Early developmental milestones in Duchenne muscular dystrophy

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ABBREVIATIONS

DDI	Dutch Development Instrument
DMD	Duchenne muscular dystrophy

AIM To investigate the differences in attainment of developmental milestones between young males with Duchenne muscular dystrophy (DMD) and young males from the general population.
METHOD As part of the case–control 4D-DMD study (Detection by Developmental Delay in Dutch boys with Duchenne Muscular Dystrophy), data on developmental milestones for 76 young males with DMD and 12 414 young males from a control group were extracted from the health care records of youth health care services. The characteristics of DMD were acquired from questionnaires completed by parents. Logistic regression analyses were performed with milestone attainment (yes/no) as the dependent variable and DMD (yes/no) as the independent variable, with and without adjustment for age at visit.
RESULTS The mean number of available milestones was 43 (standard deviation [SD]=13, range: 1–59) in the DMD group and 40 (SD=15, range: 1–60) in the control group. The presence of developmental delay was evident at 2 to 3 months of age, with a higher proportion of young males with DMD failing to attain milestones of gross/fine motor activity, adaptive behaviour, personal/social behaviour, and communication (range age-adjusted odds ratios [ORs]=2.3–4.0, $p<0.01$). Between 12 and 36 months of age, differences in the attainment of developmental milestones concerning gross motor activity increased with age (range age-adjusted ORs=10.3–532, $p<0.001$). We also found differences in developmental milestones concerning fine motor activity, adaptive behaviour, personal/social behaviour, and communication between 12 and 48 months of age (range age-adjusted ORs=2.5–9.7, $p<0.01$).
INTERPRETATION We found delays in the attainment of motor and non-motor milestones in young males with DMD compared to the control group. Such delays were already evident a few months after birth. Developmental milestones that show a delay in attainment have the potential to aid the earlier diagnosis of DMD.

Duchenne muscular dystrophy (DMD) is an inherited X-linked recessive neuromuscular disorder affecting approximately 1 in 5000 live male births.[1,2] DMD is caused by a defect in the dystrophin gene and is characterized by delayed motor development,[3–7] progressive muscle weakness, loss of ambulation, and subsequent cardiac and respiratory complications that are eventually fatal.[8–10] DMD is also often associated with non-progressive cognitive deficits, language deficits,[4] and psychiatric comorbidity, which are thought to result from defective isoforms of the dystrophin protein typically expressed in parts of the brain.[10–14] With advances in treatment and supportive care, it is possible for patients with DMD to survive into their fourth decade with improved quality of life.[8,15,16]

In patients without a family history of the disorder, DMD is typically diagnosed at around 4 to 5 years of age.[5,16,17] While newborn screening provides a potential means to reduce delayed diagnosis,[18,19] its implementation is controversial due to lack of evidence that early treatment improves clinical outcomes.[20] Currently, no country universally screens for DMD at birth. However, it is important to diagnose DMD during infancy or at the toddler stage because late diagnosis has several detrimental consequences. This includes delayed access to treatments such as ataluren,[21] which is approved in Europe to treat ambulatory patients with DMD over 2 years of age who have a nonsense mutation in the dystrophin gene.[22]

This also includes missed opportunities for reproductive options, doing what is best for one's child (good parenting), and enrolment in clinical trials, as well as the strain and costs associated with a protracted diagnostic pathway.[23,24]

We hypothesized that detecting patterns of developmental delay associated with DMD, thereby prompting further diagnostic investigation, can provide improved and timely diagnosis. As a first step towards the validation of this method, the attainment of individual developmental milestones should be investigated.

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Previous studies laid the foundation for this study because they provided evidence that more young males with DMD fail to attain a number of early developmental milestones compared to the general population.[3,4,6,7,12] Another major contribution are studies that recognized the delay from parents noting signs and symptoms (such as gross motor delay, muscle weakness, and trouble walking, running, climbing) to age at diagnosis of individuals with DMD.[5] Previous studies mainly focused on gross motor activity and communication; there may also be a delay in fine motor activity, as well as adaptive and personal/social behaviour. Previous studies included only a small number of milestones (range: 1–10)[3,4,6,7] or a small number of participants (n<20).[3,6] Some studies included a large number of young males with DMD[4,5] but were either based on retrospective parental reporting,[4] which may suffer from recall bias, or did not include milestones recorded by health professionals.[5] Additionally, most studies did not include a control group.[3,5,7,12] However, some studies used the Bayley Scales of Infant and Toddler Development, Third Edition[6] or the Griffiths Mental Development Scales as an appropriate alternative method for a control group.[12] Furthermore, to our knowledge, no other studies have investigated developmental milestones in individuals with DMD in the first months of life while health professionals were unaware of (blinded for) the diagnosis.

To better understand all domains of child development in young males with DMD, we aimed to investigate the differences in attainment of a large number of developmental milestones during regular day-to-day health assessments between young males with DMD and young males from the general population, assessed between 1 and 48 months of age.

What this paper adds

- Young males with Duchenne muscular dystrophy (DMD) experienced a delay in all domains of child development.
- Developmental delay was already evident a few months after birth.
- Delay in gross motor activity strongly increased with age in young males with DMD.

METHOD

Data collection

The following data were collected from the case–control 4D-DMD study (Detection by Developmental Delay in Dutch boys with Duchenne Muscular Dystrophy): (1) health records of young males with DMD; (2) questionnaires completed by the parents of young males with DMD; and (3) health records of the control group. The analyses used the birth characteristics and results from the Dutch Development Instrument (DDI) obtained from the health records of young males with DMD and the control group. The diagnosis and date of diagnosis were obtained from the Dutch DMD patient registry.

Health records of young males with DMD

Participants were identified and invited to participate in the study by two patient support organizations, the Duchenne Parent Project and the Dutch Association for People with a Neuromuscular Disease (Spierziekten Nederland). Members with offspring with DMD aged up to 26 years and alive as of July 2017 were eligible for inclusion. If parents and/or children (depending on the age of the child) agreed to participate, they were asked to provide written informed consent for the collection of their health records, their date of diagnosis, and publication of the results. The following information was extracted: participant characteristics; referrals to secondary and tertiary care; educational interventions; clinical descriptions typical of DMD; and DDI scores. Data from individual health records were entered manually and checked by three researchers to ensure high-quality data. Participant diagnoses and dates of diagnosis were verified through an independent database, the Dutch DMD patient registry of the Laboratory for Diagnostic Genome Analysis, Leiden University Medical Center, the Netherlands.

Questionnaire completed by parents

In June 2018, parents of young males with DMD aged 26 years and younger were invited by an online newsletter to complete a questionnaire. Parents who completed the questionnaire were offered a gift certificate. Parents who had given permission to access their offspring's health records, but had not completed the questionnaire, were sent a reminder by e-mail. The questionnaire requested information on the type of diagnosis, recall of developmental milestones, health care referrals, symptoms, functional outcomes, participation in daily life activities, and comorbid cognitive and behavioural disorders. The relevance of outcomes was decided in consultation with a committee that consisted of several parents of children with DMD and several medical specialists, including youth health care physicians, paediatricians, a paediatric neurologist, and a DDI instructor. The parent questionnaire was only used to supplement missing health record information on gestational age, birthweight, and type of diagnosis in young males with DMD. Other information provided in the questionnaire (e.g. recall of developmental milestones) was not used in the current study.

Health records of the control group

We obtained permission from the youth health care service of The Hague to extract anonymous data from the electronic health records of all children born between 2011 and 2013. This registry contained children's characteristics, longitudinal data on DDI results, and referrals to other health professionals; we excluded all females and one male who was diagnosed with DMD (to create a non-DMD group). Males with DMD who were not yet diagnosed at the time of data extraction may still be in the control group. No other selections were applied.

Developmental milestones

In the Netherlands, the DDI,[25] a modification of the Gesell test, is used by youth health care to assess the

development of children. The DDI is a set of 72 developmental milestones that cover three domains of child development: (1) fine motor activity, adaptive behaviour, and personal/social behaviour; (2) communication; and (3) gross motor activity. The DDI is administered by trained youth health care professionals at visits scheduled at the ages of 1, 2, 3, 6, 9, 12, 15, 18, 24, 30, 36, 42, and 48 months. In many youth health care services, visits at 30 and 42 months are only scheduled for children considered at risk; therefore, the milestones registered during these visits were excluded (available milestones [*n*=60] are shown in Table S1, online supporting information). Youth health care professionals administer and register each milestone according to a uniform protocol. Two to seven specific milestones are registered in the health records at each youth health care visit; however, some milestones may also be registered based on the observations made by caregivers if the behaviour is not observed during the examination.

Statistical analysis

Although children were invited by the youth health care services at specific ages to assess the DDI, differences were found in the age when milestones were assessed. Therefore, we selected the age nearest to the scheduled age and excluded values outside the ranges of 0 to 2, 1 to 3, 2 to 4, 4 to 7, 7 to 10, 10 to 13, 13 to 16, 15 to 21, 20 to 27, 32 to 39, and 44 to 52 months for the scheduled ages of 1, 2, 3, 6, 9, 12, 15, 18, 24, 36, and 48 months. This data selection was applied to both DMD and control groups. Descriptive statistics, as well as logistic regression analyses, were obtained with milestone attainment (yes/no) as the dependent variable and DMD (yes/no) as the independent variable, with and without adjustment for age (continuous) at visit. The cut-off for statistical significance for the age-adjusted odds ratio (OR) was set at 0.01 in consideration of multiple comparisons. The Haldane–Anscombe correction was applied when the proportion achieving a milestone was 100% (with zero failures). χ^2 tests were performed to examine differences in achieving a milestone between young males with DMD as yet to be diagnosed versus young males already diagnosed at the time of the visit. The positive predictive values for several milestones were calculated using the failure rates in the DMD (sensitivity) and control groups (1-specificity), and a DMD prevalence rate of 1 in 5000.

All analyses were conducted in R v3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS v25 (IBM Corp., Armonk, NY, USA).

Ethical consent

The study research protocol (registration no. 2017-001) was submitted to the Netherlands Organisation for Applied Scientific Research TNO institutional review board. The board approved the non-interventional research proposal. In its deliberations, the board considered the research design and privacy aspects, as well as the ethical aspects and the burden and risks to the research participants. Written informed consent was obtained from parents and/or children with DMD who agreed to participate in the study.

RESULTS

In total, 229 young males with DMD and/or their parents (depending on the age of the child) who met the inclusion criteria were invited to participate; 87 gave permission for the retrieval of their health records. Retrieval was unsuccessful in 10 cases: data were missing or not available for nine and one young male did not survive during the retrieval of his records. In total, the health records of 76 young males with DMD were obtained (Fig. S1, online supporting information). In addition, 71 parents of young males with DMD fully or partly completed the questionnaire. Data from the questionnaire and information from health records were available for 43 young males with DMD. The epidemiological and disease characteristics of young males with DMD and control group are summarized in Table 1. The proportions of young males with DMD (cases) and young males without DMD (control group) who failed the developmental milestones at each age are shown in Table S1. In total, 60 developmental milestones

Table 1: General characteristics of young males with Duchenne muscular dystrophy (DMD) and young males in the control group

	DMD (*n*=76)			Control group (*n*=12 414)	
Characteristics	*n*	Mean (SD)	%	*n*	Mean (SD)
Gestational age (wks)	70	39.1 (2.2)	–	11 509	38.9 (1.9)
Birthweight (g)	69	3400 (760)	–	11 550	3399 (582)
Age at diagnosis (y)					
Entire study cohort	76	4.0 (2.0)	–	–	–
Young males without a family history of DMD	68	4.3 (1.9)	–	–	–
Young males with a known family history of DMD	6	1.5 (1.2)	–	–	–
Young males with a family history of another neuromuscular disease	2	1.4 (1.3)	–	–	–
Type of diagnosis					
Deletion in *DMD* gene	25	–	63	–	–
Insertion in *DMD* gene	8	–	20	–	–
Small or other mutation	7	–	18	–	–

Table 2: Proportion of young males with Duchenne muscular dystrophy (DMD) and young males in the control group who failed to attain developmental milestones at specific ages

		All young males with DMD (*n*=76)			Young males with DMD before diagnosis		Control group (*n*=12 414)			Young males with DMD (all vs control group)	
Age[a] (mo)	Milestones[b]	Age at visit (mo), mean (SD)	Fail (*n*)	Fail%	Fail (*n*)	Fail%	Age at visit (mo), mean (SD)	Fail (*n*)	Fail%	OR[c] (95% CI)	Age-adjusted OR[c] (95% CI)
2	Smiles in response (C)	2.2 (0.6)	4/63	6	4/62	6	2.2 (0.5)	146/8859	1.6	4.0 (1.5–11.3)[d]	4.0 (1.2–9.8)[d]
2	Follows with eyes and head 30° <0° 30° (F)	2.3 (0.6)	13/63	21	12/62	19	2.2 (0.5)	860/8533	10.1	2.3 (1.3–4.3)[d]	2.4 (1.3–4.4)[d]
3	Lifts head to 45° in prone position (G)	3.1 (0.4)	14/63	22	14/62	23	3.2 (0.5)	944/9069	10.4	2.5 (1.4–4.5)[d]	2.3 (1.2–4.1)[d]
9	Rolls over back and forth (G)	9.1 (0.7)	5/57	9	5/55	9	8.7 (0.8)	250/8893	2.8	3.3 (1.3–8.4)[d]	3.5 (1.2–8.1)[d]
9	Plays with both feet (F)	9.2 (0.7)	3/54	6	3/53	6	8.8 (0.9)	84/7384	1.1	5.1 (1.6–16.7)[d]	6.3 (1.5–17.8)[d]
9	Balances head well while sitting (G)	9.1 (0.6)	4/58	7	4/55	7	8.7 (0.8)	99/8891	1.1	6.6 (2.3–18.5)[e]	7.9 (2.3–19.9)[e]
9	Sits on buttocks while legs stretched (G)	9.2 (0.7)	8/54	15	8/51	16	8.8 (0.8)	488/8454	5.8	2.8 (1.3–6)[d]	3.4 (1.5–6.9)[d]
12	Crawls forward on abdomen on the floor (G)	11.4 (0.6)	22/55	40	22/53	42	11.3 (0.6)	487/7112	6.8	9.1 (5.2–15.7)[e]	10.3 (5.8–17.8)[e]
12	Pulls up to standing position (G)	11.4 (0.6)	35/51	69	34/49	69	11.3 (0.5)	753/8645	8.7	22.9 (12.6–41.6)[e]	26.2 (14.5–49.3)[e]
12	Waves 'bye bye'(C)	11.5 (0.7)	17/50	34	17/49	35	11.2 (0.4)	924/8154	11.3	4.0 (2.2–7.3)[e]	4.7 (2.5–8.4)[e]
12	Picks up pellet between thumb and index finger (F)	11.4 (0.6)	9/49	18	9/48	19	11.2 (0.4)	613/7772	7.9	2.6 (1.3–5.4)[d]	2.8 (1.3–5.5)[d]
12	Sits in stable position without support (G)	11.4 (0.7)	21/57	37	20/54	37	11.3 (0.6)	248/8193	3.0	18.7 (10.8–32.5)[e]	20.1 (11.3–35)[e]
12	Reacts to a verbal request (C)	11.5 (0.5)	7/41	17	7/40	18	11.2 (0.4)	176/7990	2.2	9.1 (4–20.9)[e]	9.7 (3.9–21)[e]
15	Crawls, abdomen off the floor (G)	14.6 (0.6)	28/55	51	27/53	51	14.2 (0.5)	237/7840	3.0	33.3 (19.3–57.3)[e]	35.7 (20.5–62.6)[e]
15	Walks along/cruises (G)	14.5 (0.5)	23/57	40	22/55	40	14.2 (0.5)	290/7638	3.8	17.1 (10–29.5)[e]	18.6 (10.6–32.1)[e]
18	Says three 'words' (C)	18.9 (1.5)	13/43	30	13/41	32	18.3 (0.8)	975/8107	12.0	3.2 (1.6–6.1)[e]	3.7 (1.8–7)[e]
18	Walks alone (G)	18.5 (1.6)	28/52	54	27/50	54	18.3 (0.9)	378/8137	4.6	23.9 (13.7–41.7)[e]	27.5 (15.5–49.3)[e]
24	Walks well alone (G)	24.5 (1.5)	22/64	34	19/59	32	24.8 (1.3)	54/8112	0.7	78.2 (43.7–139.8)[e]	75.3 (41.5–134.3)[e]
24	Imitates others (F)	24.9 (1.2)	3/52	6	3/48	6	24.9 (1.1)	74/7838	0.9	6.4 (2–21.1)[d]	6.4 (1.5–18)[d]
24	Says 'sentences' of two words (C)	24.7 (1.4)	23/57	40	19/51	37	24.9 (1.2)	1664/8357	19.9	2.7 (1.6–4.6)[e]	2.6 (1.5–4.5)[e]
24	Squats or bends to pick up things (G)	24.9 (1.3)	13/56	23	10/49	20	24.9 (1.2)	179/7810	2.3	12.9 (6.8–24.4)[e]	12.9 (6.6–23.7)[e]
36	Says 'sentences' of three or more words (C)	36.7 (1.2)	9/57	16	6/41	15	36.9 (1.0)	483/7615	6.3	2.8 (1.4–5.7)[d]	2.6 (1.2–5.1)[d]
36	Speech is understood by acquaintances (C)	36.7 (1.1)	9/50	18	5/34	15	37.0 (1.0)	449/7372	6.1	3.4 (1.6–7)[d]	3.3 (1.5–6.5)[d]
36	Rides (tri)cycle (G)	36.6 (1.2)	35/49	71	24/34	71	37.0 (1.0)	990/5893	16.8	12.4 (6.6–23.1)[e]	11.8 (6.4–22.8)[e]
36	Imitates drawing a vertical line (F)	36.7 (1.2)	16/48	33	13/35	37	37.0 (1.0)	596/6409	9.3	4.9 (2.7–8.9)[e]	4.7 (2.5–8.5)[e]
36	Walks smoothly (G)	36.4 (1.3)	17/57	30	9/43	21[f]	36.9 (1.0)	6/7217	0.1	511 (192–1363)[e]	532 (205–1568)[e]
48	Copies a circle (F)	46.4 (1.5)	13/42	31	4/20	20[g]	47.6 (1.5)	507/5987	8.5	4.8 (2.5–9.4)[e]	3.9 (1.9–7.5)[e]

Table 2. Continued

Age[a] (mo)	Milestones[b]	All young males with DMD (n=76)			Young males with DMD before diagnosis		Control group (n=12 414)			Young males with DMD (all vs control group)	
		Age at visit (mo), mean (SD)	Fail (n)	Fail%	Fail (n)	Fail%	Age at visit (mo), mean (SD)	Fail (n)	Fail%	OR[c] (95% CI)	Age-adjusted OR[c] (95% CI)
48	Speech is easily understood by examiner (C)	46.5 (1.5)	13/44	30	6/21	29	47.6 (1.5)	713/5605	12.7	2.9 (1.5–5.5)[d]	2.5 (1.3–4.7)[d]

[a]Age in months (mo) at scheduled visits. [b]Developmental domains: C, communication; F, fine motor activity, adaptive behaviour, and personal/social behaviour; G, gross motor activity. [c]Results are based on logistic regression analyses with milestone attainment (yes/no) as the dependent variable and DMD (yes/no) as the independent variable, without (OR) and with adjustment (adjusted OR) for age at visit. [d]p<0.01. [e]p<0.001. [f]Statistically significant difference of passing this milestone between young males without a diagnosis of DMD (9/43, 21%) vs young males with a diagnosis of DMD (8/14, 57%) (p=0.02). [g]No statistically significant difference, but a clinically relevant difference. OR, odds ratio; CI, confidence interval.

were available. The mean number of available milestones was 43 (standard deviation [SD]=13, range: 1–59) in the DMD group and 40 (SD=15, range: 1–60) in the control group.

Table 2 shows the developmental milestones with statistically significant, age-adjusted ORs. The presence of developmental delay in the group of young males with DMD was evident shortly after birth, with a higher proportion failing to attain milestones of gross and fine motor activity, adaptive behaviour, personal/social behaviour, and communication at 2 to 3 months of age (range age-adjusted ORs=2.3–4.0, p<0.01). Between 12 and 36 months of age, differences in the attainment of milestones concerning gross motor activity increased with age between the DMD and control groups (range age-adjusted ORs=10.3–532, p<0.001). We also found differences in milestone attainment concerning fine motor activity, adaptive behaviour, personal/social behaviour, and communication between 12 and 48 months of age (range age-adjusted ORs=2.5–9.7, p<0.01).

Except for 'walks smoothly' at 36 months and 'copies a circle' at 48 months, the proportion failing to attain a developmental milestone was comparable between the entire cohort of young males with DMD and young males with DMD who had not been diagnosed at that visit.

Several individual DDI milestones were strongly associated with an increased risk for DMD. Not being able to walk well at 24 months predicted an increased risk for DMD from 1 in 5000 to approximately 1 in 100 young males (positive predictive value=0.01); not being able to walk smoothly at 36 months was related to an increased risk of approximately 1 in 16 young males (positive predictive value=0.06). If diagnostic investigation takes place in males who are not able to walk well at 24 months of age, age at diagnosis could be reduced in 86% of cases, with detection occurring 21 months earlier on average. Similarly, diagnostic investigation in males who are not able to walk smoothly at 36 months could reduce the age at diagnosis in 59% of cases, with detection occurring 12 months earlier on average.

DISCUSSION

Our study showed a delay in all domains of child development in young males with DMD aged 2 to 48 months, with developmental delay already evident a few months after birth and delay in gross motor activity strongly increasing with age.

DMD affects all domains of child development

While earlier studies mainly focused on gross motor activity and communication,[3–7] our study also showed a developmental delay in fine motor activity, adaptive behaviour, and personal/social behaviour.

Our findings on gross motor activity and communication are consistent with previous reports in preschool-aged males with DMD, that is, high failure rates (35–89%) for motor activity and communication milestones,[3] gross

motor delay in 39% to 58%,[5] a delay in walking in 42%,[7] late attainment in sitting, crawling, standing, walking, speaking their first word, and constructing sentences,[4] and lower gross motor and language scores on the Bayley Scales of Infant and Toddler Development, Third Edition.[6]

Developmental delay is evident at a young age

Developmental delay was evident at 2 to 3 months after birth in all domains of child development. Between 2 and 12 months of age, 13 DDI milestones showed differences between young males with DMD and the control group. A previous study investigated 'sitting alone' in the first year of life in young males with DMD (n=18) and found that 72% were late (defined as >7.6mo).[3] To our knowledge, no other study investigated developmental milestones in DMD in the first months of life while youth health care professionals were mainly unaware of (blinded for) the diagnosis. Our results could be useful in research on early development measures to test therapies in infants and toddlers with DMD.

Gross motor activity delay increases with age

As children age and master more complex and demanding skills, the developmental gap between children with and without DMD is more apparent. As expected, we found that milestones related to gross motor activity at an older age (crawls, abdomen off the floor; walks along/cruises at 15mo; walks alone at 18mo; walks well alone at 24mo; and walks smoothly at 36mo) showed stronger associations with DMD than milestones related to gross motor activity at a younger age. This was consistent with previous reports of high proportions of young males with DMD having a delay in gross motor activity.[3–7]

Study strengths and limitations

A strength of our study is that milestones were determined during real-world, regular, day-to-day health assessments. This increases the generalizability of our results to support the use of milestones in daily practice for the early detection of DMD. Our sample comprised 76 young males with DMD, which is a high number considering the low prevalence, and we also used a control group. We used a case–control design because it is more efficient and less costly; a cohort study would have necessitated follow-up of at least 380 000 young males for several years to include a similar number of cases. Another strength of our study is that the data on milestones were mainly collected before the outcome (DMD, no DMD) was known. In other words, youth health care professionals were mainly unaware of (blinded for) the diagnosis because most data were registered before DMD was diagnosed.

A limitation is that the number of observations varied between milestones and visits. Although youth health care in the Netherlands is highly standardized, with attendance of almost 95%,[26] parents do not always attend all 13 visits when their child is 1 to 48 months of age. Also, youth health care professionals do not always register all milestones during a visit; this is partly attributable to time pressures in clinical practice. However, approximately the same attendance rates and method of registering occurred for both DMD and control groups; therefore, we do not expect a bias due to missing data. Another limitation is that we did not study the inter- and intrarater reliability of the DDI. Although the DDI has a uniform protocol, there is a chance that professionals also include other child and parental factors, such as (subjective) information from the parent, in their final assessment. The experience and knowledge of the professional may play a role in this. This should be investigated further.

Clinical implications

In our study, the average age at diagnosis in the entire cohort of young males with DMD was 4 years; the average age at diagnosis in young males without a family history of DMD was 4 years 4 months. This is consistent with reported national and international averages.[5,6,17] A potential method of achieving an earlier diagnosis of DMD, in most cases before the age of 4 years, would be to identify young males at increased risk based on their developmental milestones, to investigate further DMD-related signs and symptoms, followed by creatine kinase testing. Creatine kinase is extremely elevated in young males with DMD and testing has been used successfully in newborn screening programmes (as first-tier testing).[18] An advantage of our proposed approach is a lower rate of false positive results compared to newborn screening because the prevalence of DMD in the tested group would be higher. It also avoids the potential confounding factor of elevated creatine kinase levels in neonates due to birth trauma.[19] Delays in several milestones concerning motor activity, communication, and global development has been suggested to justify creatine kinase testing.[27] Based on our results, the individual milestones 'walks well alone at 24 months' and 'walks smoothly at 36 months' were most promising in detecting young males with DMD. One should keep in mind that this approach may detect children who have other neuromuscular diseases. When targeting other neuromuscular diseases or disorders that present with delayed development, children with such disorders should be excluded from the analysis; a lower proportion of children failing to attain developmental milestones is then expected in the control group.

Our study is a first step towards validating the detection of DMD based on developmental delay. Our hypothesis is that a short risk assessment instrument[28] based on the milestones that showed a delay in attainment in this study, together with an examination of other DMD-specific symptoms (such as pseudohypertrophy), medical history, received therapies, and parents' and health care professionals' opinions and concerns about the developmental delay may contribute to the early detection of DMD in young males.

Further research is needed to investigate the impact of failure on combinations of milestones on predictive validity and develop a short risk assessment instrument for DMD. The number of indicators considered sufficient for further testing will depend on the desired sensitivity and specificity, impact on age at diagnosis, and the costs of a screening programme.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Proportion of young males who failed to attain developmental milestones at specific ages

Figure S1: Flow chart showing how information was retrieved from the records of youth health care services and the questionnaire completed by young males with DMD and/or their parents.

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HITOS DEL DESARROLLO TEMPRANO EN LA DISTROFIA MUSCULAR DE DUCHENNE

OBJETIVO

Investigar las diferencias en el logro de los hitos del desarrollo entre los varones jóvenes con distrofia muscular de Duchenne (DMD) y los varones jóvenes de la población general.

MÉTODO

Como parte del estudio 4D-DMD de casos y controles (Detección por retraso del desarrollo en niños holandeses con distrofia muscular de Duchenne), se extrajeron datos de las historias clínicas sobre los hitos del desarrollo de 76 varones jóvenes con DMD y 12.414 varones jóvenes de un grupo control. Obtenidos de registros de atención de los servicios de atención médica para jóvenes. Las características de DMD se adquirieron de cuestionarios completados por los padres. Los análisis de regresión logística se realizaron con el logro de hitos (sí / no) como la variable dependiente y DMD (sí / no) como la variable independiente, con y sin ajuste por edad en la visita.

RESULTADOS

El número medio de hitos disponibles fue 43 (desviación estándar [DE] = 13, rango: 1–59) en el grupo DMD y 40 (DE = 15, rango: 1–60) en el grupo control. La presencia de retraso en el desarrollo fue evidente a los 2 o 3 meses de edad, con una mayor proporción de varones jóvenes con DMD que no lograron hitos de actividad motora gruesa / fina, comportamiento adaptativo, comportamiento personal / social y comunicación (rango ajustado por edad odds ratios [OR] = 2,3–4,0, p <0,01). Entre los 12 y 36 meses de edad, las diferencias en el logro de los hitos del desarrollo con respecto a la actividad motora gruesa aumentaron con la edad (OR ajustados por edad de rango = 10,3–532, p <0,001). También encontramos diferencias en los hitos del desarrollo con respecto a la actividad motora fina, el comportamiento adaptativo, el comportamiento personal / social y la comunicación entre los 12 y 48 meses de edad (OR ajustados por edad de rango = 2,5–9,7, p <0,01).

INTERPRETACIÓN

Encontramos retrasos en el logro de hitos motores y no motores en varones jóvenes con DMD en comparación con el grupo control. Estos retrasos ya eran evidentes unos meses después del nacimiento. Los hitos del desarrollo que muestran un retraso en el logro tienen el potencial de ayudar al diagnóstico temprano de DMD.

MARCOS PRECOCES DO DESENVOLVIMENTO EM DISTROFIA MUSCULAR DE DUCHENNE

OBJETIVO

Investigar as diferenças na obtenção dos marcos do desenvolvimento entre jovens meninos com distrofia muscular de Duchenne (DMD) e meninos da população em geral.

MÉTODO

Como parte do estudo de caso-controle 4D-DMD (Detecção por Atraso no Desenvolvimento em meninos holandeses com Distrofia Muscular de Duchenne), dados sobre marcos do desenvolvimento para 76 jovens meninos com DMD e 12.414 jovens de um grupo controle foram extraídos de registros de saúde de serviços de cuidados em saúde para jovens. As características de DMD foram adquiridas de questionários completados pelos pais. Análises de regressão logística foram realizadas com obtenção de marcos (sim/não) como variável dependente e DMD (sim/não) como variável dependente, com e sem ajuste para a idade no momento da visita.

RESULTADOS

O número médio de marcos disponíveis foi 43 (desvio padrão [DP]=13, variação: 1–59) no grupo DMD e 40 (DP=15, variação: 1–60) no grupo controle. A presença de atraso do desenvolvimento foi evidente aos 2 a 3 meses de idade, com maior proporção de jovens meninos com DMD falhando em obter marcos de atividade motora grossa/fina, comportamento adaptativo, comportamento pessoal/social e comunicação (variação das taxas de risco [TR] ajustada para idade =2,3–4.0, p<0,01). Entre 12 e 36 meses de idade, diferenças na obtenção de marcos do desenvolvimento com relação a atividade motora grossa aumentou com a idade (variação TR ajustada para idade =10,3–532, p<0,001). Também encontramos diferença nos marcos do desenvolvimento quanto a atividade motora fina, comportamento adaptativo, comportamento pessoal/social, e comunicação entre 12 e 48 meses de idade (variação TR ajustada para idade =2,5–9,7, p<0,01).

INTERPRETAÇÃO

Encontramos atrasos na obtenção de marcos motores e não motores em meninos com DMD comparados ao grupo controle. Tais atrasos já foram evidentes poucos meses após o nascimento. Marcos do desenvolvimento que mostram atraso na obtenção tem potencial para auxiliar o diagnóstico mais precoce da DMD.