Motor and cognitive assessment of infants and young boys with Duchenne Muscular Dystrophy: results from the Muscular Dystrophy Association DMD Clinical Research Network

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Abstract

Therapeutic trials in Duchenne Muscular Dystrophy (DMD) exclude young boys because traditional outcome measures rely on cooperation. The Bayley III Scales of Infant and Toddler Development (Bayley III) have been validated in developing children and those with developmental disorders but have not been studied in DMD. Expanded Hammersmith Functional Motor Scale (HFMSE) and North Star Ambulatory Assessment (NSAA) may also be useful in this young DMD population. Clinical evaluators from the MDA-DMD Clinical Research Network were trained in these assessment tools. Infants and boys with DMD ($n = 24$; 1.9 ± 0.7 years) were assessed. The mean Bayley III motor composite score was low (82.8 ± 8; $p \leqslant .0001$) (normal $= 100 \pm 15$). Mean gross motor and fine motor function scaled scores were low (both $p \leqslant .0001$). The mean cognitive comprehensive ($p = .0002$), receptive language ($p \leqslant .0001$), and expressive language ($p = .0001$) were also low compared to normal children. Age was negatively associated with Bayley III gross motor ($r = -0.44$; $p = .02$) but not with fine motor, cognitive, or language scores. HFMSE ($n = 23$) showed a mean score of 31 ± 13. NSAA ($n = 18$ boys; 2.2 ± 0.4 years) showed a mean score of 12 ± 5. Outcome assessments of young boys with DMD are feasible and in this multicenter study were best demonstrated using the Bayley III.
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Keywords: Duchenne Muscular Dystrophy; Bayley III Scales of Infant and Toddler Development; Hammersmith Functional Motor Scale Extended; North Star Ambulatory Assessment; Infant

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1. Introduction

1.1. Early motor development in DMD infants and boys

There are many excellent multicenter studies that demonstrate progression of weakness in boys with Duchenne Muscular Dystrophy (DMD). Most use measures that require active cooperation. Early careful DMD natural history studies relied on manual muscle testing using Medical Research Council (MRC) testing and functional outcomes [1–4]. These outcomes have been extended to include quantitative measurements, which allow better inter-rater reliability for ambulatory boys and are currently used in multicenter trials [5–13]. Additional functional measures including timed functional tests [4,10,14–17] activity monitoring [18,19] and the six-minute walk test [10,19,20] are also very reliable for ambulatory boys. The North Star Ambulatory Assessment (NSAA) tests 17 items ranging from standing to running 10 m has recently been shown to have excellent inter-rater reliability in a multicenter trial of boys with DMD as young as 5 years [21–23].

Few clinical trials have included younger boys or infants because traditional MRC or quantitative testing may not be reliable or even possible. Both manual muscle testing and quantitative strength testing have been shown to be less reliable in children younger than age six years [4,24]. Furthermore, motor skills do improve in pre-school boys with DMD, albeit at a slower rate than normal boys. Prior studies of untreated younger boys demonstrate effectively this "honeymoon" period in DMD when function and strength may improve but does not equal the improvement present in normal children [1,10,19,25,26]. This can complicate interpretation of functional gains during clinical trials in younger boys with DMD. Reliable, age-normed measures are needed that can be performed in infants and younger boys with DMD. A pilot study of baseline motor function in 33 young boys with DMD (mean age 3.4 years) shows markedly different gross motor skills compared to age-matched controls using the Hammersmith Motor Ability Score [27]. However, there was a "ceiling effect" using this early form of the Hammersmith. In the same study, the locomotor quotient of the Griffiths' scales demonstrated deterioration in young boys with DMD [27]. This latter measurement showed a highly significant negative correlation with age.

An expanded version of the Hammersmith Functional Motor Scales (HFMSE) has recently been validated in both SMA-II and SMA-III and includes additional gross motor skills including jumping and climbing up and down stairs [28,29]. Finally, the Bayley III infant motor scale, while not yet tested in children with neuromuscular disorders, has been validated in many studies of children with motor delay in the first years of life [30–38]. Novel therapeutic interventions for boys with DMD may be most effective in the youngest age group, but these boys present significant difficulties for clinical trials because of the lack of validated outcomes. In order to have this challenging population of infants and young boys "trial ready" we studied outcomes in a multicenter cohort after careful clinical evaluator training. We wanted to capture data from the youngest boys and therefore chose the Bayley III and the HFMSE which have both been validated in infants from birth. We also studied the NSAA to test its ability to assess the youngest ambulatory boys with DMD.

1.2. Early mental development in DMD infants and boys

Cyrulnik et al. demonstrated that cognitive delay in some boys with DMD is clearly recognized by parents [39]. Hinton et al. have also characterized verbal and memory skills in older boys with DMD [40]. The earliest study of mental development in young boys with DMD (6 boys who were a subset of Brooke et al.'s original study) was done using the Denver developmental assessment [1]. This diagnostic tool has since been revised to improve both social and speech/language assessments [41]. However, as it does not provide a quotient, it is not possible to quantify and would also be difficult to standardize between sites. The most detailed work in mental development of young boys with DMD using the Griffith's Mental Development Scales (GMDS) shows that early delays can be detected using careful standardized assessments [42].

The most validated scales of language and cognition in all infants and young children through age 6 years are the Bayley III scales of infant development which are validated through 42 months of age [43] and the Stanford Binet Intelligence Scale 5th edition (ages 3 years and older) [44]. Both provide measurable quotients. While the Bayley III has not been used in boys with DMD, it has been used in hundreds of studies of children at risk for both motor and mental delays including premature infants, children with hypoxic ischemic injuries, children with Down syndrome and children with immune deficiency [30–38].

We had two objectives in determining if we could reliably assess motor, cognitive, language, and social emotional development in young boys with DMD. First, if a reliable scale can measure development in infants and young boys with DMD, it could be used as and outcome measure in clinical trials. Some treatments may work best in infants and young boys before severe fibrosis develop and this would allow inclusion of this important group. Second, information about early cognitive or intellectual deficits may lead to specific early cognitive or social intervention for infants and boys with DMD.

2. Methods

2.1. Participants

We included boys with DMD who were at least one month but less than three years old. All six DMD

Table 1
Age and DMD mutations.

Subject	Age (years)	Family History	Mutation	Exon(s)	Frame	Disruption of Dp140 isoform	Disruption of Dp71 isoform
1	0.37	Yes	Deletion	3–32	In	No	No
2	0.41	No	Deletion	3–41	In	No	No
3	0.63	Yes	Deletion	45	Out	Yes	No
4	0.69	Yes	Nonsense[a] (c.615T>A; p.TyrX)	7	Out	No	No
5	1.22	Yes	Duplication	2	Out	No	No
6	1.23	Yes	Deletion	45–50	Out	Yes	No
7	1.42	Yes	Deletion	46–50	Out	Yes	No
8	1.7	No	Deletion	12	Out	No	No
9	1.72	Yes	Deletion[a]	46	Out	Yes	No
10	1.81	Yes	Deletion	45–50	Out	Yes	No
11	2.02	No	Deletion	58	Out	Yes	No
12	2.07	Yes	Deletion[a]	8–9	Out	No	No
13	2.21	Yes	Nonsense (c.2353C>T; p.Gln785X)	19	Out	No	No
14	2.24	No	Deletion	51–57	Out	Yes	No
15	2.41	No	Deletion	53–55	Out	Yes	No
16	2.41	No	Deletion	45	Out	Yes	No
17	2.43	No	Deletion	49–52	Out	Yes	No
18	2.44	No	Deletion	58–64	Out	Yes	Yes
19	2.61	Yes	Deletion	18–25	In	No	No
20	2.71	No	Deletion	46–52	Out	Yes	No
21	2.8	No	Nonsense (c.2791G>T; p.Glu931X)	21	Out	No	No
22	2.82	No	Deletion	45	Out	Yes	No
23	2.85	Yes	Deletion	12–44	Out	Unknown	No
24	2.99	No	Deletion	17	Out	No	No

The last two columns describe predicted effect of the mutation on expression of other relevant DMD isoforms by deletion of either the appropriate promoter/exon 1 or by downstream domains.

[a] Subjects in whom mutation analysis from an affected brother was accepted. Implications of reading frame are discussed in the text.

Clinical Research sites received human studies approval and informed consent was obtained from a parent prior to enrollment in the study. Every site enrolled at least three boys for this study which involved a single visit; Washington University ($n = 5$), Nationwide Children's ($n = 5$), University of California-Davis ($n = 4$), University of Minnesota ($n = 4$), Boston Children's ($n = 3$), Newcastle ($n = 3$). Mutations in the *DMD* gene were defined for all boys (Table 1). Thirteen had a primary relative (brother or uncle) with DMD; three of these boys were enrolled based on an elevated serum CK consistent with DMD, and the results of mutation analysis in their brothers were accepted. Three boys were identified by newborn screening [45]. None were taking corticosteroids.

2.2. Measures

The clinical assessments included are summarized in Table 2. Total testing time was generally 90–150 min. The tests administered included the following:

(a) *Bayley III Scales of Infant Development*. The Bayley III Scales of infant development includes assessment of cognition, language (receptive and expressive) and motor function (gross and fine). The Bayley III provides a measureable and validated cognitive quotient [43]. Bayley III language assessment is divided into two subtests consisting of receptive and expressive assessments. When these two language subtests are combined a composite score is determined. Bayley III Motor assessment includes scaled scores for fine motor and gross motor as well as a composite score. In addition, the Bayley III social emotional scale includes items which test both social emotional competence and sensory processing and is based on earlier work by Greenspan [46].

(b) *Adaptive Behavioral Subtest of Bayley* (ABS) is a detailed, validated parental questionnaire which allows calculation of social emotional and adaptive behavioral assessment scores [43]. Subscales include Communication, Community Use, Functional Pre-Academic, Home Living, Health and Safety, Leisure, Self-Care, Self-Direction, Social, and Motor. Subscale scores in normal children are standardized to a mean of 10 and a standard deviation of 3. Based on these subscales, four composite scores are calculated which include the general adaptive composite (GAC), conceptual adaptive domain (CON), social adaptive domain (SO) and practical adaptive domain (PR). The general adaptive composite (GAC) reflects all subscales. The conceptual adaptive domain (CON) is calculated by adding the communication, Functional

Table 2
Clinical assessments used in infants and young boys with DMD.

Test	Age range	Domains	Test Administration	Time to administer
Bayley III Scales of Infant development	0–42 months	• Cognition • Language (receptive and expressive) • Motor function (gross and fine)	Trained clinical evaluator	90–120 min
Adaptive Behavior Subtest of Bayley III	0–42 months	• Communication • Community Use • Functional Pre-Academic • Home Living • Health and Safety • Leisure • Self-Care • Self-Direction • Social • Motor	Parent self-report	15–30 min
HMFSE	0–6 years[a]	Gross motor	Trained clinical evaluator	20–30 min
North Star[b]	Ambulatory	Gross motor	Trained clinical evaluator	10–15 min

[a] The age range of the HMFSE is approximate as these skills are gained over time but typically developing children would have achieved all by six years.
[b] The 17 activities tested with the North Star include standing (1), walking (2), standing up from a chair(3), standing on each leg (4, 5), climbing on a box step with each leg (6, 7), descending from box step with each leg (8, 9), getting to sitting (10), rising from the floor (11), lifting head(12), standing on heels (13), jumping (14), hopping on each leg (15, 16) and running 10 m (17).

Pre-Academics, and Self-Direction subscale scores. The social adaptive (SO) composite score considers the leisure and the social subscale scores. Finally, the practical adaptive domain reflects the Community Use, Health and Safety, Home Living, and Self-Care subscales. The norms for these composite scores in normal children are mean = 100, s.d. = 15.

(c) *Expanded Hammersmith Functional Motor Scales (HFMSE)* (Table 3). The HFMSE was administered to all participants with DMD. While this scale and prior forms of it were originally developed for children with SMA-II and SMA-III, we thought recent work suggested the HFMSE might be useful in young DMD boys [47,48]. Over the last decade, several versions of the Hammersmith Functional Motor Scales have been developed [29,47,49–51]. The first version, by Main et al. [50] showed good reliability in children over age 30 months in both SMA and normal children but poor reliability in younger children. Krosshell et al. then showed that a modified version Hammersmith Functional Motor Scale (MHFMS) showed excellent reliability (ICC 0.96) in very young, non ambulatory children with SMA-II or SMA-III (range 9–30 months) [29]. Healthy participants had MHFMS scores ranging from 36 to 40 and achieved maximum test scores at 12 months of age [29]. The Expanded Hammersmith Functional Motor Scale the (HFMSE) was developed using some skills from the Hammersmith Functional Motor Scale developed by Main et al. [50] and skills from the Gross Motor Function Measure [52] including standing, squatting, jumping, and stair climbing and showed good reliability in a large cohort of ambulatory subjects with SMA-I and SMA-III, extending to as young as 20 months [47,48]. We chose to use the HFMSE because of this reliability and because it would capture early ambulation milestones.

(d) *North Star Ambulatory Assessment (NSAA)* (Table 4). The NSAA tests functional activities including standing, getting up from the floor, negotiating steps,

Table 3
Expanded Hammersmith Functional Motor Scale.

Activity tested	Estimated age range when normal children should complete this activity
1. Sitting on chair	6–10 months
2. Long sitting, legs extended	7–11 months
3. Hand To head while sitting	10–12 months
4. Two hands to head while sitting	10–12 months
5. Rolling to each side	4–5 months
6/7. Rolling prone to supine right and left	5–9 months
8. Rolling supine to prone to right	6–9 months
9. Rolling supine to prone to left	6–9 months
10. Sitting to lying	6–8 months
11. Props on forearms	4–6 months
12. Lifts head from prone	1–2 months
13. Props on extended arms	8–11 months
14. Lying to sitting	7–11 months
15. Four-point kneeling	7–10 months
16. Crawling	7–12 months
17. Lifts head from supine	8–11 months
18. Supported standing	8–10 months
19. Stand unsupported	9–13 months
20. Stepping	12–15 months
21/22. Right and left hip flexion in supine	8–15 months
23/24. High kneeling to right/left half Kneel	18–36 months
25/26. High kneeling to standing, leading with right/left leg	18–36 months
27. Stand to sitting on floor	9–13 months
28. Squat	10–15months
29. Jumps 12 in. forward	24–38 months
30. Ascends 4 stairs with railing	18–24 months
31. Descends 4 stairs with railing	24–48 months
32. Ascends 4 stairs without arm support	36–48 months
33. Descends 4 stairs without arm support	36–56 months

Each activity is scored on a three point scale 0–2 (0, unable to complete, 1, completes with modification, 2, completes fully).

Table 4
North Star Ambulatory Assessment.

Activity tested	Estimated age range when normal children should complete this activity
1. Stand	9–13 months
2. Walk	9–15 months
3. Stand up from a chair	9–14 months
4/5. Stand on right/left leg for three seconds	2.5–3.5 years
6/7. Climb on box step (15 cm high) with right/left leg leading	14–22 months
8/9. Descend from box step with right /left leg leading	16–26 months
10. Gets from lying to a sitting position	6–11 months
11. Rises from supine to standing	10–14 months
12. Lifts head from supine position	8–11 months
13. Stands on heels	3–4 years
14. Jump up	20–38 months
15/16. Hop on right/left leg clearing floor	3–5 years
17. Run 10 m	15–26 months

Each activity is scored on a three point scale 0–2 (0, unable to complete; 1, completes with modification; 2, completes fully).

hopping, and running [22,23,53,54]. It was designed to be used in boys with DMD who are able to stand and has been validated in boys over the age of 3 years. The assessment is based on a 3 point rating scale of 2 = ability to perform the test normally, 1 = modified method or assistance to perform test, 0 = unable to perform the test. Thus, total score can range from 0 (completely non-ambulant) to 34 (able to complete all tasks fully). The 17 activities tested become progressively difficult (Table 4). Item 1 requires a boy be able to stand. We therefore used this assessment only in those who were at least able to stand using a modified method, thus achieving at least 1 point. We realized that the NSAA is limited because there is not yet data in typically developing children and we could only score those who were already ambulating.

2.3. Training

Training required all clinical evaluators (CE) to attend a three-day session at Washington University in Saint Louis. All CEs completed didactic and interactive training for the HFMSE (by SOR and ES, Boston Children's Hospital) and the NSAA (by ME, Newcastle). For the Bayley III, CE's received didactic and healthy infant training (by MMC, Washington University). Then each site was required to recruit at least two additional well infants (under and over age 18 months) and perform a videotaped practice Bayley III. This was reviewed and scored by MMC and if needed, additional well infants were evaluated. Upon completion, CEs at each site were certified (prior to recruitment of boys with DMD). Training for the HFMSE (by SOR and ES) and NSAA (by ME) was also performed during this meeting. Retraining for all outcomes was performed 12 months into the study.

2.4. Statistical analyses

Descriptive statistics were performed with SAS 9.3 (SAS Institute, Cary, NC) and GraphPad Prism (GraphPad Software, La Jolla, CA). p-Values are all 2-tailed.

3. Results

3.1. Bayley III scales of infant development and Adaptive Behavioral Assessment Score (ABAS)

All 24 infants and young boys with DMD were able to complete the gross motor component of the Bayley III (mean age 1.9 ± 0.7 years; range = 0.37–2.99) and 23 were able to complete fine motor component. One child (age 2.4 years) became irritable and did not complete the fine motor component. All 24 completed the language and cognitive assessment of the Bayley III.

3.1.1. Bayley III cognitive
On the Bayley III cognitive scale, the mean cognitive comprehensive score for the group was 89.6 with a range of 65–115. The plot of the individual children demonstrated a clear shift to the left very similar to what has been described for standard IQ testing in older boys with DMD ($t = -4.43$, $p = .0002$) (Fig. 1A).

3.1.2. Bayley III language (Table 5)
On the Bayley III receptive and expressive language assessments and the composite language assessment, infants and young boys with DMD again demonstrated mean performances that were lower than average (Table 5) with a shift of data to the left ($t = -4.61$, $p = .0001$) (Fig. 1B).

3.1.3. Bayley III motor assessment
On the Bayley III motor assessment, motor composite assessment showed average performance that was lower than normal children ($t = -7.99$, $p \leqslant .0001$) (Fig. 1C). Gross motor, as expected appeared more affected being more affected than fine motor (Table 6). The data showed that most boys performed more than a standard deviation less than the mean.

3.2. Comparison of DMD boys' performance of Bayley III with age

3.2.1. Bayley III gross and fine motor scaled scores versus age
Lower gross motor-scaled scores were associated with increasing age ($r = -0.44$; $p = .02$) (Fig. 2A). This may be a function of the test better identifying deficits as boys get slightly older or may suggest that these children are losing ground compared to their peers even in this early age group. Fine motor-scaled scores, while low, did not vary significantly with age ($r = -0.12$; $p = 0.5$).
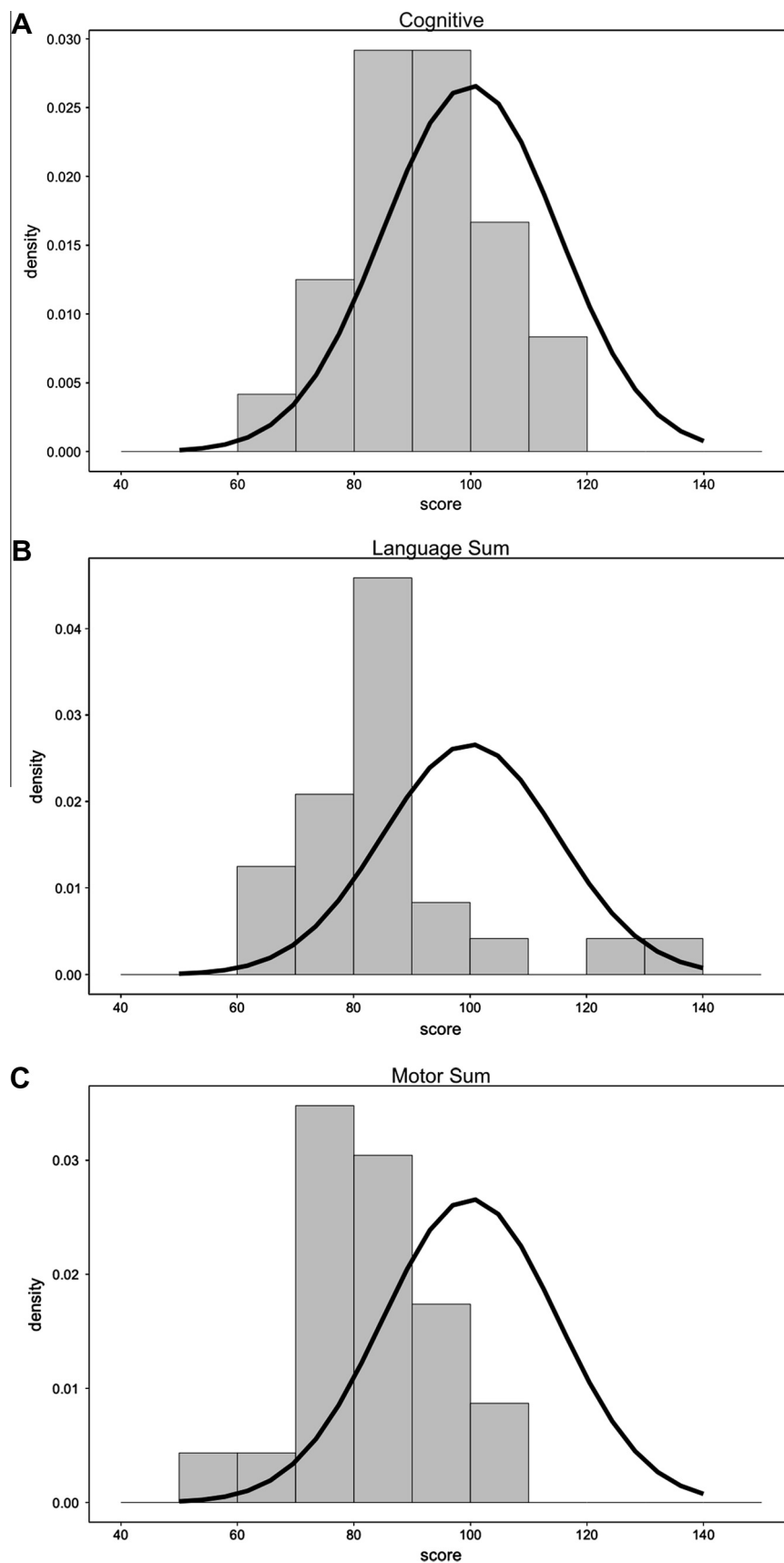
Fig. 1. (A) Distribution of Bayley-III Cognitive Composite scores of DMD boys compared to normal children. There was a shift of the distribution to the left ($t = -4.36$, $p = .0001$). (B) Distribution of Bayley III Language Composite scores of DMD boys compared to normal children ($n = 24$). There was a shift of the distribution to the left ($t = -4.42$, $p < .0001$). (C) Distribution of Bayley III motor composite scores of DMD boys compared to normal children ($n = 23$). There was a shift of the distribution to the left ($t = -7.60$, $p \leqslant .0001$).

Table 5
Bayley-III Language and Cognitive assessment of infants and young boys with DMD ($n = 24$).

Subtest	Normal	DMD	t test and p values
Language receptive scaled score	10 ± 3	7.0 ± 1.6 (2–14)	$t = -5.98$ ($p \leqslant .0001$)
Language expressive scaled score	10 ± 3	8.0 ± 2.3 (3–18)	$t = -3.01$ ($p = .005$)
Language composite	100 ± 15	85.8 ± 9.9 (5–135)	$t = -4.42$ ($p = .0001$)
Cognitive composite	100 ± 15	89.5 ± 8.7 (65–115)	$t = -4.36$ ($p = .0001$)

Both receptive and expressive language means were significantly lower than normal children. The language composite score combines these two scaled scores.

Table 6
Bayley III motor assessment of infants and young boys with DMD.

Subtest	Normal	DMD	t test and p values
Fine motor scaled score ($n = 23$)	10 ± 3	7.9 ± 1.9 (3–11)	$t = -4.4$ ($p = .0001$)
Gross motor scaled score ($n = 24$)	10 ± 3	6.1 ± 1.5 (3–10)	$t = -9.8$ ($p \leqslant .0001$)
Motor composite score ($n = 23$)	100 ± 15	82.2 ± 8.4 (58–103)	$t = -7.60$ ($p \leqslant .0001$)

One infant was not able to complete the fine motor testing and therefore the motor composite score (which combines both Fine and gross motor scaled scores) is also calculated with $n = 24$.

3.2.2. Bayley III cognitive and language scores versus age

The Bayley III cognitive and language composite scores did not vary significantly with age ($r = -0.13$ and $r = 0.10$; $p = 0.5$ and 0.6). However, cognitive and language composite scores were very tightly correlated with each other ($r = 0.80$; $p \leqslant .0001$). This positive correlation between cognitive and language is commonly seen in other populations including typically developing children [43].

3.3. Adaptive Behavior Subtest (ABS)

The results for each ABS are shown in Table 7. The lowest ABS subscale scores were Functional Pre-Academic (7.8 ± 2.8, Self-Care (6.2 ± 2.9) and Motor (7.4 ± 4.0). The general adaptive composite (GAC) reflects all subscales and showed a mean composite score of 84 ± 15. The conceptual adaptive domain (CON) composite score for our population was 86 ± 15. The mean social adaptive (SO) composite score was 86 ± 10. Finally, the mean practical adaptive (PR) was 85 ± 13. Despite the fact that the motor subscale (7.4 ± 4.0) is not considered in the CON, SO or PR composite scores, on average the infants and young boys are one standard deviation lower than normally developing boys. The ABS questionnaire reflects similar pattern of performance demonstrated by direct examination (Bayley III) and provides good evidence that these deficits are apparent to their primary caregiver.

3.4. Social Emotional Scale of the Bayley III

Twenty-two completed the Social Emotional Scale of the Bayley III. The social emotional composite scores ranged from 55 to 135 (mean 92 ± 17). Six boys had social emotional scores less than 75 which correspond to the 5th percentile or less. The social emotional scores did not vary with age ($r = 0.1$; $p = 0.47$).

3.5. Expanded Hammersmith Functional Motor Scale (HFMSE)

The HFMSE was performed on 23 boys. The mean total score was 36.7 ± 13. As expected, this score increased with age ($r = 0.63$; $p = .001$) (Fig. 2B). HFMSE scores for population based typically developing children do not yet exist. However, we demonstrate that is feasible to perform this assessment and in time may allow one to detect early motor plateau or decline in individual children.

3.6. Performance on the North Star Ambulatory Assessment

We tested only the 18 boys who were able to stand independently for at least 3 s (thus achieving 2 points). As expected the mean age was older (2.2 ± 0.5 years) compared to those who could not (0.9 ± 0.6 years). As with the HFMSE, the NSAA has also not yet been studied in typically developing children. The scores in this group of boys with DMD boys did not correlate with age ($r = 0.24$; $p = 0.3$) (Fig. 2C). We also noted striking variability in the performance of different boys of similar ages. This observation corresponds to the clinical fact that some DMD boys meet some early milestones and are therefore are not recognized as delayed in these first years. However, we do demonstrate it is feasible to begin to use the early skills in this scale (standing, walking) in the boys over age two years. Following this scale across time may be useful if data in typically developing children is obtained.

4. Discussion

There is limited evidence of the motor, cognitive and language function in boys with DMD who are less than 5 years old. Previous work using the Griffiths' scale supports this approach where normative controls allowed
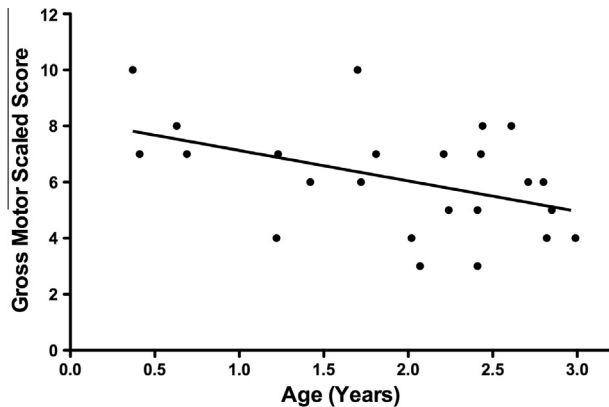
Fig. 2A. Bayley-III gross motor scaled scores versus Age ($n = 24$). There was a negative correlation with age ($r = -0.45$; $p = .03$) demonstrating motor function relative to typically developing children is low.
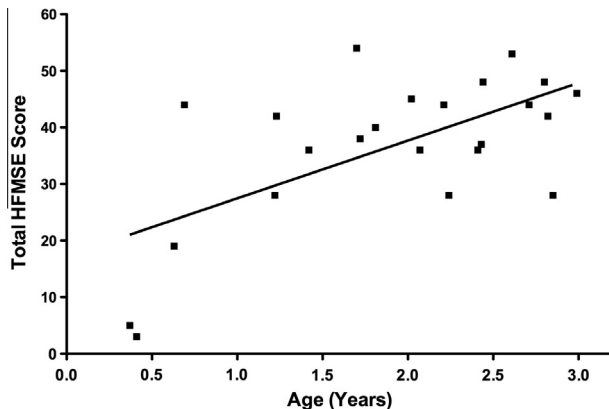

Fig. 2B. Hammersmith Functional Motor Extended versus Age ($n = 23$). There was a positive correlation with age ($r = 0.63$; $p = .001$) showing absolute motor gains are demonstrated across time.
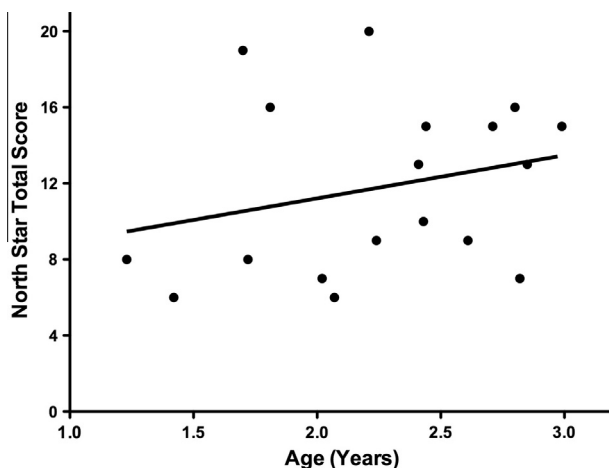

Fig. 2C. North Star Ambulatory Assessment ($n = 18$). There was not a significant correlation with age ($r = 0.26$; $p = .3$).

Smith et al. to compare development of boys with DMD to that of typically developing children at a single site [27,42]. The Bayley III is the most widely used standardized

measure in the clinical research and early intervention setting for children with developmental delay. Earlier versions of the Bayley have been favorably compared to the Griffiths' scale in children with other severe developmental disabilities [55]. We chose to study infants and young boys with DMD using the Bayley III for two reasons. First, we had the ability to train clinical evaluators in its use whereas training in the Griffiths' scale is not widely available. Second, we wanted to determine if, with careful training, a multicenter outcome trial would allow comparison of this challenging group across ages and against normative populations. In this cross sectional population of boys with DMD, we demonstrate that these infants and young boys have measurable differences in motor, cognitive, language, and social development compared to typically developing children.

The normative sample for the Bayley III which includes the Adaptive Behavior Questionnaire included 1700 children from age 1 through 42 months and was stratified using by gender, region, race/ethnicity, and parent education. The Bayley III is not designed to be predictive but descriptive and may underreport deficits. However, in this multi-center study we were able to reliably identify group differences in infants and young boys with DMD compared to typically developing children.

With regard to gross motor development, we demonstrated that Bayley III scaled gross motor scores correlated negatively with age of the infants and boys. It has been known for many years that boys with DMD gain motor skills and function over the first 6–7 years (the "honeymoon" period). Our work suggests that while there are gains in motor skills (demonstrated on the HFMSE), relative to their peers, even infants and young boys with DMD may be losing ground and show less maturational improvement with age. Follow-up of this cohort of boys will further clarify this question and determine if these tools are sensitive to change across time. Given the gain in skills with age on the HFMSE, it is likely that a therapeutic agent would need to produce greater improvement over time in skills on this instrument or a greater percentage of patients achieving defined levels of performance or milestones. This fact makes scales such as the HFMSE and the NSAA much less useful as they have not been validated in typically developing children.

Early motor deficits in young boys with DMD under age three have also not been reported using the HFMSE or the NSAA. While we demonstrate that the HFMSE can be tested in young boys with DMD, and that the absolute scores increase with age as expected, this measure did not have any advantage over the Bayley III which has the strong advantage of being well standardized in normal children. Once ambulatory, we were also able to score all boys with DMD using the North Star Ambulatory Assessment. The lack of relationship with age of the NSAA may imply that it might not be a useful measure

Table 7
Adaptive Behavior Subtest of Bayley III in infants and young boys with DMD.

Sub-scale	Communication	Community Use	Functional Pre-Academic	Home Living	Health and Safety	Leisure	Self-Care	Self-Direction	Social	Motor
$n =$	22	18	18	18	22	22	22	22	22	22
nl mean = 10	8.4	8.8	7.8	8.7	7.9	8.4	6.2	8.7	7.8	7.4
s.d. ±3	±2.9	±2.9	±2.8	±3.3	±2.6	±3.1	±2.9	±3.2	±2.9	±4.0
t value	−1.6	−1.7	−3.2	−1.7	−3.8	−2.3	−6.1	−1.8	−3.4	−3.1
p value	.01	.04	.002	.05	.0006	.03	<.0001	.04	.001	.002

Incomplete reports and age of infants account for the variable numbers. Community Use, Functional use, and Home Living are only scored for infants over one year of age.

of disease progression in the under age three population. Longitudinal assessments will be required to determine this. Furthermore, both the HFMSE and the NSAA suffer from lack of validation in typically developing children.

Many boys with DMD have social deficits which have generally been appreciated at or just before school age [40,56,57]. Here, we also demonstrate lower average performance on measures of cognitive and social emotional development based both on objective clinical evaluator assessments (via the SE Scale of the Bayley III) and by parent observation (via the Adaptive Behavior Subscale) in children younger than three years. These two assessments correlated well with each other. In the study of other populations of children, this correlation has also been recognized. Early recognition of these cognitive and social deficits may have implications regarding therapy and early intervention services. Social and cognitive deficits are not typically included as outcome in neuromuscular treatment trials. Our data shows that both objective raters and caregivers may detect these deficits and that these deficits are present early in the disease course.

Our subjects were genetically well characterized. Only three had mutations predicted to preserve an open reading frame, more commonly associated with the milder Becker muscular dystrophy (BMD) phenotype. However, two of these in-frame mutations (deletion of exons 3–41, and deletion of exons 18–25) have been previously reported to be associated with DMD. The third (deletion of exons 3–32) has been reported only once to the Leiden database (www.dmd.nl) without a clearly defined phenotype, but may be expected to be associated with a DMD-like phenotype by analogy to many other large deletions affecting the N-terminus of the dystrophin protein [58].

It has been previously reported that deletions affecting expression of either the Dp140 or Dp71 isoforms of dystrophin may be related to cognitive impairment in DMD patients [59,60]. As seen in Table 1, the vast majority (23 out of 24) of mutations represented in our cohort are predicted not to affect Dp71 expression. Effects on Dp140 expression could be predicted in 23 subjects, among whom expression would be expected to be disrupted in 13. In boys whose mutations did not disrupt the Dp140 brain dystrophin, there were trends for higher cognitive comprehensive (mean 93.5 versus 86.9;

$p = .10$) and language comprehensive scores (mean 91.4 versus 81.7; $p = .10$) but no difference in motor scores (83.5 versus 81.5; $p = .35$).

Clinical trials are underway which may fundamentally change the natural history of DMD. Some therapeutic options may work best early, prior to the secondary sequella of fibrosis of muscle. Traditionally, these clinical trials have excluded all young boys and infants as traditional outcome measures have not been possible in this age group. While the very young, less than six month, age group will remain challenging, developmental scales such as the Bayley III allow them to be studied. In this study, we demonstrate that is possible to characterize and quantitate cognitive, language, and motor deficits at baseline evaluation. The most consistent deficits in the young population were in the gross motor domain. Since future treatments are likely to preserve skeletal muscle fibers and improve muscle function, it is likely that the motor scales of the Bayley III, and other functional scales which focus on gross motor function (such as the HFMSE and North Star) will play an important role in these clinical trials. Over time, we hope to demonstrate sensitivity to change for each of these assessment tools in this challenging population.

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