Early Diagnosis and Intervention in DMD

Patient #2: DMD Delayed Diagnosis, Treatment Interruption

17 y/o Boy

Case contributor and commentary:
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Age 4

Symptoms:
Family first noticed abnormal gait (toe walking and abnormal running/walking), which gradually progressed over time.

Background:
- No family history of neuromuscular disease
- Patient was under the routine care of a pediatrician, who was aware of these symptoms; however, they did not initially raise any "red flags"

Age 4 to 7

Approximately 2-3 years of a "wait and see" approach.

Commentary: ***Recognizing symptoms*** *of neuromuscular disease can be difficult, especially in early stages when the presenting symptoms are subtle variants of normal behavior and development. As a result,* ***delay in diagnosis*** *is an important problem in DMD. Despite educational efforts to streamline the diagnostic process and speed up diagnosis, we are still seeing a number of patients with DMD who were initially referred to a gastroenterologist for an elevated liver function test. Some of these patients even undergo liver biopsy prior to being referred to a neuromuscular specialist.*

COMMON REASONS FOR DIAGNOSTIC DELAY [1,2]

- Lack of awareness of DMD symptoms
- "Wait-and-see" approach by PCP
- Long wait times to see a specialist
- Referral to provider (PT/OT) who cannot order CK
- Unnecessary specialist referrals (eg GI for elevated LFTs)

Age 7

Pediatrician Workup:
Parents grew increasingly concerned about their son's motor symptoms and conveyed their concerns to the pediatrician, who then followed the standard protocol for assessing motor delay.

Findings:
- Brain MRI showed normal findings
- CK was 11,000

Neurology Workup:
Neurology consult was immediately scheduled at age 7 and the patient was seen promptly.

Findings:
Genetic testing showed duplication of exon 2 in *DMD* gene.

Treatment:
Steroid treatment (daily prednisone 0.75 mg/kg) was promptly initiated.

Progression of muscle weakness slowed slightly after initiation of steroid treatment.

Side Effect:
Rapid weight gain of approximately 7 lbs after initiation of prednisone.

Tinea infection during the first year of treatment, likely secondary to prednisone.

CINRG-DNHS; 277 DMD patients received steroids for >1yr, average follow up: 3.8 yrs [3]

Drug/Dose	No. (%)	Start age (SD)	Age at LOA$_{med}$	Cushingoid	Growth delay	Cataracts
PRED daily	94 (33.9)	6.6 (1.9)	11.2	50%	27%	5%
DFZ daily	80 (28.9)	7.2 (2)	13.9	72%	60%	29%

PRED = prednisone DFZ = deflazacort LOA=loss of ambulation; SD=standard deviation; med=median

Commentary: *Long-term steroids improve muscle strength and function, pulmonary function and slow progression of weakness. In the US, glucocorticoids used in the treatment of DMD include* ***prednisone and deflazacort****. The most clinically relevant difference between these two corticosteroids is their* ***side effect profiles****; in particular, deflazacort is associated with less weight gain and fewer behavioral effects than prednisone.*

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Age 8

Treatment Interruption:
After approximately 1 year of treatment, the patient discontinued prednisone due to side effects and was then lost to follow up for approximately 2 years.

Age 8 to 10

The patient was off treatment during this time.

Age 10

Symptoms:
Patient returned to clinic at age 10 with more pronounced muscle weakness. Family did not report any effects of abrupt steroid discontinuation.

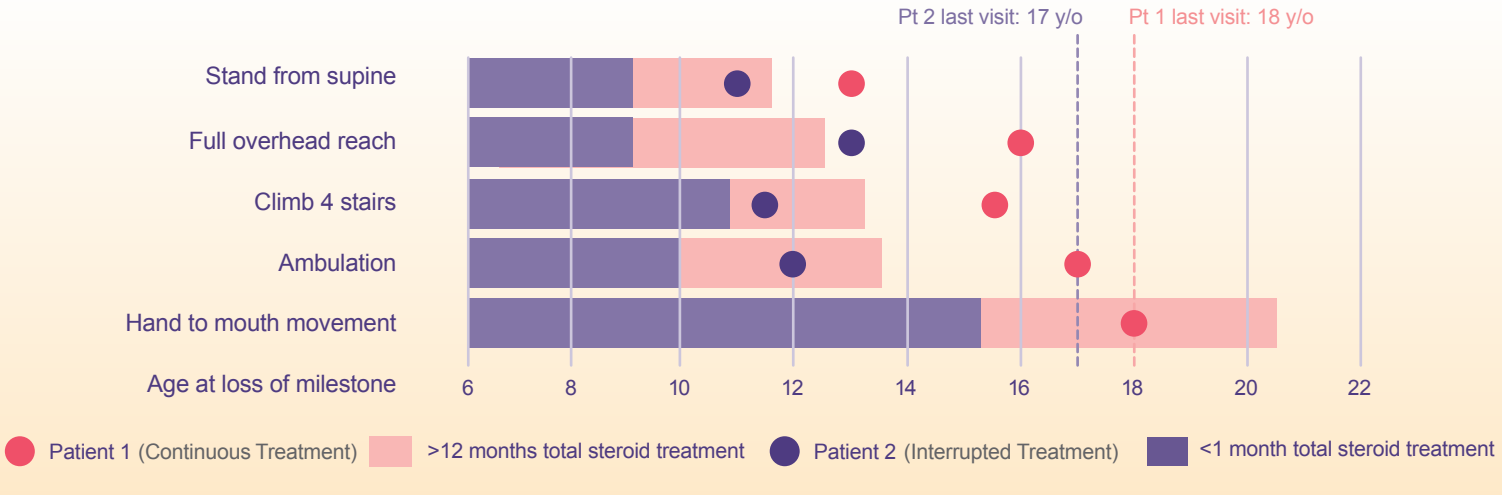
Treatment:
Patient began taking deflazacort 0.9 mg/kg once daily.

Results:
- The patient's weakness continued to slowly worsen on deflazacort.
- Weight gain was minimal compared to interval of prednisone treatment
- No other steroid-related side effects have been observed
- Deflazacort regimen remained stable over time

Commentary: *The primary challenge that treating physicians face when starting patients on deflazacort is obtaining insurance coverage. Most **insurance policies require documentation** that a patient "failed" an initial trial of prednisone, with failure typically defined as the **occurrence of intolerable steroid-related side effects**. Policies often mandate a minimum duration of the prednisone trial, for example at least 3 months or at least six months, before prednisone failure is established and the switch to deflazacort can be made.*

Cardiovascular Status:
Losartan prophylaxis initiated at age 10 years per treatment guidelines. No cardiovascular issues so far.

Loss of milestones in Patient 1 and Patient 2: Comparison with CINRG natural history study [4]



Age 12

Ambulation Status:
Loss of ambulation at age 12; currently wheelchair dependent.

Age 16

Respiratory Symptoms:
Sleep apnea and the use of nocturnal BiPAP since the age of 16 years. No other respiratory issues so far.

Age 17

Musculoskeletal
Positive for scoliosis; no other musculoskeletal issues (eg osteoporosis) or surgical procedures.

Activities of daily living
Patient requires assistance with transfers but is able to feed himself.

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 Pediatrics. 2009; 155(3):380 – 385
2. Aartsma-Rus A, Hegde M, Ben-Omran T, et al. Evidence-Based Consensus and Systematic Review on Reducing the Time to Diagnosis of Duchenne Muscular Dystrophy. J Pediatrics. 2019; 204: 305-313
3. Bello L, Gordish-Dressman H, Morgenroth LP, et al. Prednisone/prednisone and deflazacort regimens in the CINRG Duchenne Natural History Study. Neurology Sep 2015, 85 (12) 1048-1055
4. McDonald CM, Henricson EK, Abresch RT, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 2018 Feb 3;391(10119):451-461.

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MDA Muscular Dystrophy Association