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. 2001[1]

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 promptly*[2]
- *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]

Patients' initials and photo are for illustrative purposes only.

Think CK Test

Developmental delay? Order a CK test today

PTC THERAPEUTICS

This material has been developed and funded by PTC Therapeutics.
It is intended for healthcare professionals 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 mutations[2]*
- *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 diagnosis[2–4]
- 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]

PATIENT WITH ELEVATED CK LEVELS (>250 U/L)*

TEST FOR *DMD* GENE DELETION OR DUPLICATION USING MLPA OR CGH	✓ **MUTATION FOUND:**† DUCHENNE DIAGNOSIS	~70-80% of DMD patients
✗ **NO MUTATION FOUND:** PERFORM SANGER OR NGS TO TEST FOR SMALL SCALE MUTATIONS IN THE *DMD* GENE	✓ **MUTATION FOUND:**† DUCHENNE DIAGNOSIS	~20-30% of DMD patients
✗ **NO MUTATION FOUND:** PERFORM MUSCLE BIOPSY	✓ **DYSTROPHIN ABSENT:** DMD DIAGNOSIS; TEST FOR DEEP INTRONIC MUTATIONS IN *DMD* GENE WITH mRNA ANALYSIS	~0.3% of DMD patients have a deep intronic mutation
✗ **DYSTROPHIN PRESENT:** DMD UNLIKELY; CONSIDER ALTERNATIVE DIAGNOSES		

Adapted from references 2, 6 and 10.

*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.

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