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Case report

First familial Becker muscular dystrophy in Tanzania: Clinical and genetic features☆

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Abstract

In African neurological practice, muscle disorders are either underdiagnosed or underrepresented. This may in part be due to the large burden of other more common neurological disorders. In this report we describe the first Tanzanian patient with genetically confirmed Becker muscular dystrophy. His phenotype and genotype were compatible with elsewhere in the world. Remarkably, this patient reported his progressive weakness of the legs with difficulty in walking only after a fall. We demonstrate that muscular dystrophies occur in sub-Saharan Africa. Neurologists must however be aware that patients are likely to delay seeking medical care for muscle disorders.

Keywords: Becker muscular dystrophy; Africa; Muscular dystrophy; Global neurology.

1. Introduction

Muscle disorders in sub-Saharan Africa are likely underreported or underrepresented in African neurological practice due to a large burden of infection and the evolving epidemic of non-communicable disease [1]. In a hospital-based study on neurological disorders in Northern Tanzania, only 46 of the 2040 patients (2,3%) were diagnosed with myopathies and muscular dystrophies, and 14 patients (0,7%) with dermatomyositis [W. Howlett unpublished data]. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are X-linked recessive disorders caused by mutations in the dystrophin gene. They lead to absent or reduced expression of dystrophin in both skeletal and heart muscles. Mutations associated with DMD and BMD have been described in patients from various ethnicities and spanning the globe, including a South-African study on DMD with a mutation detection rate up to 46% using multiplex ligation-dependent probe amplification (MLPA) [2,3].

In areas of the world with limited healthcare facilities and training, most cases of neuromuscular disorders are either unrecognised or undiagnosed [2]. In muscular dystrophies the loss of muscle force and ensuing disability may frequently have adult onset and be slow in progression. In particular those patients with preserved mobility and the ability to work may only present when significant function is lost or a complication occurs. This particularly applies in a setting where access to healthcare is limited and healthcare insurance coverage rates are low.

We report a middle-aged man whose muscle weakness only came to medical attention when he admitted to the Urology Ward, where he presented with a urethral stricture as a result of a fall secondary due to his limb weakness. Upon neurological examination he was diagnosed as having Becker muscular dystrophy (BMD), which was genetically confirmed.

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2. Case report

The patient and his mother presented in Kilimanjaro Christian Medical Centre (KCMC) in Moshi, a tertiary referral and teaching hospital in the North of Tanzania. They were examined by two neurologists, for which written informed consent was obtained in English and Swahili with regards to photographs and venepuncture for biochemical and genetic testing. Medical ethical clearance for this case report was obtained from Kilimanjaro Christian Medical University College in the framework of an ongoing study into neurological conditions in Northern Tanzania.

This 48-year-old male was admitted to the Urology Department of KCMC due to urethral stricture secondary to a fall with perineal injury a number of years before. His main complaint was progressive weakness of limbs, mostly legs, with difficulty in walking. He tended to fall when trying to get up from a squatting position. This was accompanied by muscle wasting of thighs, shoulders and arms which had evolved slowly over more than 30 years with its onset at around 15 years of age. He denied muscle pain, dark urine or sensory loss. Apart from intermittent dyspnoea he had no other cardiac symptoms. He had normal childhood motor milestones, and his past medical history otherwise was unremarkable. He neither smoked nor drank alcohol. His family history was remarkable in that he had five brothers with a similar history of muscle weakness and waddling gait (pedigree in Fig. 1). The patient's mother, illiterate and now about 80 years old had an unremarkable general examination with normal blood pressure and no cardiac murmurs upon auscultation.

Neurological examination showed no evidence of a neuromuscular disease. The patient's father had died at a young age. One affected brother of the index patient had three young children (at least one boy and one girl) estimated to be around 10 years old or younger, all of whom were said to be asymptomatic for weakness. The other four affected brothers had no children, and there was no information about the other siblings' families. None had previously consulted a health care worker or doctor because of muscle weakness.

The patient had normal affect and cognitive function and was independent in ambulation. Physical examination showed no dysmorphisms and normal appendages (hairs and hairline, teeth, nails). Neurological examination showed generalised muscle atrophy most pronounced in the proximal shoulder and pelvic girdle region and winging of the scapulae (Fig. 2). The musculature of hands and feet was only minimally atrophied. The calves, however, looked relatively bulky and upon palpation, there was a distinct rubbery feel to the enlarged calf muscles (Fig. 3). The patient walked with hyperlordosis and a typical Trendelenburg gait and Gower's sign was positive. There were no joint contractures and action or percussion myotonia could not be induced in the hands. According to the Medical Research Council (MRC) scale (0–5 points) [4] the muscle strength had reduced and showed a symmetrical pattern of weakness ranging between MRC grades 2–4, with biceps 2, triceps 3, handflexors 4, abdominal muscles 4, psoas and quadriceps 3, hamstrings 3, and gastrocnemius 3–4. Sensation was normal and reflexes were either decreased or absent. Plantar reflexes were both downgoing. Laboratory investigations reported an elevated level of creatine kinase (1025 IU/L; normal 39-308 IU/L). Full blood count, erythrocyte sedimentation rate and creatinine were normal and screening for the presence of HIV infection was negative. Echocardiogram showed a hypertrophic septum with normal ejection fraction.

Venous blood was sampled and sent to the Genome Diagnostics Laboratory of Leiden University Medical Center, Leiden, the Netherlands, for confirmation of the clinical diagnosis. Genetic testing through MLPA for exons DP427C and 1 through 79 of the DMD gene, MRC Holland Kit P034-B2 and P035-B1) showed a hemizygous in-frame deletion of exons 45 through to 48. This confirmed the clinical diagnosis of BMD. The patient's mother was shown to be heterozygous for the deletion of exons 45 through to 48 which confirmed carriership of BMD.

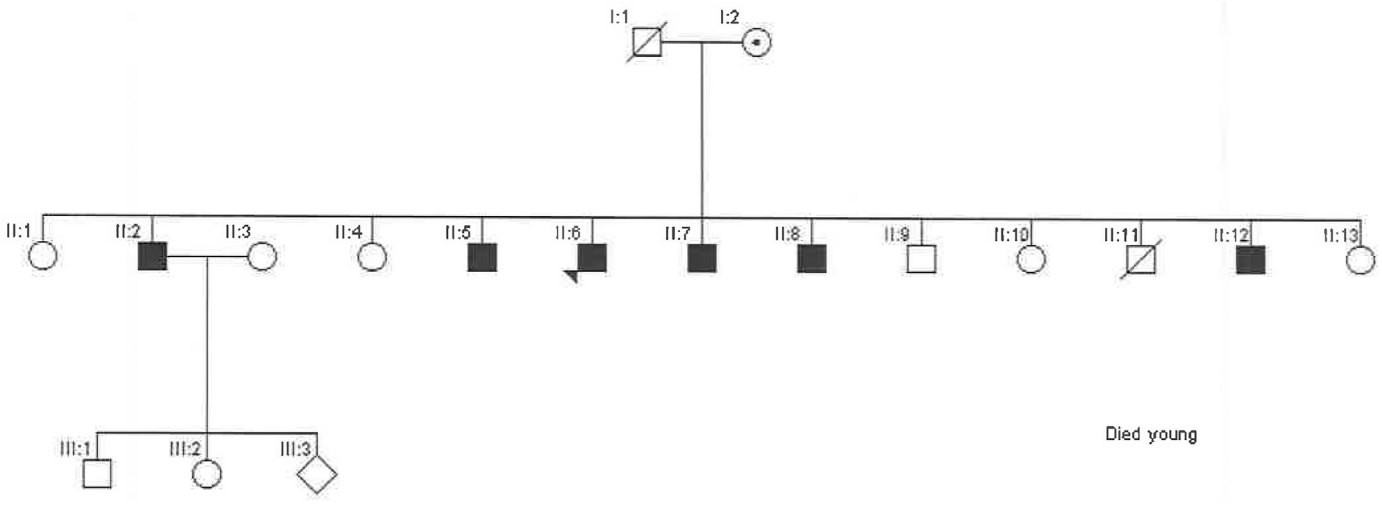

Fig. 1. Pedigree, index patient indicated with arrow.

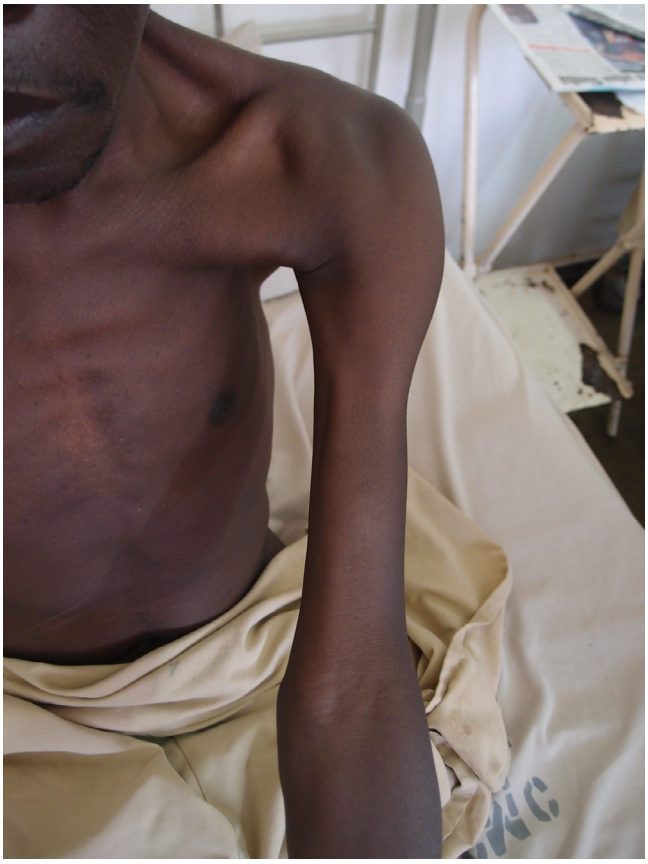

Fig. 2. Proximal muscle atrophy of the upper limb in index patient.

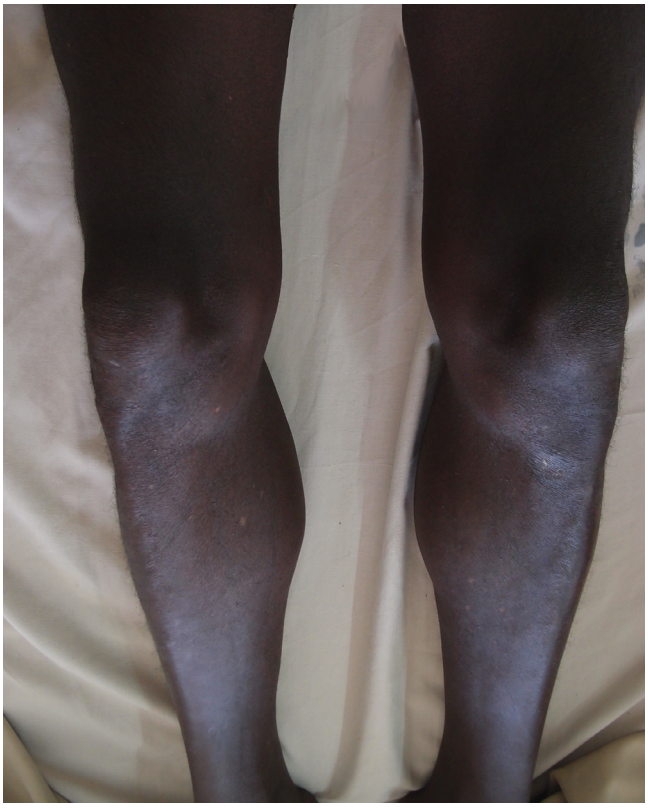

Fig. 3. Pseudohypertrophy of calf muscles in index patient.

The long, 30-year history with teenage onset of a progressive muscular disorder, symmetrical proximal rather than distal weakness, pseudohypertrophy of calf muscles and restriction to male family members led to a working diagnosis of Becker muscular dystrophy (BMD), which could be genetically confirmed.

3. Discussion

This Tanzanian middle-aged patient presented with a urethral stricture as a result of a fall secondary due to his limb weakness. The patient's history indicated slowly progressive adolescent-onset weakness of the limbs for a period of thirty years. The adult-age presentation was slightly confusing but suggested a muscular dystrophy. Calf pseudohypertrophy, hyperlordosis along with cardiac involvement as defined by echocardiogram, and mildly elevated serum creatine kinase further increased the clinical probability of BMD. Our clinical diagnosis was genetically confirmed with an in-frame deletion of exons 45 through to 48 in the dystrophin gene implying reduced expression of dystrophin in skeletal and heart muscles.

These findings genetically confirm BMD in Tanzania, Eastern Africa. There is a clinical description of a DMD family dating decades back from another Tanzanian hospital [5]. Six genetically confirmed DMD patients from the Eastern African region [6] and a large population of genetically confirmed DMD and BMD patients ($n = 128$) in the Southern African region [7] illustrate that this type of muscular dystrophy exists in Africa, as well as in many other ethnicities [2,8,9]. The mutation itself (deletion of exons 45–48) has not been described in the nearby Rwandan population [6], but the range of contiguous distal exon deletions (exons 45–79) was identified in a South African sample of DMD and BMD patients [3,10].

In a large sample of neurological diagnosis in consecutive inpatients from our Medical Centre [W. Howlett unpublished data 2007–2013], muscle disorders were not commonly seen. There were 68 patients diagnosed with a neuromuscular disorder (here defined as including disorders of neuromuscular transmission and clinical stiff person syndrome), constituting 20% of the group "others" ($n = 347$), which is 3% of his total neurological population. In a historical neuroepidemiological study by Osuntokun [11], who characterised almost 9600 neurological patients in terms of their diagnoses in Western Africa, muscle disorders (here also defined as ranging from myasthenia gravis to muscular dystrophy) were diagnosed in 324 patients (3,4%), with 12 cases of limb-girdle type muscular dystrophy, 10 cases of DMD, one family with four cases of myotonic dystrophy type 1 (DM1), and three cases of facioscapulohumeral dystrophy. This is similar to Howlett's patient sample, stressing the rarity of muscle disorders observed in sub-Saharan African neurological practice. Osuntokun did identify DMD, but it should be noted that he also included paediatric cases. Furthermore the distinction of BMD was not yet commonly made in that

period, as BMD was commonly called a 'mild variant of DMD'.

Interestingly DM1, the most common of the inherited muscle diseases worldwide has not yet been identified in a single patient in our clinical practice, nor by East African neurology colleagues (from Dar-es-Salaam, Tanzania and Nairobi, Kenya) [2]. In a single Nigerian kindred and in four patients from Ethiopia, however, DM1 has been described. [8,12-14] In South Africa, DM1 is more prevalent in the Caucasoid Afrikaans-speaking families due to a founder effect but not seen in the regional ethnic populations [14]. Its excessive rarity here is thought to be explained by the migration of the human species out of Africa [13,14].

In our hospital late presentation of muscular disease, illustrated by the above BMD patient, is inherent to the difficult socio-economic situation in this geographical area [2]. Access to healthcare facilities is limited by financial, geographical and cultural factors. This patient only presented to hospital because of urethral injury after a fall. Genetic counselling was provided to the index patient and his mother who tried to invite other family members to clinic; not one of the siblings had ever been examined by a medical doctor for muscle weakness. This fact emphasizes the challenge to the local healthcare capacity in this continent. Therefore neurologists must be extra aware that patients are likely to delay in seeking medical care for muscle disorders.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2019.01.006.

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