Time to diagnosis of Duchenne muscular dystrophy remains unchanged: Findings from the Muscular Dystrophy Surveillance, Tracking, and Research Network, 2000–2015

Shiny Thomas, MBBS, MPH[1], **Kristin M. Conway, PhD**[2], **Olushola Fapo, MPH**[1], **Natalie Street, MS**[3], **Katherine D. Mathews, MD**[4], **Joshua R. Mann, MD, MPH**[5], **Paul A. Romitti, PhD**[2], **Aida Soim, MD, PhD**[1], **Christina Westfield, BSN, MS**[1], **Deborah J. Fox, MPH**[1], **Emma Ciafaloni, MD**[6] **Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*)**

[1]New York State Department of Health, Albany, New York, USA

[2]Department of Epidemiology, University of Iowa, College of Public Health, Iowa City, Iowa, USA

[3]Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities, Atlanta, Georgia, USA

[4]Stead Family Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA

[5]University of Mississippi Medical Center, Jackson, Mississippi, USA

[6]Department of Neurology, University of Rochester, Rochester, New York, USA

Abstract

Introduction/Aims: With current and anticipated disease-modifying treatments, including gene therapy, an early diagnosis for Duchenne muscular dystrophy (DMD) is crucial to assure maximum benefit. In 2009, a study from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*) showed an average diagnosis age of 5 years among males with

DMD born from January 1, 1982 to December 31, 2000. Initiatives were implemented by the US Centers for Disease Control and Prevention (CDC) and patient organizations to reduce time to diagnosis. We conducted a follow-up study in a surveillance cohort born after January 1, 2000 to determine whether there has been an improvement in time to diagnosis.

Methods: We assessed the age of diagnosis among males with DMD born from January 1, 2000 to December 31, 2015 using data collected by six US MD STAR*net* surveillance sites (Colorado, Iowa, western New York State, the Piedmont region of North Carolina, South Carolina, and Utah). The analytic cohort included 221 males with definite or probable DMD diagnosis without a documented family history. We computed frequency count and percentage for categorical variables, and mean, median, and standard deviation (SD) for continuous variables.

Results: The mean [median] ages in years of diagnostic milestones were: first signs, 2.7 [2.0]; first creatine kinase (CK), 4.6 [4.6]; DNA/muscle biopsy testing, 4.9 [4.8]; and time from first signs to diagnostic confirmation, 2.2 [1.4].

Discussion: The time interval between first signs of DMD and diagnosis remains unchanged at 2.2 years. This results in lost opportunities for timely genetic counseling, implementation of standards of care, initiation of glucocorticoids, and participation in clinical trials.

INTRODUCTION

Studies of individuals with Duchenne muscular dystrophy (DMD) have shown an average age at diagnosis of approximately 5 years, which has not changed over time.[1–4] Creatine kinase (CK) level is almost always elevated in patients with DMD and is therefore a useful, although underutilized, screening test in patients suspected of having DMD.

Achieving an early diagnosis is important. Implementation of established care guidelines for patients with DMD that focus on proactive monitoring of disease progression and the use of corticosteroids have proven critical in guiding clinicians to establish a standard of treatment.[5–7] New disease-modifying treatments, such as exon-skipping drugs, have recently been approved, and promising gene replacement therapies are under development.[8–12] As a result, there is continued interest from clinical and patient communities to diagnose DMD as early in life as possible.

Using data from four sites of the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*), we found an interval of 2.5 years between recognition of the first signs and symptoms of DMD and a confirmatory diagnosis (mean age, 4.9 years) among individuals born from January 1, 1982 through December 12, 2000.[1] This finding represented a lack of change from the previous two decades.[2,3] We conducted a follow-up study using a surveillance cohort born after January 1, 2000 to determine whether there has been an improvement in time to diagnosis.

METHODS

Individuals with DMD were identified through the MD STAR*net*; methods for surveillance activities have been described previously.[13] Briefly, MD STAR*net* is a population-based surveillance system for childhood-onset dystrophinopathy among individuals born between January 1, 2000 and December 31, 2015 and residing in one of six sites (Colorado [CO], Iowa [IA], 21 counties in western New York State [wNY], 33 counties in the Piedmont region of North Carolina [NC], South Carolina [SC], and Utah/Nevada [UT]).

Trained personnel identified cases and obtained data from medical records (ie, neuromuscular clinics, physical medicine and rehabilitation clinics, hospitals, outpatient clinics) and administrative sources (ie, birth defects registries, birth and death certificates, state hospital discharge databases). A clinical review committee reviewed and classified each of the cases using published case classification definitions (definite, probable, possible, asymptomatic, female).[14] All sites obtained institutional review board approval or exemption. Most sites (CO, IA, NC, wNY, SC) also had public health authority to conduct surveillance for muscular dystrophy (MD).

Figure S1 shows the analytic cohort with study inclusion and exclusion criteria. Individuals from Nevada were excluded due to incomplete data on early diagnostic milestones. The final analytic cohort included 221 individuals with DMD.

We computed frequency count and percentage for categorical variables, and mean, median (Md), and standard deviation (SD) for continuous variables. Due to violations of variance homogeneity across race/ethnicity, the Kruskal-Wallis test was used to determine overall significance, and the Dwass-Steel-Critchlow-Fligner method was used to evaluate all pairwise comparisons. For analysis of mean changes by year of birth, analysis of variance with planned comparisons (2000 vs each subsequent year through 2005) was used. Data analysis was performed using SAS version 9.4 software (SAS Institute).

RESULTS

Family/primary caregivers were most commonly the first to note concerns, followed by the child's primary care provider. Initial medical evaluation was performed most frequently by a primary care provider, followed by a neurologist or neuromuscular specialist (Table 1). For the total sample, the mean age at first signs and symptoms reported by the caregiver was 2.7 (SD = 1.8, Md = 2.0) years, followed by first CK at 4.6 (SD = 2.3, Md = 4.6) years and DNA/muscle biopsy confirmatory testing at 4.9 (SD = 2.3, Md = 4.8) years. The average time from first symptoms to diagnostic confirmation was 2.2 (SD = 2.5, Md = 1.4) years. The ages at first concern, and subsequent CK testing and initial visit to a neurology or neuromuscular specialist, were significantly later among non-Hispanic black individuals compared with non-Hispanic white individuals (Figure 1). In addition, the age at CK testing was significantly later among Hispanics compared with non-Hispanic whites. No other differences in ages by race/ethnicity were found. Additional details are available in Table S1.

The diagnosis was genetically confirmed by DNA testing in 96.4% of all individuals, whereas muscle biopsy was performed in only a small number (n = 27). Definitive diagnosis (DNA testing or muscular biopsy) occurred at earlier mean ages for non-Hispanic whites and showed statistically significant later ages among Hispanics and non-Hispanic blacks compared with non-Hispanic whites (Table S1).

Of the individuals in the final analytic cohort, 39 were diagnosed incidentally after CK testing ordered for other medical reasons revealed elevated CK. The time to definitive diagnosis was 2.6 (SD = 2.4, Md = 1.9) years among those not diagnosed due to an incidental CK test result, whereas this interval was 0.5 (SD = 2.1, Md = 0.9) year in those suspected of muscular dystrophy due to incidental CK testing.

We found no significant differences over time in mean ages for diagnostic milestones, including time from earliest symptom to confirmatory testing, for males born from 2000 to 2005 (Figure S2 A–F).

DISCUSSION

In this study we have demonstrated a persistent 2.2-year time interval between first signs and symptoms of DMD and diagnostic confirmation and an average age of 4.9 years at diagnosis among males without a family history of DMD in selected geographical regions in the United States. This interval between symptom onset and diagnosis has not changed in the past three decades[1–4] and is persistently later in minority groups, as reported elsewhere.[15]

Our study also showed that nearly all patients born and diagnosed after January 1, 2000 were genetically confirmed. Knowing a patient's specific genetic mutation is very important because there are now four US Food and Drug Administration (FDA)-approved exon-skipping drugs that are indicated for specific subgroups of DMD patients with mutations amenable to exon 45, 51, or 53 skipping. Precise genetic confirmation is also a requirement for participation in the ongoing gene therapy and mutation-specific treatment clinical trials.

With partial support from the CDC, a National Task Force for Early Identification of Childhood Neuromuscular Disorders was convened. This group was comprised of representatives from a range of professional organizations involved in the care of children and from several pediatric neuromuscular disease advocacy groups. The task force developed a tool to assist health-care providers in early identification and evaluation of children with motor delay with the goal of decreasing the age at pediatric neuromuscular disease diagnosis, including DMD.[16] This resource includes a modified algorithm emphasizing early CK testing in children with motor delays. In addition, the American Academy of Pediatrics published a complementary algorithm for the surveillance and screening of children for motor delays for pediatric care providers[17] and developed a website, Physical Developmental Delay: What to Look For, to provide a resource for parents who may be worried about the motor development of their child.[18]

Although such ongoing educational efforts may improve early recognition of DMD, newborn screening (NBS) for DMD could ensure early diagnosis and help to mitigate racial disparities that currently exist. The unchanged time interval to diagnosis, recent

FDA approval of four exon-skipping drugs, and preliminary results of successful gene transfer in children with DMD age 4 to 7 years have underscored the potential value of NBS for DMD.[8–10,19] Since 1976, 10 DMD NBS programs have screened more than 1.8 million newborns[20] and current programs are underway in New York, North Carolina, and Boston.[21,22] Many ethical, legal, and social issues have been identified and are important to consider in the design of DMD NBS programs before widespread implementation including: (1) whether both males and females should be screened for an X-linked disorder; (2) genetic treatment availability for a subset of the DMD population; and (3) identification and follow-up of newborns with other conditions in which CK is elevated.[20,23,24]

The time to diagnosis of DMD among males without family history remains unchanged and results in lost opportunities for timely genetic counseling, implementation of standards of care, access to newly approved disease-modifying medications, and participation in clinical trials. Educating pediatric providers to identify children with DMD and other conditions causing muscle weakness or motor delay has been one approach to reducing the time to diagnosis. More studies can inform whether early treatment improves the outcomes of children with DMD and whether newborn screening is a feasible approach to achieving early and equitable diagnosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

DATA AVAILABILITY STATEMENT

Due to privacy concerns (detailed personal information was obtained from a small number of individuals living in a defined surveillance area), data from the MD STARnet is not publicly available. Data used for this analysis are maintained at the Centers for Disease Control and Prevention. Researchers interested in MD STARnet should contact MD STARnet at MDSTARnet@CDC.gov.

Abbreviations:

CDC	US Centers for Disease Control and Prevention
CK	creatine kinase

DMD	Duchenne muscular dystrophy
FDA	US Food and Drug Administration
MD	muscular dystrophy
Md	median
MD STAR*net*	Muscular Dystrophy Surveillance, Tracking, and Research Network
NBS	newborn screening

REFERENCES

1. Ciafaloni E, Fox DJ, Pandya S, et al. Delayed diagnosis in Duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatr. 2009;155:380–385. [PubMed: 19394035]

2. Bushby KM, Hill A, Steele JG. Failure of early diagnosis in symptomatic Duchenne muscular dystrophy. Lancet. 1999;353:557–558. [PubMed: 10028989]

3. Mohamed K, Appleton R, Nicolaides P. Delayed diagnosis of Duchenne muscular dystrophy. Eur J Paediatr Neurol. 2000;4:219–223. [PubMed: 11030068]

4. van Ruiten HJ, Straub V, Bushby K, et al. Improving recognition of Duchenne muscular dystrophy: a retrospective case note review. Arch Dis Child. 2014;99:1074–1077. [PubMed: 25187493]

5. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018;17:251–267. [PubMed: 29395989]

6. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018;17:347–361. [PubMed: 29395990]

7. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet Neurol. 2018;17:445–455. [PubMed: 29398641]

8. Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. Neurology. 2020;94:e2270–e2282. [PubMed: 32139505]

9. Clemens PR, Rao VK, Connolly AM, et al. Safety, tolerability, and efficacy of Viltolarsen in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: a phase 2 randomized clinical trial. JAMA Neurol. 2020;77:982–991. [PubMed: 32453377]

10. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. Ann Neurol. 2016;79:257–271. [PubMed: 26573217]

11. Ho PP, Lahey LJ, Mourkioti F, et al. Engineered DNA plasmid reduces immunity to dystrophin while improving muscle force in a model of gene therapy of Duchenne dystrophy. Proc Natl Acad Sci USA. 2018;115:E9182–E9191. [PubMed: 30181272]

12. Mendell JR, Sahenk Z, Lehman K, et al. Assessment of systemic delivery of rAAVrh74.MHCK7. Micro-dystrophin in children with Duchenne muscular dystrophy: a nonrandomized controlled trial. JAMA Neurol. 2020;77:1122–1131. [PubMed: 32539076]

13. lMiller LA, Romitti PA, Cunniff C, et al. The muscular dystrophy surveillance tracking and research network (MD STARnet): surveillance methodology. Birth Defects Res A Clin Mol Teratol. 2006;76:793–797. [PubMed: 17036307]

14. Mathews KD, Cunniff C, Kantamneni JR, et al. Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet): case definition in surveillance for childhood-onset Duchenne/Becker muscular dystrophy. J Child Neurol. 2010;25:1098–1102. [PubMed: 20817884]

15. Holtzer C, Meaney FJ, Andrews J, et al. Disparities in the diagnostic process of Duchenne and Becker muscular dystrophy. Genet Med. 2011;13:942–947. [PubMed: 21836521]

16. American Academy of Pediatrics. Does my child have physical developmental delays? Updated 2022. https://www.healthychildren.org/English/MotorDelay/Pages/default.aspx. Accessed January 21, 2022.

17. Noritz GH, Murphy NA. Motor delays: early identification and evaluation. Pediatrics. 2013;131:e2016–e2027. [PubMed: 23713113]

18. American Academy of Pediatrics. Does my child have physical developmental delays? Updated 2022. https://www.healthychildren.org/english/motordelay/pages/default.aspx. Accessed January 21, 2022.

19. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. N Engl J Med. 2017;377:1713–1722. [PubMed: 29091557]

20. Gatheridge MA, Kwon JM, Mendell JM, et al. Identifying non-Duchenne muscular dystrophy-positive and false negative results in prior Duchenne muscular dystrophy newborn screening programs: a review. JAMA Neurol. 2016;73:111–116. [PubMed: 26594870]

21. Al-Zaidy SA, Lloyd-Puryear M, Kennedy A, et al. A roadmap to newborn screening for Duchenne muscular dystrophy. Int J Neonatal Screen. 2017;3:8. [PubMed: 31588416]

22. Parad RB, Sheldon Y, Bhattacharjee A. Implementation of hospital-based supplemental Duchenne muscular dystrophy newborn screening (sDMDNBS): a pathway to broadening adoption. Int J Neonatal Screen. 2021;7:77. [PubMed: 34842620]

23. Lloyd-Puryear MA, Crawford TO, Brower A, et al. Duchenne muscular dystrophy newborn screening, a case study for examining ethical and legal issues for pilots for emerging disorders: considerations and recommendations. Int J Neonatal Screen. 2018;4:6. [PubMed: 33072932]

24. Ross LF, Clarke AJ. A historical and current review of newborn screening for neuromuscular disorders from around the world: lessons for the United States. Pediatr Neurol. 2017;77:12–22. [PubMed: 29079012]
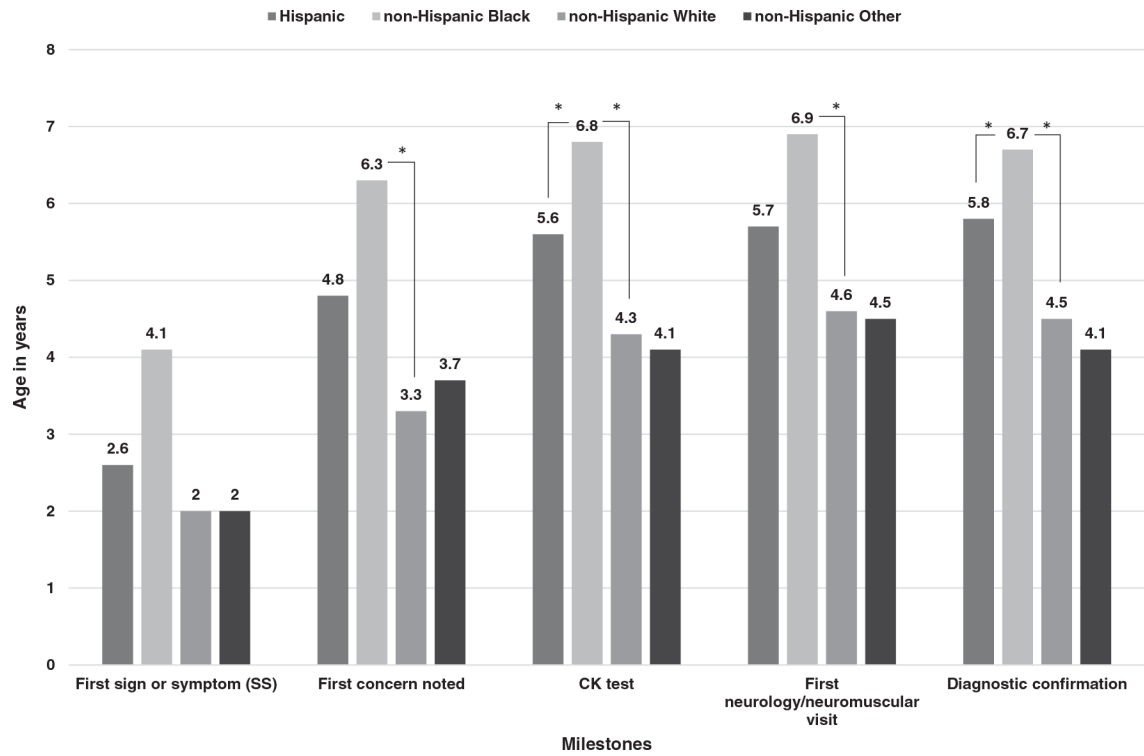
FIGURE 1.

Histogram of age in years at important clinical and diagnostic milestones by race/ethnicity among males with Duchenne muscular dystrophy in the Muscular Dystrophy Surveillance, Tracking and Research Network, 2000–2015. Statistically significant differences ($P < .05$) were determined by Dwass-Steel-Critchlow-Fligner method pairwise analysis and denoted by asterisk

TABLE 1

Demographic and characteristics of individuals with Duchenne muscular dystrophy in the Muscular Dystrophy Surveillance, Tracking, and Research Network, 2000–2015

Characteristics	n(%)
Total	221
Race/ethnicity	
Hispanic	37 (16.7)
Non-Hispanic black	15 (6.8)
Non-Hispanic white	150 (67.9)
Unknown	19 (8.6)
First concern noted by:	
Family or primary caregiver	117 (52.9)
Child's primary care provider	50 (22.6)
School (teacher, RN, PT, PE)	25 (11.3)
Therapist (PT, OP)	9 (4.1)
Other specialities[a]	5 (2.3)
Orthopedist/podiatrist	2 (0.1)
Unknown	13 (15.9)
First professional evaluating concerns	
Primary care provider[a]	93 (42.1)
Neurologist/neuromuscular specialist	32 (14.5)
First professional evaluating concerns	
Therapist (early intervention, PT, ST)	23 (10.4)
Orthopedist/podiatrist	23 (10.4)
Gastroenterology/hepatology	20 (9.0)
Developmental pediatrician/rehabilitation medicine	11 (5.0)
Other specialties[b]	11 (5.0)
Unknown	8 (3.6)

Abbreviations: OP, occupational therapy; PE, physical education; PT, physical therapist; RN, registered nurse; ST, speech therapy.

[a] Emergency physician, gastroenterologist, hospital physician, or hematologist/oncologist.

[b] Family practice, nurse practitioner, pediatrician, or unknown specialty.