Early Diagnosis and Intervention in DMD

Patient #3: DMD Delayed Diagnosis, Declined Steroid Treatment

9 y/o Male

Case contributor and commentary:
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Age 3

Symptoms:

- Family first noticed abnormal gait (toe walking, clumsiness, slower compared to his peers, lack of motor progression)
- The patient's pediatrician and the parents were aware of these symptoms. However, the pediatrician deferred to the parents' desire to "watch and wait" and hope that the symptoms would improve

Background:
No family history of neuromuscular disease

Age 3 to 7

Approximately 3-4 years of a "wait-and-see" approach.

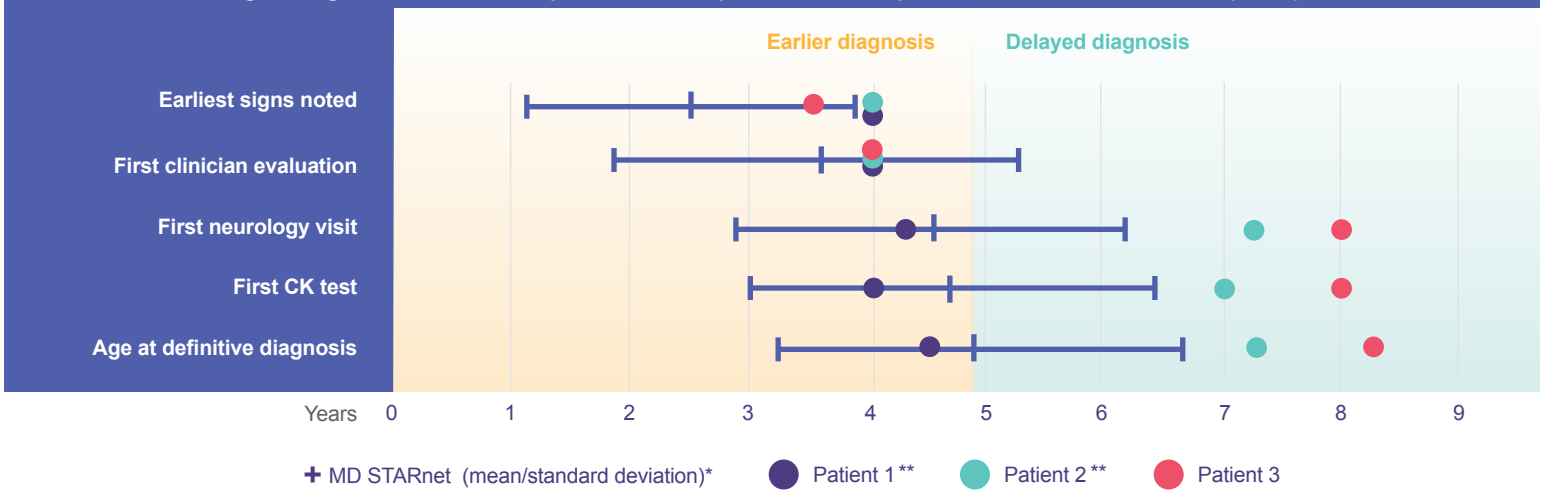
Age 7

Delay in Specialist Referral:
When the patient was approximately 6-7 years old, the parents became increasingly alarmed at worsening symptoms, which had progressed to waddling when walking, difficulty getting up from the floor, and difficulty climbing stairs.

At this point, the pediatrician requested a neurology consult. Logistical barriers (long distance between patient's home and neurology clinic, and the need to accommodate parents' schedule) resulted in an additional 8-month delay in scheduling the initial neurology consultation.

Commentary: *A simple test of checking **creatinine kinase** (CK) levels routinely in boys with gross motor or speech delays can **avoid unnecessary referrals and testing** as boys with DMD typically have significantly elevated CK levels. Boys with DMD can have features suggestive of autism spectrum disorder, so neurobehavioral symptoms should also trigger CK testing.*

Age at diagnostic milestones for patients 1-3: comparison with DMD patients in MD STARnet database (n=156)* [1]



*Analysis of patients with no known family history of DMD SD: standard deviation.
**Case Studies pertaining to Patients 1 and 2 can be found here: http://tiny.cc/MDAProfMedEd.

Age 8

Neurology Workup:
Neurologist promptly ordered CK testing.

- CK was 14,000

Genetic testing showed deletion of exons 8-27

Treatment:
Steroid treatment was promptly recommended but family refused steroid treatment initially and at all subsequent visits.

Except for refusing steroid treatment, patient/family were compliant with follow-up care and other treatment recommendations and continued to receive multidisciplinary care, including PT and OT.

Reasons for not initiating corticosteroids therapy (Duchenne Registry) [2]	
Worried about side effects	25.4%
Doctor never prescribed/recommended	22.8%
Other (starting soon, too young most common)	17.5%
Worried about not getting enough benefits	6.1%
Does not like the use of long-term medicine	0.9%
Age 3 or younger	27.2%

MDA Muscular Dystrophy Association

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Age 9

Ambulation Status:
- Patient is able to walk independently.
- Gradual worsening of proximal weakness and ambulation
- Supine to stand time is gradually increasing (18 seconds at age 8.5; 25 seconds at age 9)
- Ability to walk independently has decreased (3 miles per day at age 8 to 1.5 miles per day at age 9)
- Patient uses a wheelchair for long distances

Cardiovascular/Respiratory:
- No cardiac or respiratory complications thus far
- Losartan prophylaxis initiated at age 9 per treatment guidelines

Musculoskeletal
- No musculoskeletal complications thus far

Activities of daily living
- Patient can perform all ADLs with minimal assistance

Trends and Questions in Steroid Use [3,4]

Trend to starting steroids earlier

Trend to higher steroid treatment rate

Deflazacort age indication expanded

Increased appreciation for potential risks of early steroid treatment

MD STARnet (2015): comparison of boys with DMD born between '82-'86 vs between '97-'01.		
	'82-'86	'97-'01
Mean age at steroid initiation	8.1 y/o	7.1 y/o
Steroid treatment rate	54%	72%

Deflazacort label recently expanded to include patients 2-5 years of age.

Earlier (<5 y/o) age at steroid initiation may be associated with increased risks of cardiomyopathy & fracture vs later (>5 y/o) initiation.

FOR DMD[5]

International study to determine which of 3 steroid regimens is associated with the greatest improvement in muscle strength and has the fewest side effects.

- **Study population:** boys age 4-7 with DMD
- **Steroid regimens:** Prednisolone daily, prednisolone 10 days on/10 days off, or deflazacort daily
- **Results** are expected to be released in 2020 – will provide clarity on when to start steroids and which steroid regimen to prescribe

Summary:

Manifold barriers exist to early diagnosis (e.g., clinician awareness, parental "optimism," scheduling and logistics)

Early diagnosis impacts disease management, family planning, clinical trial participation

CK testing as soon as developmental delay is even suspected could greatly shorten the time to DMD diagnosis

Steroids clearly delay loss of ambulation and other functional milestones, though uncertainties remain on when to start and how long to continue

Data from FOR DMD should help to clarify optimal steroid dosing regimen

1. Ciafaloni E, Fox DJ, Pandya S, et al. Delayed Diagnosis in Duch enne Muscular Dystrophy: Data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatrics. 2009; 155(3):380-385
2. Cowen L, Mancini M, Martin A, et al. Variability and trends in corticosteroid use by male United States participants with Duchenne muscular dystrophy in the Duchenne Registry. BMC Neurol. 2019;19:84
3. Fox DJ, Kumar A, West NA, et al. Trends with corticosteroid use in males with Duchenne muscular dystrophy born 1982-2001. J Child Neurol. 2014;30:21-26
4. Kim S, Zhu Y, Romitti PA, et al. Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy. Neuromuscul Disord. 2017;27:730-737.
5. https://for-dmd.org/en/

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