Bethlem myopathy: An autosomal dominant myopathy with flexion contractures, keloids, and follicular hyperkeratosis

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Abstract

Bethlem myopathy and Ullrich congenital muscular dystrophy form a spectrum of collagenopathies caused by genetic mutations encoding for any of the three subunits of collagen VI. Bethlem phenotype is relatively benign and is characterized by proximal dominant myopathy, keloids, contractures, distal hyperextensibility, and follicular hyperkeratosis. Three patients from a single family were diagnosed to have Bethlem myopathy based on European Neuromuscular Centre Bethlem Consortium criteria. Affected father and his both sons had slowly progressive proximal dominant weakness and recurrent falls from the first decade. Both children aged 18 and 20 years were ambulant at presentation. All had flexion contractures, keloids, and follicular hyperkeratosis without muscle hypertrophy. Creatinine kinase was mildly elevated and electromyography revealed myopathic features. Muscle imaging revealed severe involvement of glutei and vasti with "central shadow" in rectus femoris. Muscle biopsy in the father showed dystrophic changes with normal immmunostaining for collagen VI, sarcoglycans, and dysferlin.

Key Words

Bethlem myopathy, collagen VI, contractures, immunohistochemistry, keloids

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Ann Indian Acad Neurol 2013;16:712-5

Introduction

Bethlem myopathy (BM) and Ullrich congenital muscular dystrophy (UCMD) are due to mutations in the genes encoding collagen VI subunits which are the important components of the extracellular matrix.[1,2] UCMD has autosomal recessive inheritance with severe phenotype whereas BM is autosomal dominant, relatively benign, and is characterized by slowly progressive myopathy, flexion contractures of joints, hypermobility of interphalangeal joints, keloid formation, and follicular hyeprkeratosis. Though respiratory muscle involvement can occur in late stages of BM, cardiac involvement is uncommon.[3] Diagnosis of BM is based on clinical features, molecular diagnosis, and immmunostaining for collagen VI in muscle and skin fibroblast cultures.[4-7] The prevalence of BM is 0.77 per 100,000 and that of UCMD is 0.13 per 100,000.[8] We report three male patients from a single family with clinical phenotype of BM.

Access this article online	
Quick Response Code:	Website: www.annalsofian.org
	DOI: 10.4103/0972-2327.120453

Case Report

The proband was a 45-year-old teacher born of non-consanguineous parentage presenting with recurrent falls since the age of 10 years. His mental and motor milestones were normal. He noticed predominantly proximal weakness of all four limbs and continued to perform his daily activities without assistance. He had difficulty in climbing stairs and rising from the floor. He had sustained multiple injuries from recurrent falls resulting in multiple keloids over sites of injury. The weakness progressed very slowly till 40 years of age after which the weakness progressed more rapidly and he stopped riding a two-wheeler. One month prior to admission he developed cough, breathlessness with worsening of weakness which prevented him from attending work and became dependent for activities of daily life.

On examination, he was breathless with 24 breaths per minute. Cardiovascular examination was normal. There were

multiple keloids over chest and both feet [Figure 1] along with follicular hyperkeratosis [Figure 2]. Contractures were noted at elbow, knee, hip, and ankle with hyperextensibility of fingers. He was alert with normal mental functions and cranial nerves function. Neck muscles were mildly weak with symmetrical quadriparesis (Medical Research Council grade 2 to 3/5 proximally and 4/5 distally) with atrophy of proximal muscles. Sensations were intact and muscle stretch reflexes were absent. Contractures were noted at elbow, knee, hip, and ankle with distal hyperextensibility of fingers. He succumbed to respiratory insufficiency few weeks after discharge.

Both his sons too presented with predominant proximal muscle weakness of all four limbs. Elder son was 20-years-old with symptom onset at 7 years of age. He had recurrent falls with infected keloids over both feet that had been excised. He needed maximum help to stand and could walk with difficulty. The second son was 18-years-old with onset at 9 years of age. He had mild proximal weakness of all four limbs and had occasional falls. He was independent for activities of daily life. Both had high arched palate, follicular hyperkeratosis and proximal dominant quadriparesis with flexion contractures involving elbow, knee, and ankles with distal hyperextensibility of fingers. Higher mental functions were normal in all the three patients. There was no history of similar illness in any of the family members traced back to four generations [Figure 3].

Electrocardiography and echocardiography were normal in all the three patients. Muscle enzymes were normal in the father, and mildly elevated in both children. Needle electromyography in father and the elder son revealed myopathic features with normal nerve conduction studies. Left biceps brachii muscle biopsy in the father revealed effaced architecture with fibrosis, adipose tissue infiltration, rounding of muscle fibers, increased variability of fiber diameter and myonecrosis. Myophagocytosis with few regenerating fibers in addition to mild perivascular inflammation was seen [Figure 4]. Enzyme histochemistry revealed numerous lobulated fibers and type I fiber predominance. A few ragged fibers were noted on modified Gomori trichrome. Immunostaining with monoclonal antibodies against collagen VI A1, dysferlin, and sarcoglycans (α, β, γ, and δ) revealed normal staining pattern [Figure 5].

Magnetic resonance imaging (MRI) of the thigh muscles revealed selective involvement of anterior thigh muscles in the father. Computerized tomography (CT) of thigh in the elder son revealed preferential involvement of vasti and glutei compared to the hamstrings, adductors, and sartorius. There was central hypodensity in rectus femoris suggestive of "central shadow" sign [Figure 6].

Discussion

We describe a family with classical phenotype of BM with keloids, follicular hyperkeratosis, and characteristic findings on muscle imaging. BM is a rare disease presenting with early onset myopathy and disabling contractures and tendency to keloid formation. It is grouped under collagenopathies with mutations of collagen VI encoding genes.[6,7,9] Myopathy with contractures is seen in Emery Dreifuss muscular dystrophy (EDMD),

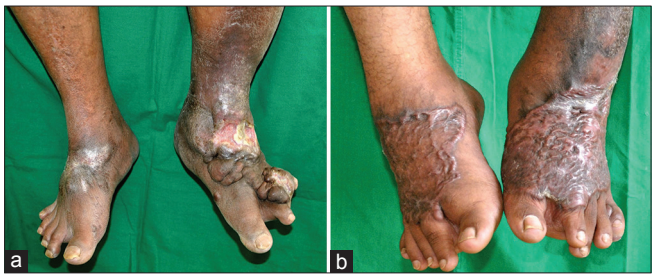

Figure 1: (a) Keloids in the left foot with loss of third toe and non-healing ulcers in the father and (b) scars after removal of the infected keloids in the elder son

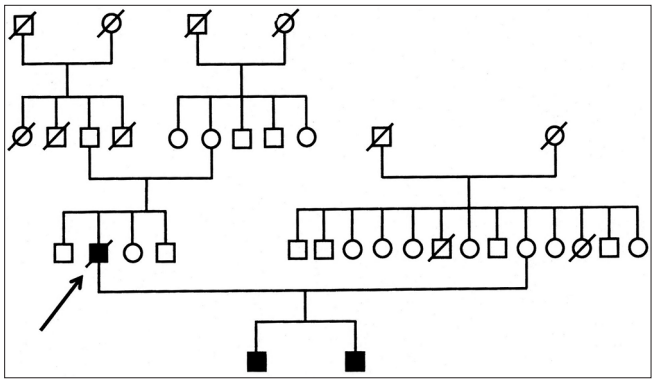

Figure 3: The pedigree chart of the Bethlem myopathy family

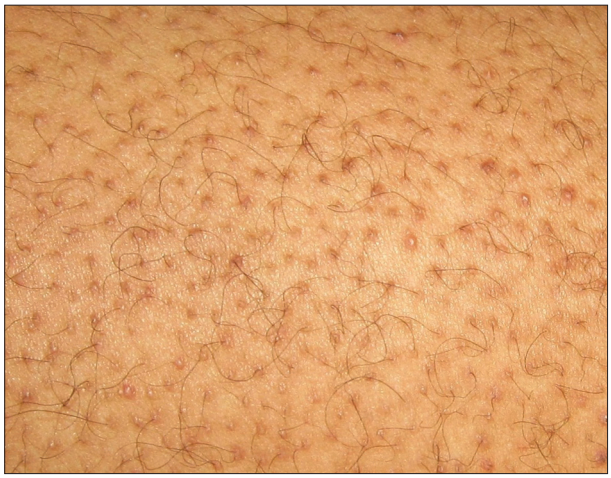

Figure 2: Cutaneous follicular hyperkeratosis in the elder son

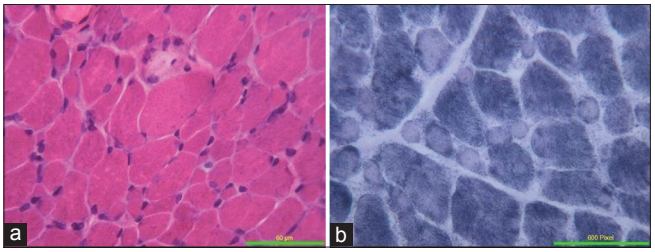

Figure 4: Transverse section of left biceps brachii muscle. (a) Variation in diameter with myophagocytosis and muscle fiber splitting are seen in H and E stain. (b) Oxidative stain for succinic dehydrogenase reveals lobulated fibres

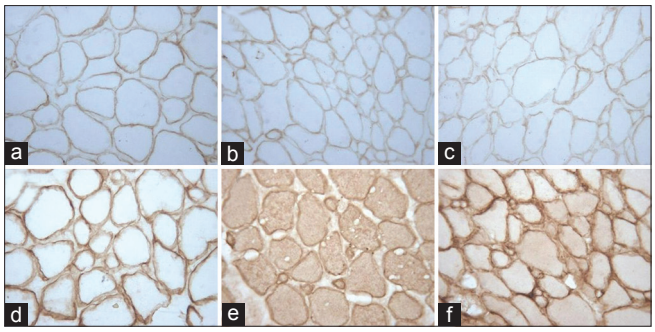

Figure 5: Uniform labeling in all muscle fibers in immunohistochemistry using monoclonal antibodies to α, β, γ and δ sarcoglycans (a, b, c and d), dysferlin (e) and collagen α6 (f)

Xp21 myopathy, early onset limb girdle muscular dystrophy, congenital muscular dystrophy, BM, and UCMD. BM was described by Bethlem and Wijngaarden in 1976 in 28 affected members from three families.[10] UCMD and BM form two ends of clinical spectrum of collagenopathies with UCMD having severe manifestations.[3] UCMD patients have severe muscle weakness progressing to respiratory insufficiency, velvety skin, and posteriorly prominent calcanei.[9] The characteristic common phenotypes of these two disorders include flexion contractures, keloid formation, follicular hyperkeratosis, and predominantly proximal myopathy.

Our patients had childhood onset autosomal dominant proximal myopathy with relatively benign course and multiple keloids conforming to the clinical criteria of the European Neuromuscular Centre Bethlem Consortium.[11] Though BM is inherited as autosomal dominant and UCMD as autosomal recessive, heterogeneous inheritance has also been described in both the conditions.[12] Common differential diagnosis of BM include autosomal dominant form of EDMD2 due to mutations in lamin A gene, as the latter disease also has early contractures with humeroperoneal weakness. Presence of dilated cardiomyopathy and conduction defects in EDMD2 differentiate it from BM.

Muscle imaging with CT scan and MRI plays an additional important diagnostic tool in the evaluation of myopathies. CT scan and MRI of thigh and leg muscles reveal specific pattern of muscle involvement in EDMD and collagen VI related myopathies. Anterior group of thigh muscles are more involved with fatty infiltration within the muscle showing peripheral involvement in selected muscles. Rectus femoris revealed "central shadow" sign due to selective fat deposition. In EDMD2, hamstring muscles are significantly involved with sparing of rectus femoris. In the more advanced BM and UCMD patients, there is diffuse involvement of thigh muscles with relative sparing of medial muscles. Limb girdle muscular dystrophy 2A phenotype has predominant involvement of adductor magnus and posterior thigh muscles and in laminopathies, vasti were more predominantly affected.[13] MRI and CT scan in our patients revealed central shadow sign in rectus femoris and dominant involvement of anterior thigh muscles with relative sparing of hamstring muscles which has been reported to be specific for collagen VI deficiency.[14]

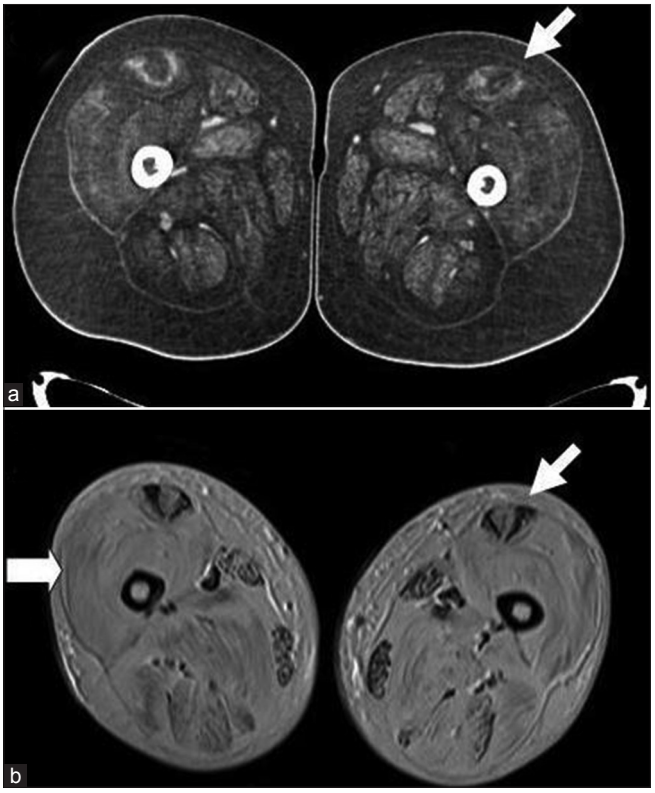

Figure 6: Axial CT scan in the elder son (a) and T2 weighted axial MR image in the father (b). Images show "central shadow" in rectus femoris in both (white arrow head) and predominant quadriceps involvement (thick white arrow)

Muscle biopsy in the father showed dystrophic changes with normal staining for collagen VI. Immunofluorescent (IF) labeling in muscle biopsies of mild to moderately involved BM patients may be normal. In contrast, IF labeling of cultured fibroblasts from skin biopsies show abnormal collagen VI staining in patients with BM thereby ascertaining role of fibroblast culture in diagnosis of BM.[3] Though molecular genetic study is the gold standard for the diagnosis of BM, it is expensive and not easily available. Genetic abnormalities in BM are linked to chromosome 21q (COL6A1 and COL6A2) and chromosome 2q (COL6A3). There can be single amino acid substitution, mutations in N-terminal region of triple helical domain causing kinking of tetramers and reduced formation of microfibrils. Splice mutations causing skipping of COL6A1 exon-14 can also be seen.[6,7]

Extracellular matrix and basal lamina molecules are crucial for the stability of the muscle, regeneration, and maintain integrity of the myocytes during the contraction. Collagen VI forms a microfibrillar network in association with basement membrane. Disruption of assembly of collagen VI due to genetic mutations lead to impaired binding of collagen in the extracellular matrix leading to myopathy.[1,6] Mitochondrial defect due to inappropriate opening of permeability transition pores leading to muscle cell death has been demonstrated in mouse models of collagen VI deficiency.[9]

Patients with BM are known to have an early onset hypotonia, dynamic contractures, and a relatively prolonged benign course. Half the patients are reported to attain wheelchair-bound state

by fifth decade of life. The more severe forms of BM may develop respiratory insufficiency. Our proband had progressed to severe disability in fifth decade and succumbed to respiratory insufficiency as in markedly progressive Bethlem phenotypes. Three members from two different families presenting with characteristic features of BM and muscle biopsy findings were reported earlier from India.[15] We report another family with Bethlem phenotype, pattern of muscle involvement on imaging, enzyme histochemistry with immunostaining for collagen VI in muscle biopsy from Indian subcontinent.

Conclusion

BM is a rare disease presenting with early onset myopathy and disabling contractures, with tendency to keloid formation. It is grouped under collagenopathies with mutations of collagen VI encoding genes.

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How to cite this article: Saroja AO, Naik KR, Nalini A, Gayathri N. Bethlem myopathy: An autosomal dominant myopathy with flexion contractures, keloids, and follicular hyperkeratosis. Ann Indian Acad Neurol 2013;16:712-5.
Received: 25-08-12, **Revised:** 16-10-12, **Accepted:** 31-10-12
Source of Support: Nil, **Conflict of Interest:** Nil