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# A rare case of dystrophinopathy: Duchenne muscular dystrophy–Becker muscular dystrophy intermediate complex

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## Abstract

An 18-year-old boy with no significant perinatal history presented with insidious onset of slowly progressive flaccid paraparesis with muscle wasting in thighs. On examination, the patient had flaccid motor quadriparesis and partial atrophy of proximal thigh muscles. This was accompanied by pseudohypertrophy of calf muscles and extensor muscles in the dorsum of foot. Investigations revealed very high levels of creatinine phosphokinase in the patient (6495 IU/l in contrast to normal range of 55–170 IU/l) and in his sister (718 IU/l). Echocardiography showed dilated cardiomyopathy with severe left ventricular dysfunction. The multiplex ligation-dependent probe amplification revealed deletion of exons 3 to 7 in the short arm of X chromosome (Xp21). Based on the clinical features and investigation reports, a diagnosis of intermediate phenotype of Duchenne and Becker muscular dystrophy was made.

**Keywords:** Becker Muscular Dystrophy, Duchenne muscular dystrophy, paraparesis

## INTRODUCTION

Muscular dystrophies encompass progressive diseases like Duchenne, Becker, Emery-Dreifuss, myotonic, and limb-girdle. Among these muscular dystrophies, Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) share the two ends of syndromic presentations related to dystrophin gene mutation (X-linked recessive). Dystrophin gene, which is located on chromosome Xp21, encodes for a sarcolemmal protein – dystrophin, and its abnormal formation or absence leads not only to muscular dystrophy but also to associated conditions related to myocardium and brain because of its presence in those regions [1,2].

At one end, DMD is a severe form of dystrophy with higher incidence of 1 in 3500 males with an early presentation at 3–5 years and progressive deterioration, resulting in death at around 16–18 years, whereas BMD is rarer with an incidence of around 1 in 20 000 males, with a late presentation at around 11–12 years of age and surviving till late adulthood [1,3–6].

There is an intermediate type between the two which is even rarer in presentation and diagnosis as the features are mid-way between the two ends of the spectrum. Recently, a study in

India reported only six (1.9%) cases of intermediate type among 379 cases of DMD and BMD, which were reviewed retrospectively after confirmatory diagnosis with multiplex ligation-dependent probe amplification (MLPA) [1].

We present here a case that had features of both DMD and BMD and a cytogenetic abnormality in X chromosome. The case discussion holds importance to stress on the systematic approach in diagnosis of a muscle disease and to emphasize the value of meticulous examination and relevant investigations (including genetic evaluation) in correct diagnosis.

## CASE REPORT

An 18-year-old male patient studying in the first year in college reported to medical OPD along with his mother with complaint of weakness of both lower limbs. The weakness

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was first noticed when the patient was 3 years old. From the history, it was apparent that weakness was insidious in onset and slowly progressive in course.

The patient was second of three siblings, born out of nonconsanguineous marriage. He had a twin brother and an elder sister. The patient had an uneventful prenatal period and was born out of normal vaginal delivery at 38 weeks of gestation and had cried immediately after birth. The patient had been fully immunized during childhood, and there was no history of past hospitalization.

There was some motor developmental delay during childhood as the patient started crawling at 1 year, standing without support at one and half years, and walking at two and half years. There was, however, no delay in fine motor, speech, and social milestones.

Besides, it was noticed in childhood that the patient was unable to physically compete with siblings, was unable to run/jump, had difficulty in climbing stairs, had difficulty in getting up from squatting position, had difficulty in clearing obstacles while walking at around 4 years of age, walked with sideways and forward bending, and had history of thinning of thigh muscles. There was no history of difficulty in getting up from lying position, difficulty turning in bed, difficulty in holding objects overhead/combing hair, buttoning/unbuttoning of shirt or raising head above pillow, drooping of eyelids/diplopia, diurnal variation in weakness, seizures/headache, or disturbance of bowel/bladder function.

There was no history suggestive of any addictions or of high-risk behavior. The patient's twin brother and his sister were asymptomatic, and there was no history of similar illness in the paternal or maternal side.

The patient was performing well academically in his college. There was no history suggestive of recurrent respiratory infection or of weight loss during the last 6 months.

The patient had sought medical help intermittently through private practitioners who advised some medication; however, no documents pertaining to this were available with the patient or his mother.

The general examination showed that the patient was afebrile with regular pulse (84/min), normal blood pressure (112/74 mmHg), regular respiratory rate of 18/min, weight of 66 kg, and nonraised JVP. There was no pallor/icterus/edema/cyanosis.

Neurological examination showed the patient to be oriented to time, place, and person. The speech was normal with no language problems or cranial nerves deficit. The motor examination showed mild atrophy of muscles of thigh, suprascapular and intrascapular region, with hypertrophy of calf and extensor muscles in the dorsum of foot (Figs. 1 and 2). The tone of upper and lower limb muscles was reduced. Gower sign was positive – when asked to get up from supine position, the patient rolled over to kneeling position, pushed on the



**Figure 1:** Pseudohypertrophy of calf muscles.

ground with extended arms to raise the rump. Subsequently, he straightened the legs and moved the hands to the knees to push himself to standing position. Contracture of tendo-achilles was also present. No abnormal movements/fasciculations were seen.

Power of various groups of muscles was tested, and findings are shown in Table 1.

The deep tendon and abdominal reflexes were normal and plantars were flexor. There was no sensory dysfunction or any signs of meningism. The gait showed lordotic posture (Fig. 3) with toe walking.

Based on the clinical examination, a four-tier diagnosis was made:

- (1) Functional.
  - (a) Flaccid paraparesis.
- (2) Physiological.
  - (a) LMN.
- (3) Anatomical
  - (a) Muscle.
  - (b) Polyradiculopathy.
  - (c) Motor neuropathy.
- (4) Etiologic
  - (a) Dystrophinopathy.
  - (b) Sarcoglycanopathy.

To further confirm the diagnosis, relevant investigations were done. The hemogram and biochemical investigation findings are shown in Table 2. The investigations revealed very high levels of creatinine phosphokinase (CPK) in the patient (6495 IU/l in contrast to normal range of 55–170 IU/l). The patient's sister also had elevated levels of CPK (718 IU/l) but much lower than her brother.

ECG and chest radiograph were unremarkable.

Electromyography (EMG) study on quadriceps femoris muscles of the thigh was carried out. EMG of vastus lateralis muscle at



**Figure 2:** Pseudohypertrophy of extensor muscles in dorsum of foot

rest showed normal pattern. However, when patient was asked to extend thigh as in getting up from the ground, the EMG showed haphazard wave formation that did not follow any pattern.

The two-dimensional echocardiography of the patient revealed the following:

- (1) Global hypokinesia.
- (2) Left ventricular ejection fraction 25%.
- (3) Mild mitral regurgitation, no mitral or aortic stenosis, and no aortic or tricuspid regurgitation.
- (4) Dilated cardiomyopathy with severe left ventricular dysfunction.

The pulmonary function tests showed normal spirometry. The nerve conduction studies showed no abnormality.

As for genetic testing, MLPA testing was carried out, with specific reference to possible mutation/deletion of dystrophin gene on P arm of X chromosome. The MLPA revealed deletion of exons 3 to 7 in the short arm of X chromosome (Xp21).

Diagnosis: on the basis of history, clinical examination, investigations, and genetic testing, it was apparent that this patient was suffering from either dystrophinopathy or sarcoglycanopathy. Sarcoglycanopathy is an autosomal recessive disorder involving limb girdle muscular dystrophy. This case fits into dystrophinopathy (either DMD or BMD, both of whom are X-linked recessive disorders). Clinical features strongly point to intermediate stage of DMD/BMD. Hence, this patient was diagnosed with ‘Dystrophinopathy: DMD–BMD Intermediate Complex.’

## DISCUSSION

The present case holds importance in being one of the intermediate types of DMD–BMD accounting for clinical presentations that may be quite difficult to interpret in the first instant. Such cases of intermediate type of DMD–BMD have been seldom reported in literature among various countries [1].

In one of the cohort studies, published from India [1], six cases of intermediate phenotype were reported among a total



**Figure 3:** Lordotic posture

**Table 1: Power of various groups of muscles of upper and lower limb**

Muscle group	Right	Left
Shoulder abductors (deltoid, supraspinatus, infraspinatus, teres minor, and subscapularis)	4+	4+
Elbow flexors (biceps, brachialis, and coracobrachialis)	5	5
Wrist extensors (extensor digitorum, extensor carpi radialis and ulnaris )	5	5
Hip flexors (psoas major and iliacus)	4–	4–
Hip extensors (gluteus maximus and hamstrings)	4–	4–
Knee flexors (hamstrings)	4–	4–
Knee extensors (quadriceps femoris)	4–	4–
Ankle plantar flexors (gastrocnemius, soleus and tibialis posterior)	4–	4–
Ankle dorsi flexors (tibialis anterior, extensor hallucis longus, extensor digitorum longus)	4+	4+

**Table 2: Investigational findings**

Parameters	Patient value
Hb	14.8 gm%
TLC	7900/mm <sup>3</sup>
DLC	P52L38M06E04
Platelets	3.20 lakh/mm <sup>3</sup>
Urea/creatinine	24/0.4 mg %
Na/K	142/3.8 mEq/l
BiI/AST/ALT	0.4/132/148
Total protein/albumin	7.8/3.4 mg %
CPK (patient)	6492 IU/l
CPK (mother)	138 IU/l
CPK (brother)	166 IU/l
CPK (sister)	718 IU/l

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bil, bilirubin; CPK, creatinine phosphokinase; Hb, hemoglobin; K, potassium; Na, sodium TLC, total leukocyte count.

of 317 patients with DMD–BMD. The differences in the phenotypic expressions of the patients are accounted by the type of mutations among which deletions and duplications are the most common.

MLPA is one of the most reliable used screening tool to analyze the cases of muscular dystrophies, which shows high sensitivity in identifying deletions and applications in the DMD gene in the range of 63–79.5% [7–9].

In the present study also MLPA identified exon deletions of 3 to 7 in the short arm of X chromosome, which is typical of DMD–BMD. In comparison with our study, Vengalil *et al.* [1] also found all intermediate cases occurring due to deletions with most common being single exon deletion (Exon 50).

Our case had an age of 18 years with raised serum CPK levels (due to muscle degeneration) and cardiomyopathy, which can be accounted for by the deposition of connective tissue in the myocardium during the developmental process of the child. This was accompanied by a delay in motor activities as shown by the history of the parents. Although no family history of similar disease was present, the sibling also showed increased CPK levels.

The age of presentation has varied across studies based on the phenotypic expression, like in Vengalil *et al.* [1], where the age of presentation was 9.5 years, in Miao *et al.* [4], where the age of presentation was 9 years, in Eashwar *et al.* [6], and in Nassoro *et al.* [3], where the age of presentation was 11 years.

Owing to a defect in the sarcolemmal protein-DMD, there is progressive weakness with motor delays since the childhood depending upon the proportion of the gene that is defective [1–5]. The pathogenesis rests on the defective cycles of muscle contraction causing depositions of fibro fatty tissue, weakening of the limb muscles, resulting in symptoms like motor delays and dependency on wheelchair. The symptoms are not only restricted to the limb muscles but also involve the heart muscles as this protein is present in the myocardium and is involved in its functioning. The subtle and overt cardiac involvement as seen by defective protein leads to defective contraction causing low ejection fraction and resultant dilated cardiomyopathy. This has been observed to be one of the causes leading to death of the patient [2,6].

Besides the association with cardiac involvement, the brain involvement has also been seen, wherein a case of BMD presented with epilepsy and dysgnosia in relation to duplication mutation of the dystrophin gene [4].

Literature presents that cardiac involvement and brain involvement are the two associated complaints in relation to muscle weakness which are more seen in BMD as compared to DMD [4]. Our case presented with only cardiac involvement with no brain involvement (average academic performance) without overt cardiac failure which led to a promising diagnosis of intermediate type of DMD–BMD.

The importance of proper history and examination in a case of suspected myopathy cannot be over-emphasized. The perinatal history is important to rule out birth defects, genetic diseases like down syndrome, and associated complications, which could have led to such symptoms.

It is essential to have certain differentials in mind while diagnosing such a case. The predominantly motor syndromes that may mimic the condition include amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, polymyositis, dermatomyositis, myasthenia gravis, and channelopathies. In addition, certain conditions like spinal muscular atrophy, Kennedy’s disease, hypothyroid myopathy, focal myositis, sarcoidosis, amyloidosis, cysticercosis, limb-girdle muscular dystrophies, and muscle tumors may show pseudohypertrophy of calf muscles which may create a diagnostic dilemma with DMD–BMD.

From the point of view of investigations, raised CPK levels seem to be very specific in diagnosing muscular dystrophy set is DMD–BMD. In relation to this, conditions like motor neuron diseases, amyotrophic lateral sclerosis, spinal muscular atrophy, postpolio syndrome, drug toxicity, hypothyroidism, hypoparathyroidism, Guillain-Barré syndrome, and chronic inflammatory demyelinating polyneuropathy must be differentiated as these patients may also have markedly elevated CPK level.

Similar to the present patient who revealed global hypokinesia, dilated cardiomyopathy with severe left ventricular dysfunction, the cardiac conditions that can be associated with muscle disease include Kearns-Sayre syndrome, Andersen syndrome, carnitine deficiency, acid maltase deficiency, nemaline myopathy, nemaline myopathy, Emery-Dreifuss, myotonic, and limb-girdle dystrophy.

The clinical diagnosis of DMD–BMD after ruling out the aforementioned plethora of conditions can be made by remembering certain common essential characteristics of muscular dystrophies. First, there is no evidence of denervation or sensory loss unless there is a co-existing neuronal disease. Second, the clinical features are due to limb or cranial muscle weakness. There may be cardiac and visceral smooth muscle involvement. Third, there is progressive worsening of symptoms.

To further aid the diagnosis, muscle biopsy can be done from biceps or vastus lateralis which may show specific changes in the sarcolemmal complex and degeneration and regeneration of muscle fibers, without any abnormal storage of metabolic product. At a well-equipped center, genetic analysis holds the key as it may clinch the deletions and duplications in the dystrophin gene located in the short arm of chromosome X.

## CONCLUSION

The intermediate form of DMD–BMD shows progressive muscle weakness which may start at the age of 3 years without wheelchair dependency even by the age of 18 years.

This case presentation highlights the importance of thorough history taking and meticulous examination in arriving at a clinical diagnosis. This should be supplemented with proper investigations, which include hematological and biochemical

tests, radiography and echocardiography, EMG, muscle biopsy, and genetic tests to make a definitive diagnosis.

A definitive diagnosis helps the clinician provide necessary counseling to patient and his parents, especially regarding the course and prognosis of this disorder. As conditions like DMD and BMD do not have any cure, counseling helps parents to accept the presence of this genetic disorder in their sibling and provide him/her with maximum supportive care.

#### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

#### Conflicts of interest

There are no conflicts of interest.

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