Published in final edited form as:

J Pediatr. 2007 May ; 150(5): 474–478.

Delayed Developmental Language Milestones in Children with Duchenne's Muscular Dystrophy

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Abstract

Objectives—To document the attainment of developmental milestones in children with Duchenne's muscular dystrophy (DMD) and to determine whether early delays are associated with later performance on measures of cognition.

Study design—Retrospective parental report was utilized to document the acquisition of 10 common developmental milestones in children with DMD (n = 130) and their unaffected siblings (n = 59). Children completed tests of cognitive functioning.

Results—Parents rated children with DMD as delayed on achieving both language and motor milestones more frequently than their unaffected siblings. Furthermore, those children with DMD who were rated as late *talkers* or late *walkers* performed more poorly on tests of cognitive function than their on-time peers.

Conclusions—In addition to the commonly reported delays in motor milestones, the current study documents delays in the acquisition of language milestones as well. These early delays are associated with significant impairments in later cognitive functioning.

Duchenne's muscular dystrophy (DMD) is an X-linked disorder that occurs in 1 in 3500 male births.¹ It is known primarily as a disease of the muscle, as children present with progressive muscular weakness. DMD is also associated with delays in the acquisition of motor milestones.^{1–3} Interestingly, in some cases delayed *language* milestones—not motor milestones—may be the earliest signs of DMD that give rise to clinical concern. Unfortunately, those early indications of DMD often go unnoticed because most clinicians still do not associate early language impairment with DMD.⁴ Indeed, with the exception of several case studies,^{5,6} this link has never been studied systematically. Given the ubiquitous screening for general milestone attainment, determining how children with DMD present from a cognitive perspective may provide a promising avenue for improving the likelihood of early diagnosis and intervention.

There is ample evidence of cognitive involvement in DMD, although the presentation is much more variable than the motor symptoms of the illness. On average, the mean IQ in children with DMD is shifted down one standard deviation from the population mean, and verbal IQ scores are more compromised than performance IQ scores.⁷ However, no relationship has been

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Sponsored by the NICHD and NINDS and the Muscular Dystrophy Association (PI: V. J. Hinton).

documented between levels of muscular degeneration and cognitive impairment,⁸⁻¹² nor is there a relationship between creatine kinase levels and cognitive impairment.⁹

There are considerable data attesting to specific verbal deficits in children and adolescents with DMD.¹³⁻²⁵ Moreover, there is a clear association between brain function and cognition in DMD.^{26,27} Few studies have focused on early development (<5 years of age) in this population.²⁸⁻³⁰

The purpose of the current study, therefore, is to examine reports of early developmental milestones in children with DMD. We hypothesize that children with DMD will be reported as having more early language delays than their unaffected siblings or than expected for the general population. We also hypothesize that evidence of early language delays will be associated with lower scores on cognitive tests administered after 4 years of age.

METHODS

Children with DMD (n = 130) and unaffected sibling controls (n = 59) participated in a large-scale study investigating cognitive skills in boys with muscular dystrophy. Diagnosis of muscular dystrophy was based on clinical onset of progressive weakness before 5 years of age, and either molecular assessment of mutation in the DMD gene or muscle biopsy that was deficient in dystrophin and compatible with DMD. Siblings were within 5 years of age of the proband. When more than one comparison child was available, preference was given first to male sex and then to closeness in age. Children with DMD were between 4 and 14 years of age, with a mean age of 9.00 years (SD = 2.52), and sibling controls ranged from 3 to 16 years of age, with a mean age of 9.85 years (SD = 3.61). Approximately one third of the probands (38%) were in a wheelchair at the time of assessment, and none of the sibling controls were wheelchair-bound. Racial composition of the sample consisted of persons who identified themselves as Caucasian (88%), Hispanic (7%), African-American (3%), and Indian (2%).

Participants for this study were recruited through the Muscular Dystrophy Association clinics of Columbia Presbyterian Hospital, New York, and Children's Healthcare of Atlanta at Scottish Rite Children's Medical Center. Additionally, newsletters with a description of the study were sent to Parent Project Muscular Dystrophy, regional Muscular Dystrophy Association clinics, and parent support groups. Interested persons returned the response form directly to the investigator.

This study was approved by the Columbia University and New York Presbyterian Hospital Institutional Review Board, by the Queens College of the City University of New York Institutional Review Board, and by the Children's Healthcare of Atlanta at Scottish Rite Children's Medical Center Institutional Review Board.

As part of several ongoing studies, parents completed a developmental milestone questionnaire; they were asked to indicate whether their child was "on-time" or "late" for 10 developmental milestones listed. These included when the child first began to: smile, sit, crawl, stand, walk, say single words, construct complete sentences, read, and become bowel and bladder trained. In addition, parents had the option of recording the month at which their child achieved each milestone. Parents also completed the Child Behavior Checklist,³¹ a 118-item questionnaire in which parents rate the frequency with which their child engages in a variety of behaviors.

Children enrolled participated in different neuropsychological studies involving a number of measures of language, memory, and visuospatial skills. Measures included in the battery required minimal motor involvement. Some of the test measures have been described in detail elsewhere.²⁰ This article will report results from two tests used across batteries to ensure the

largest sample size: the Peabody Picture Vocabulary Test, 3rd edition,³² and the Raven's Colored Progressive Matrices.³³ Both tests were scored twice to ensure consistency; discrepancies were resolved by consensus.

After obtaining written informed consent from the parent and verbal assent from the child, parents completed questionnaires while their children were administered the complete battery of neuropsychological tests. Testing was done in English. Most testing was completed at the Columbia Presbyterian Medical Center. In some cases, however, children were tested in their home, in a quiet room.

Based on the retrospective history of early developmental milestones provided by the parents, children were classified as either "on-time" or "late" in achieving developmental milestones. In the event that the parent did not indicate whether their child was on-time or late, but recorded the month at which their child achieved each milestone, the data were converted to on-time or late by determining whether the child achieved the milestone within the same period or after 90% of the general population did. Norms for the general population were based on the Denver Developmental Screening Test,³⁴ with the exception of bowel and bladder control norms, which were extracted from Copeland and Kimmel.³⁵ In the event that a parent both endorsed on-time or late and recorded the month, preference was given to the on-time/late variable; however, these data were checked for accuracy. Because of the variable manner in which parents responded to items on this questionnaire, the total number of responses for each developmental milestone is different. As such, data are presented as percentages, and the lowest number of responses ($n = 130$) was used as the total N .

To determine the percentage of children with DMD ($n = 130$) reported to be on-time versus late for each developmental milestone, a frequency count was used.

To determine whether the likelihood of delay for each developmental milestone was equivalent between the probands and their siblings, χ^2 analyses were performed only on those probands with unaffected siblings controls ($n = 59$). The null hypothesis predicted an equal likelihood of delay among children with DMD and their siblings as reported by their parents. Alpha was set at .005 to account for the multiple comparisons ($.05/10 = .005$).

To determine whether early delay was associated with later cognitive functioning, two variables with the largest χ^2 values were chosen: when the child first began to walk and construct complete sentences (hereafter referred to as "walk" and "sentence"). These variables were chosen because of their discriminative ability among the sibling pairs, and for the current analysis, were applied to the larger group of DMD probands only. A series of independent sample t tests were performed among DMD children to determine whether delay on the above-mentioned two variables was related to performance on the Peabody Picture Vocabulary Test, 3rd edition, the Raven's Colored Progressive Matrices, and parental report on the Child Behavior Checklist. The null hypotheses were that there would be no differences in test scores between children rated late or on-time on early milestones.

RESULTS

The percentage of children with DMD reported to be on-time versus late for each developmental milestone can be found in Table I. Data show variable ranges of responses across items. Only 3% of the children with DMD were rated late on developing their smile, and 67% were rated late on beginning to walk independently. For most items, between 30% and 50% of the group were rated late.

Results of χ^2 analyses revealed that children with DMD were rated as late more often than their unaffected siblings on most, but not all, developmental milestones (Table II). Specifically,

parents reported that their children with DMD were more often late in motor milestones such as sitting ($\chi^2 = 28.37$, $P < .001$), crawling ($\chi^2 = 40.53$, $P < .001$), standing ($\chi^2 = 44.79$, $P < .001$), and walking (70% vs 2%, $\chi^2 = 52.14$, $P < .001$) than their siblings. Furthermore, a greater percentage of children with DMD than siblings were also rated as delayed on language milestones. More children with DMD were reportedly late in speaking their first word ($\chi^2 = 24.12$, $P < .001$) and in speaking in full sentences (49% vs 4%, $\chi^2 = 29.73$, $P < .001$) than their siblings. No between-group differences were observed on other aspects of development, such as when their children first smiled, or when they achieved bowel or bladder control.

Results of independent sample *t* tests revealed that children with DMD whose parents rated them as late in constructing complete sentences were more likely to perform poorly on measures of single-word vocabulary (mean [SD]: late = 94.29 [22.26], on-time = 107.00 [17.07]; $t = 3.75$, $P < .001$) and visuospatial reasoning (mean [SD]: late = 90.87 [25.26], on-time = 101.62 [13.21]; $t = 3.17$, $P = .002$) than children with DMD who were on-time in this regard. There was no significant difference in behavioral difficulties between the two groups of children with DMD.

Children with DMD who were rated as delayed on walking performed significantly more poorly on a measure of visuospatial reasoning (mean [SD]: late = 94.35 [22.08], on-time = 103.07 [12.12]; $t = 2.38$, $P = .02$); however, there was no relationship between delayed walking and performance on a measure of single-word vocabulary. Furthermore, children with DMD who rated as delayed on walking did not exhibit later behavioral issues when compared with children with DMD who achieved this milestone on-time.

DISCUSSION

Results of the current investigation indicate that children with DMD are more likely than their siblings to be rated as delayed on most language and motor milestones. Consistent with previous reports of motor delay, children with DMD tend to be delayed in sitting, crawling, standing, and walking. The current investigation also documented delays in language milestones; children with DMD are more likely than their siblings to exhibit delays in speaking their first word and in constructing sentences. Not all aspects of development were rated as delayed. For example, parents reported that children with DMD and their siblings were equally capable of mastering bladder and bowel control at similar ages. The selectivity of these findings indicates that reports of delay among affected children are unlikely to be attributed solely to a bias in reporting.

The second goal of this study was to examine, in more detail, the relationship between early developmental delay and cognitive functioning among children with DMD. Results of this investigation revealed that late talkers performed significantly more poorly on select measures of intellectual functioning. It is important to emphasize that these findings, although statistically robust, represented subtle differences in performance. For example, children with DMD who were reported to be late talkers scored slightly below average (mean standardized score of 95) on the test of vocabulary, although those who were on-time in learning to speak scored slightly above average (mean standardized score of 107). These findings were statistically significant at the $P < .001$ level. There were no significant differences between the two groups on reports of behavior.

A similar analysis was performed on children who had been rated as delayed in walking; in contrast to late talkers, it was hypothesized that late walkers would not exhibit cognitive delays or behavioral problems. Unexpectedly, however, late walkers did significantly more poorly on the test of reasoning than their on-time peers. Although the reason for this finding is unclear, it is not uncommon to observe impaired motor skills associated with cognitive disorders.³⁶

For example, children with specific language impairment often present with poor motor skills.³⁷⁻⁴¹ It can be conjectured that the same part of the brain that is responsible for learning coordinated movement (ie, cerebellum) also contributes to cognitive functioning in this disorder. Tentative support for this hypothesis is offered by a positron emission tomography scan study in which children with DMD exhibited reduced glucose metabolism in areas normally rich in dystrophin, namely, the cerebellum.⁴²

The current study employed retrospective parental report as the primary method of investigating the attainment of developmental milestones in a large group of children with DMD and their siblings. Although the investigators are mindful of the potential drawbacks associated with the use of retrospective parental report in ascertaining timing of developmental milestones,⁴³⁻⁵² several features of the design of the current study serve to increase the likelihood of accurate parental report. The investigators chose to focus on broad categories such as “on-time” and “late” to increase the likelihood of accurate parental report. The fact that the control group consisted of siblings also enhanced the investigators’ confidence in the accuracy of parental report because the accuracy of the parent likely remained consistent between siblings. Indeed, there is substantial support for the hypothesis that most parents are capable of judging whether their child’s development is on par with other children of the same age, even when they are poor, uneducated, or lack parenting experience.^{44,53-57}

The use of siblings as controls is, in fact, one of the strengths of the current design. This method of control helps account for genetic, familial, and socioeconomic variables, and, thus, permits detection of subtle neuropsychological deficits unique to children with this disorder. Previously published data have demonstrated subtle, yet statistically robust, differences in neuropsychological test performance between children with DMD and their unaffected siblings.²⁰ Some of the cognitive deficits observed might not ordinarily suggest a need for clinical intervention, but, when compared with those of siblings, their significance is highlighted.

The findings of this study are important for several reasons: Early delays in the development of language and motor skills (ie, before the onset of significant motor weakness) demonstrate that poor performance on measures of cognition cannot be attributed solely to muscle fatigue, emotional reactions to DMD, or the loss of educational opportunities because of limited ambulation. Moreover, early delay implicates an underlying central nervous system component to DMD. Finally, the current findings underscore the need for early intervention services in this population. The initiation of early intervention may help limit later learning problems, potentially enhancing the quality of life for a group of children who face adversity in the form of enormous physical and emotional challenges.

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Table I
Percentage of children with DMD rated as “on-time” or “late” for each developmental milestone*

Milestone	On-time (%)	Late (%)
Smile	97	3
Sit	64	36
Crawl	47	50
Stand	43	53
Walk	33	67
Speak	62	38
Sentence	57	43
Bowel trained	60	40
Bladder trained	59	40
Read	51	47

* Percentages have been rounded up and may not equal 100% in all cases.

Table II
Comparison of children with DMD and sibling controls on developmental milestones: percentage late for each milestone as per parental report

Milestone	Proband: % late	Control: % late	χ^2	<i>P</i> value
Smile	3%	2%	.34	NS
Sit	38%	0%	28.37	<i>P</i> < .001
Crawl	60%	6%	40.53	<i>P</i> < .001
Stand	56%	0%	44.79	<i>P</i> < .001
Walk	70%	2%	52.14	<i>P</i> < .001
Speak	42%	4%	24.12	<i>P</i> < .001
Sentence	49%	4%	29.73	<i>P</i> < .001
Bowel trained	28%	8%	7.77	NS
Bladder trained	25%	10%	5.97	NS
Read	94%	6%	25.89	<i>P</i> < .001

NS, Not significant.