Case study: delayed diagnosis of Duchenne muscular dystrophy (DMD) in two brothers presenting with global developmental delay

Patient case based on Essex C & Roper H. 2001¹

OLDER BROTHER: M

INITIAL PRESENTATION

At 24 months of age, M was brought to his GP because his parents were concerned that he was **unable to communicate**. He showed **no signs of being able to gesture, babble or speak**, and had **started walking at 23 months**.

LABORATORY AND GENETIC TESTS

M's GP ordered metabolic and chromosomal tests, which came back normal.

FIRST REFERRAL: SPECIAL EDUCATION ASSESSMENT CENTRE

M underwent a special educational needs assessment, and was subsequently placed in a school for children with severe learning difficulties.

SECOND REFERRAL: PAEDIATRIC NEUROLOGIST

M's younger brother, C, was diagnosed with DMD at the age of 6. Shortly afterwards, M was reassessed by a paediatric neurologist.

OUTCOME

At the age of 7 years and 6 months, M was diagnosed with DMD.



DMD EARLY SIGNS AND SYMPTOMS INCLUDE:2,3

- Delayed motor milestones
- Speech delay and language impairment
- Abnormal gait (e.g. toe walking)
- Gowers' manoeuvre
- Calf hypertrophy
- Learning difficulties

IMPORTANCE OF EARLY DIAGNOSIS

- Patients with a positive family history of DMD and suspicion of abnormal muscle function should be tested promptly²
- Delayed diagnosis of DMD results in lost opportunities to initiate potentially disease-modifying treatments and specialist care, access genetic counselling and potential to enrol into clinical trials^{2,4,5}



Developmental delay? Order a CK test today

Patients' initials and photo are for illustrative purposes only



YOUNGER BROTHER: C

INITIAL PRESENTATION

M's younger brother, C, presented with similar, although somewhat milder, symptoms of developmental delay. C was unable to babble or speak, and communicated only through signing. He was placed in a school for children with severe learning difficulties. At the age of 6 years, teachers reported concerns about bruising, which was attributed to frequent falls.

REFERRAL: PAEDIATRIC NEUROLOGIST

C was referred to a paediatric neurologist for further assessment. Physical examination revealed **calf hypertrophy**, a waddling gait and use of **Gowers' manoeuvre** to get up from the floor.

LABORATORY AND GENETIC TESTS

Laboratory tests revealed elevated creatine kinase (CK) levels:

Creatine kinase	>9000 U/L
Normal level	≤250 U/L* ⁶

GENETIC ANALYSIS: No deletion in the dystrophin gene was detected. *MUSCLE BIOPSY:* Dystrophic histochemistry revealed an absence of dystrophin.

OUTCOME

A muscle biopsy confirmed a diagnosis of DMD.

CK TESTING

- A simple and rapid blood test that screens for elevated CK levels which reflect muscle damage^{4,6}
- Normal level is generally up to 250 U/L*6

GENETIC TESTING TO CONFIRM DMD

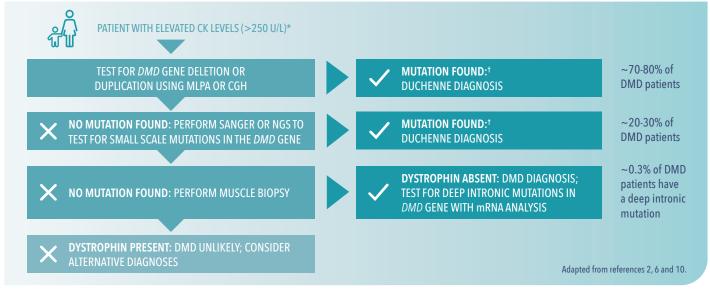
- Patients with elevated CK levels should be tested for DMD gene deletion or duplication using multiplex ligation-dependent probe amplification (MLPA)²
- If no mutation is found, genetic sequencing should be performed to detect small mutations²
- In exceptional circumstances, where genetic tests are negative or unavailable, a muscle biopsy should be performed^{2,7}

IMPORTANCE OF GENETIC TESTING

- Identifies the DMD mutation type, which helps determine a patient's eligibility for mutation-specific treatment options and potential to participate in clinical trials^{2,5}
- Informs carrier and pre-symptomatic testing of family members, genetic counselling and family planning decisions^{2,4,5}

DMD: WHAT YOU NEED TO KNOW

- DMD is a rare, progressive, disabling childhood neuromuscular disorder that is often associated with a delayed diagnosis²⁻⁴
- Given that DMD is a progressive disease with irreversible muscle loss, it is critical that patients are diagnosed as early as possible to begin potentially disease-modifying treatments and specialist care ^{2,4,5,8,9}



*The normal CK range is generally up to 250 U/L. Absolute values may differ between laboratories.⁶ [†]Reading frame rule: in general, out-of-frame mutations confirm DMD and in-frame mutations confirm Becker muscular dystrophy (BMD), a less severe form of the disease. ~4–9% of DMD gene mutations do not follow the reading frame rule.¹⁰

CGH, comparative genome hybridisation; MLPA, multiplex ligation-dependent probe amplification; NGS, next-generation sequencing.

References: 1. Essex C & Roper H. BMJ. 2001;323:37-38. 2. Birnkrant DJ, et al. Lancet Neurol. 2018;17:251-267. 3. Ciafaloni E, et al. J Pediatr. 2009;155:380-385. 4. van Ruiten HJ, et al. Arch Dis Child. 2014;99:1074-1077. 5. Aartsma-Rus A, et al. J Med Genet. 2016;53:145-151. 6. National Task Force for Early Identification of Childhood Neuromuscular Disorders. CK testing in children. Available at: https://childmuscleweakness.org/ck-test/[Accessed June 2020]. 7. Goemans N, et al. Eur Neurol Rev. 2014;9:78-82. 8. Blake DJ, et al. Physiol Rev. 2002;82:291-329. 9. Laing NG, et al. Clin Biochem Rev. 2011;32:129-134. 10. Aartsma-Rus A, et al. J Pediatr. 2019;204:305-313.



Date of preparation: July 2020 | GL-DMD-0220