

Becker's Muscular Dystrophy

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Mr. K.B., a 23 year old gentleman, presented with difficulty climbing stairs, changes in posture and toe walking. Significant calf hypertrophy was seen on examination. A muscular dystrophy was the probable diagnosis and to confirm, this various investigations were carried out, including: genetic testing, electromyography (EMG), and creatinine kinase (CK) levels. The doctors' suspicions were confirmed and the patient was diagnosed with a de novo mutation of Becker's Muscular Dystrophy (BMD). A cardiac work up followed to assess for dilated cardiomyopathy which is associated with BMD, although Mr. K.B. was still asymptomatic. BMD is a very rare disease with an incidence in males as low as 1 in 30,000 people. The prevalence in females is extremely low, as BMD is an X linked disorder. Apart from this, Mr. K.B's case is particularly more rare due to the fact that genetic studies have shown a de novo mutation, furthermore no other family member is affected by the disease, nor is a carrier. Under Dr. Aquilina's care, only one other family has been reported in Malta.

Fact File on Becker's Muscular Dystrophy

Becker's Muscular Dystrophy (BMD) is one of the various Muscular Dystrophies having a male distribution due to its X linked inheritance. The condition is significantly rare, with an incidence as low as 1 in 30,000 people and with a prevalence of 17-27 cases per 1 million population. BMD is a rarer, milder form of muscular dystrophy compared to Duchenne Muscular Dystrophy (DMD), and presents later in life between the ages of 14-20. BMD is an X linked recessive mutation and most cases involve exon deletions in the dystrophin gene Xp21. This mutation leads to the translation and production of a semi-functional dystrophin gene (unlike DMD where the resulting dystrophin gene is non functional; 30-80% normal dystrophin in BMD compared to only 5% in DMD). Nicolas et al suggested that different exon deletions resulted in different disease severity and hence, different disease progression. Nicolas et al studied four prevalent in- frame

exon deletions (45-47, 45-48, 45-49, 45-51) and showed differences in the rate of disability progression to the point of being wheelchair bound (reached earlier in deletions 45-47 and 45-49 compared to deletion 45-48), as well as differences in the age of onset of dilated cardiomyopathy (onset delayed by 11 years in deletion 45-48 and by 14 years in deletion 45-49, in comparison to exon deletions 45-47)(Nicolas et al, 2015).

BMD presents within the ages of 14 and 20 with various signs and symptoms. The most common presentation is symmetrical proximal muscle weakness and classically the patient presents with difficulty climbing stairs. Apart from this, the patient may complain of increasing clumsiness with resulting falls and toe walking. On examination a rather characteristic sign in BMD (as well as DMD) is pseudo-hypertrophy of the calves, which may be quite obvious on inspection. However, it is known that the pseudohypertrophy is realistically a combination of actual muscle hypertrophy

together with fatty deposition (Mauro et al, 2014). A sign which helps differentiate DMD from BMD is the preservation of strength of the neck flexors.

A rather serious manifestation of BMD (and DMD) is dilated cardiomyopathy, which is not necessarily related to the skeletal signs and symptoms (Mavrogeni et al, 2015). Dilated cardiomyopathy is not only seen in affected males with BMD, however it may also present in female carriers of BMD (females carry two X chromosomes, compared to males which carry one X chromosome, the other being Y. Therefore, a female will be a carrier if only one of her two X chromosomes carry the mutation of BMD). It is for this reason that BMD patients require regular cardiological work up in order to diagnose and treat such a condition. The work up includes electrocardiogram (ECG) which may show certain arrhythmias, conduction defects and hypertrophy among other electrical changes. Another important investigation is an echocardiogram which is basically an ultrasound of the heart which assesses

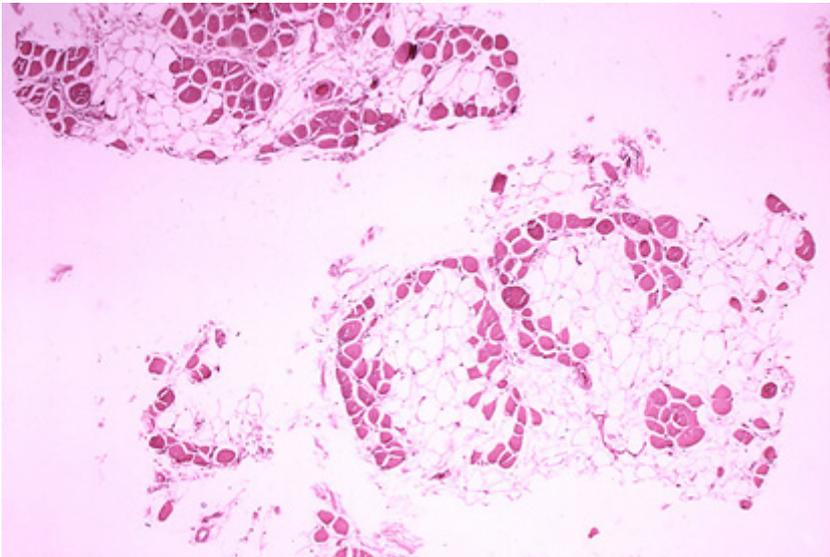


Figure 1: Histopathology of a DMD patient's Gastrocnemius muscle showing the extensive replacement of muscle fibres by adipose cells.

the heart function as well as visualises any functional defects of the heart. It is important to assess for heart failure as early as possible to avoid life-threatening conditions. Yilmaz A. et al have shown that more recent investigation approaches, mainly Cardiovascular Magnetic Resonance, have proven more efficient in detecting cardiac involvement when compared to other methods.

Regarding treatment, there is no cure for BMD. Therefore, the main aim of treatment is to control patients' symptoms as they arise, as well as a supportive approach with a multidisciplinary team in order to improve the health-related quality of life. The team should include physiotherapy, occupational therapy, as well as speech therapy. Physiotherapy focuses on strengthening muscles as well as helping the patients to be as physically functional as possible. Occupational therapy focuses on aiding the patient with activities of daily living, as well as education and job difficulties encountered due to the disease. Speech therapy is needed in BMD patients if dysphagia (difficulty swallowing) becomes a concern with increasing severity of the condition (Grootenhuus et al, 2007).

Treatment is important for cardiology and respiratory deterioration. Once the muscles used in respiration start to weaken, non-invasive respiratory intermittent positive-pressure ventilation is helpful in the care of these affected patients. With regards to cardiological

treatment the regular treatment used in heart failure is advantageous, and includes diuretics and angiotensin converting enzymes among others. The use of a pacemaker is also beneficial in the treatment of heart failure.

Surgical treatment may be considered in situations where scoliosis becomes a prominent problem and it may be beneficial to undergo spinal fusion procedure. Another surgical procedure considered in BMD patients is an Achilles tendon section for patients with severe ankle contractures in need of muscle release.

New approaches to treating DMD and BMD include stem cell transplants. Gussone E. et al have shown that intravenous injection of either normal haematopoietic stem cells or muscle-derived stem cells into mdx mice (mice models of DMD) have resulted in the partial restoration of dystrophin expression in the affected muscles. Another approach is gene therapy; Norma B. R. et al carried out an experiment on 9 patients with DMD/BMD were injected with a full-length human dystrophin plasmid into the radialis muscle. Dystrophin expression was observed in six out of the nine patients and therefore the results showed that exogenous dystrophin expression can be obtained after intramuscular transfer of the plasmid.

Case Report on Becker's Muscular Dystrophy

Presenting Complaint

A 23-year-old male presented with difficulty walking up stairs for the past two years. Mr. K.B. also complained of fatigue in the lower limbs and problems with running. The patient also described occasional falls. These symptoms have been present for the previous two years. The patient described difficulty with running and difficulty going up stairs. He explained that it is easier to go down the stairs. The symptoms came on gradually and have been slowly progressing and the patient now expressed that he is apprehensive in walking as he fears he might fall. Mr. K.B. also explained that he has problems getting up from a sitting position. Upon further questioning, there were no associated muscle cramps, no visual or swallowing problems, no active speech difficulty and no dark urine. However, the patient said he experiences some pain on walking, mainly in both calves and feet.

Past Medical & Surgical History

The patient suffered from croup as an infant, and severe acne as a teenager, which was treated successfully. He also suffered from speech difficulties as a child and was taken to a speech therapist for a few months and had a pure tone tympanogram performed to ensure that there were no auditory problems. There was also a history of lower back pain, which was investigated via plain thoracolumbar and pelvic radiography and no notable anatomical cause was found.

Drug History & Allergies

The patient takes daily multivitamins and Omega 3. Mr. K.B. was previously taking Isotretinoin (Decutan) 0.5 mg/kg/daily. After diagnosis, it was recommended he takes the influenza vaccine yearly as well as the Pneumovax vaccine. He has no known drug allergies.

Family History

There are two known cases of cerebral

palsy in Mr. K.B.'s distant family, i.e. his first cousins.

Social History

The patient is a non-smoker and does not consume any alcohol on a daily basis and has never taken any illicit drugs. He lives with his family and is currently working as an IT technician. The patient manages to drive and carry out activities of daily living. Mr. K.B. is in a stable relationship and has been for several years now.

Systemic Inquiry

Nil to note.

Physical Examination & Preliminary Investigations

Mr. K.B. had a full neurological examination carried out.

On examination of the upper limbs:

- Cranial nerves: Intact;
- Tone: Normal;
- Power: 5/5;
- Reflexes: Normal;
- Sensation: Normal.

On examination of the lower limbs:

- Tone: Normal;
- Power: 5/5;
- Reflexes: Normal;
- Sensation: Normal.

The patient was noted to have visible bilateral calf hypertrophy and a lordotic posture. On examination of the patient's gait, he also had a mild, bilateral foot drop and a waddling gait. The patient's waddling gait was more prominent on walking up stairs.

Mr. K.B. also had a cardiovascular examination:

- Pulse: 60 beats/minute;
- Blood Pressure: 130/70;
- Heart Sounds: Normal;
- Chest: Clear;
- No lower limb oedema was present.



Figure 2: Mr. K.B.'s photographs delineating bilateral calf hypertrophy.

Differential Diagnoses

1. Becker's Muscular Dystrophy;
2. Glycogen Storage Disorder.

Diagnostic Investigations

Requested Investigation: **Creatinine Kinase (CK);**

Justification for procedure: Elevated CK levels may indicate a muscular pathology;

Result & Conclusion: The CK levels were 1800 U/L, which are much higher than the normal range.

Requested Investigation: **Electromyogram (EMG);**

Justification for procedure: This test will measure muscle activity at rest and during contraction and will show any abnormality in the motor neuron unit;

Result & Conclusion: Shows a chronic, myopathic process with small, short polyphasic potentials.

Requested Investigation: **Electrocardiogram (ECG);**

Justification for procedure: To look for any arrhythmias or electrical conduction abnormalities, for example sinus tachycardia or complete left bundle

branch block;

Result & Conclusion: ECG showed narrow QRS SR segments.

Requested Investigation: **24- Hour Holter ECG;**

Justification for procedure: To exclude any cardiac electrical abnormalities;

Result & Conclusion: No ventricular arrhythmias were noted.

Requested Investigation: **Echocardiogram;**

Justification for procedure: To show any evidence of dilated cardiomyopathy or any ventricular failure;

Result & Conclusion: Showed good global left ventricular function and an ejection fraction of 55%.

Requested Investigation: **Family Genetic testing;**

Justification for procedure: To look for specific axons deletions in the dystrophin gene and to establish whether the condition was inherited from his mother;

Result & Conclusion: Tests showed a deletion of the axons 45-47 in the dystrophic gene, which is compatible with the suspected diagnosis of BMD.

However, Mr. K.B.'s mother marked negative for the gene mutation.

Diagnosis

The history of presenting complaint, with difficulty walking and getting up from chairs and occasional falls, points to the diagnosis of a Muscular Dystrophy. The characteristic features of toe walking, waddling gait and marked calf hypertrophy were also seen on examination. The test results also confirmed a chronic myopathic process, and the genetic testing confirmed the diagnosis of Becker's Muscular Dystrophy.

Management

Physiotherapy

Mr. K.B. attends physiotherapy and occupational therapy once a month and was given a series of exercises, including squats, bicycle and weighted stair lifts to perform at home daily.

Genetic Counselling

The patient was counselled about the inheritance pattern of the condition. Becker's Muscular Dystrophy is an X-linked recessive inherited disorder, meaning that Mr. K.B. was informed that there is a 100% chance that any female offspring he has will be a carrier for the disease.

Follow Up

The patient is being followed up by both the Neurology and Cardiology Departments. A yearly echocardiogram and full cardiovascular and neurological examination is done to monitor the progression of the disease.

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