning Test Verbal Fluency Trail Making Test Tower of London Memory for Faces Raven's Colored Progressive Matrices	Patients with DMD exhibited worse results in the following tests when compare to the control group: - short term memory (p-value < 0.0001); - long term memory (p-value < 0.0001); - learning (p-value < 0.001); - executive functions (p-value < 0.0001).

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Table 2 - Intelligence scales in Duchenne muscular dystrophy (continuation)

Authors	Methodology	Neuropsychological scales and tests	Results
Hinton et al. (2004)[29]	Prospective descriptive observational 26 patients with DMD (8-16 years old) 26 healthy controls (8-16 years old)	Academic performance: - Woodcock-Johnson Achievement Battery - Ravens Colored Matrices Verbal capacity: - Peabody Picture - Vocabulary Test - Wepman Auditory - Discrimination Test - WISC-III - Child behavior checklist	Patients with DMD have worse performance in the following tests (p-value < 0.005): - academic performance; - reading, mathematics and writing; - verbal capacity.
Hinton et al. (2007)[30]	Prospective descriptive observational 50 patients with DMD (average: 9 years, 4 months) 24 healthy siblings (average: 9 years, 1 month) 23 patients with with cerebral palsy (average: 7 years, 8 months)	CVLT-C CELF Peabody Picture Vocabulary Tests – III	Patients with DMD exhibited lower scores on the following tests when compared to healthy controls: - CVLT-C (p-value < 0.005); - CELF, subtests of concepts and directions and repetition of sentences (p-value 0.005). When compared to patients with cerebral palsy, patients with DMD exhibited lower output on the sentence repetition subtest (p-value < 0.002).
Cyrulnik et al. (2008)[31]	Prospective descriptive observational 20 patients with DMD (average: 4.9 years old) 20 patients without DMD (average: 5.1 years old)	Vineland Adaptive Behavior Scales Language tests: - Peabody Picture - Vocabulary Test - Clinical Evaluation of Language - Fundamentals - Preschool Version - Expressive Vocabulary Test Visual spatial tests: - WISC Attention and memory tests: - Visual Attention Subtest of the NEPSY: A Developmental Neuropsychological Assessment	Neurological development in patients with DMD: delay in the 4 domains (motor, language, adaptive and personal-social): standard deviation below the average of the controls. Cognitive development of patients with DMD: worse performance on the expressive and attention/memory language tests: 1.5 standard deviations below the average of the controls.

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Table 2 - Intelligence scales in Duchenne muscular dystrophy (continuation)

Authors	Methodology	Neuropsychological scales and tests	Results
Donders & Taneja (2009)[32]	Prospective descriptive observational 22 patients with DMD (average: 11.09 years old) 18 healthy controls (average: 10.17 years old)	WASI CMS D-KEFS	Patients with DMD exhibited worse outputs (p-value < 0.005). - Total IQ (WASI): average in the group with DMD was 90.23 *versus* the average in the control group, which was 99.89 The differences between the verbal and executive IQ were not statistically significant. - CMS Verbal Delayed: average of the group with DMD was 83.86 *versus* the average of the control group, which was 102.17; - CMS Visual Delayed: average of the group with DMD was 92.86 *versus* the average of the control group, which was 105.89; - D-KEFS Category Fluency: average of the group with DMD was 6.85 *versus* the average of the control group, which was 9.25; - D-KEFS Design Fluency: average of the group with DMD was 8.20 *versus* the average of the control group, which was 10.28.
Wingeier et al. (2009)[33]	Prospective descriptive observational 25 patients with DMD (average: 10 years old)	K-ABC SON-R WAIS-III WISC-III	Patients with DMD: Mean IQ of 88, and 24% of patients were considered mentally impaired (IQ < 70). There was no statistically significant difference between the verbal IQ score (88) and the executive IQ score (87). There was no statistical correlation between the IQ score and the seriousness of the muscular disease. Worse performance on the subtests for verbal skills, arithmetic and digit span. Those with lack of the Dp140 dystrophin isoform exhibited greater cognitive problems.

DMD = Duchenne muscular dystrophy; WISC = Wechsler Intelligence Scale for Children; WAIS = Wechsler Intelligence Scale for Adults; IQ = intelligence quotient; ADL = Activities of Daily Living (food, clothing, hygiene, movement); CVLT-C = California Verbal Learning Test for children; CELF = Clinical Evaluation of Language Fundamentals; WASI = Wechsler Abbreviated Scale of Intelligence; CMS = Children's Memory Scale; D-KEFS = Delis-Kaplan Executive Function System; K-ABC = Kaufman Assessment Battery for Children; SON-R = Snijders-Oomen Non-verbal Intelligence Test for Children; WAIS-III = Wechsler Intelligence Scale for Adults; WISC-III = Wechsler Intelligence Scale for Children.

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