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A DIAGNOSTIC DILEMMA BETWEEN POLYMYOSITIS AND DYSFERLINOPATHY – 'DIAMOND ON QUADRICEPS' SIGN CAN BE A SAVIOUR

Neurology

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ABSTRACT

Dysferlinopathies encompass a large variety of neuromuscular disease characterized by the absence of dysferlin in skeletal muscle and an autosomal recessive mode of inheritance. Dysferlin is a large protein involved in membrane repair and vesicle trafficking and interacts probably with important immunological pathways. Here we present a case of a patient who presented with bilateral proximal pure motor muscle weakness of 18 months duration followed by right upper limb proximal weakness and atrophy of distal half of biceps muscle. No significant family history was evident. Patient had grossly elevated CPK and EMG revealed features of polymyositis. Clinical examination revealed bilateral 'diamond on quadriceps' sign, specific for dysferlinopathy. Subsequently genetic analysis revealed heterozygous mutation in dysferlin gene.

KEYWORDS

Dysferlin Muscle Biopsy Myopathy LGMD

INTRODUCTION

Limb – girdle muscle dystrophy (LGMD) is the most common adult-onset muscular dystrophy in India. LGMD subtype classification is generally based on immune-characterization on muscle biopsies and clinical presentation with sarcoglycanopathies (LGMD2C – F) being the most common subtype identified in India and dysferlinopathies being the second most common identified LGMD subtype (1)(2). However, a large group of LGMD patients remain unclassified, in a vast population like India with limited diagnostic resources available to patients (1).

LGMD2B and Miyoshi myopathy (MM) are autosomal recessive forms of muscular dystrophy caused by pathogenic variants in the dysferlin gene (DYSF gene) located on chromosome 2p13 (3)(4). The dysferlin gene comprises 55 exons spanning more than 150 kb, and encodes a 230 kDa transmembrane protein which is highly expressed in the muscle (3)(5). The dysferlin protein is localized at the sarcolema of muscle cells and is known to be involved in membrane fusion events and appears necessary for calcium dependent muscle membrane repair of the muscle following damage (6). Disruption in the muscle repair mechanism leads to dysferlin deficient muscle degeneration (7).

Disease begins between ages 15 and 25 years, adult onset, predominantly with proximal muscle weakness, slow progression and with marked elevation in muscle CK levels (8)(9)(10)(11). Both MM and LGMD2B share similar features, however, the pelvic girdle distribution of weakness distinguishes LGMD2B from MM (distal onset). It is known that both LGMD2B and MM can co-exist in the same family. Both MM and LGMD2B are demonstrated to be allelic disorders with both being linked to the same locus of chromosome 2p13(8)(12)(13) and include the DYSF gene encoding the protein dysferlin (14)(15). In the present study we report the clinical characteristics, histopathological and immunohistochemical findings in patient with dysferlinopathy and how a clinical sign of diamond on quadriceps can be helpful in differentiating polymyositis and dysferlinopathy.

CASE REPORT

A 26 years old male admitted with complaints of difficulty in getting up by himself for past 18 months. Patient walk with waddling gait on either side and gradually noticed thinning of both lower limbs at hip and calf muscles. This was associated with thinned out distal half of biceps muscle and weakness of right upper limb since past 1 month and inability to perform overhead activities. No history of any imbalance / sphincter dysfunction / fasciculation / sensory abnormality reported.
On examination all the vital parameters were normal. Neurological examination revealed a conscious, alert, obeying, language / speech / higher mental functions were intact, no cranial nerves involved, orbicularis oculi normal, bilateral pupil 2mm reactive, EOM full, motor system examination revealed right upper limb biceps atrophy (distal > proximal), bilateral 'diamond on quadriceps' sign present (+). (Figure. 1,2) Bilateral calf atrophy present with power of 4-/5. Plantar flexor bilaterally. Other reflexes and sensation were normal. Patient had additional findings in the form of multiple café-au-lait macules > 1.5 mm in dimension, largest being 10 X 12 cm over right calf (Figure. 3) with multiple neurofibromas all over the body.

Nerve conduction studies (NCV + EMG) revealed myopathic pattern with multiple positive sharp waves and fibrillation potentials with early recruitment, suggestive of inflammatory myopathy – polymyositis. CPK – 7000. Serum TSH, Vitamin B12, Calcium was normal, electrocardiogram and 2D ECHO were normal. Muscle biopsy from left vastus lateralis revealed partial distortion of architecture with isolated muscle fibres degeneration and regeneration along with fibrosis with isolated necrotic fibres were also noted, suggestive of dystrophic muscle (white arrow) with no definitive evidence of polymyositis (Figure. 4, 5). Monocyte western blotting showed absent dysferlin band. Genetic analysis revealed one heterozygous disease causing mutation in exon 54, predicted to cause the replacement of an arginine residue by a cysteine at position 2042 of the dysferlin protein.

Figure. 1 Left 'diamond on quadriceps' sign

Figure. 2 Right 'diamond on quadriceps' sign

Figure. 3 Multiple café-au-lait macules > 1.5 mm in dimension, largest being 10 X 12 cm over right calf.

DISCUSSION

Dysferlin plays a role along with, and in coordination with a group of protein such as annexin, caveolin -3, tubulin, dihydropyridine receptor and ryanodine receptor in remodeling the cell skeleton. It plays a role in the repair of muscle cell membrane. A false diagnosis of polymyositis is frequent in LGMD2B. According to Dr. Sunil Pradhan's study on a clinical sign in a group of 31 patients with dysferlinopathy that included 13 with LGMD-2B and 18 with Miyoshi myopathy (MM). The patients were asked to stand with knees slightly bent so that the quadriceps muscles were in moderate action. Around 70% were found to have diamond-shaped bulge in this region with wasting of muscles above and below. This bulge was not apparent in standing or sitting position when quadriceps muscle was not in action. They inferred that nearly two-thirds of the patients with dysferlinopathy demonstrate 'diamond on quadriceps' sign (16).

Diamond on quadriceps sign indicates selectivity of dystrophic process not only among different muscles but also within a muscle as suggested earlier (17). The sign was absent in rest other muscular dystrophies, suggesting high specificity for dysferlinopathy. Massive elevation of serum CK con- centration is thought (4,13) to be one of the typical LGMD2B symptoms, but it is not a specific marker – it only suggests muscle damage. Recently, Fanin *et al*. (18) found that males with LGMD may be clinically more severely affected than females, although the mechanism remains elusive.

According to Dr. Pradhan's observation enlargement of some muscles and wasting of some other individual or group of muscles is well known in muscular dystrophies (19-21). What is less well known, however, is the fact that different parts of a particular single muscle may also show enlargement in one part and wasting in another part (22) .For example, in Duchenne muscular dystrophy it has been demonstrated that the muscle fibers of vastus lateralis part of the quadriceps muscle are often enlarged but that of vastus medialis part are wasted in their whole length. Sometimes a segment along the length of the muscle is enlarged and another segment is wasted. For example, enlarged fibers of deltoid and infraspinatus muscles in Duchenne muscular dystrophy show wasting in parts that traverse and contribute to the posterior axillary fold (22-24). Similarly, in facioscapulohumeral dystrophy deltoid muscle fibers are well preserved or enlarged in lower two-thirds of their length but are wasted in upper one-third (25). The selective wasting, selective preserved bulk, and the selective enlargement of whole or part of the muscle that becomes more conspicuous when the muscles are in action, as happens when a patient adopts a particular posture, has been made the basis of several of the clinical signs described recently (23-27). In this context, the present study demonstrates that dysferlinopathies have a tendency for wasting of quadriceps femoris muscle, particularly its two components vastus lateralis and rectus femoris, in their upper and lower parts with some sparing or somewhat enlargement in the middle part. The demarcation between wasted and the spared segments of the muscle fibers is so sharp that whenever the muscle is in action its central part bulges out in the shape of a diamond (28) .Our patient had multiple café-au-lait spots with multiple neurofibromas, although extensive literature search did not reveal any significant association of LGMD/Muscular dystrophy and neurofibromatosis. This might imply that both the findings could be mere incidental or there might be some possible genetic mechanism responsible for evolution of both diseases in the patient which needed to be evaluated in future studies.

According to these observations and from our clinical assessment of positive diamond sign we considered the possibilities of dysferlinopathies with keeping polymyositis as the closest differential diagnosis. The muscle biopsy and genetic study later confirmed the diagnosis of dysferlinopathy. Hence, we can propose that the clinical sign 'diamond on quadriceps sign' for the diagnosis of dysferlinopathies and can differentiate polymyositis with high degree of certainty and therefore this sign must be searched before ordering invasive, expensive and remotely available test, particularly in country like India.

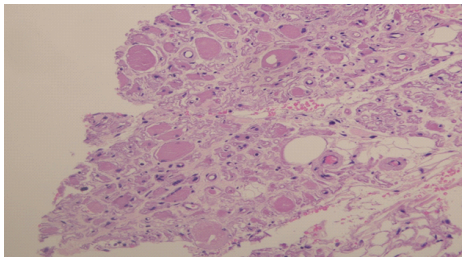

Figure. 4 a – Muscle Biopsy: Partial distortion of architecture with isolated muscle fibres.

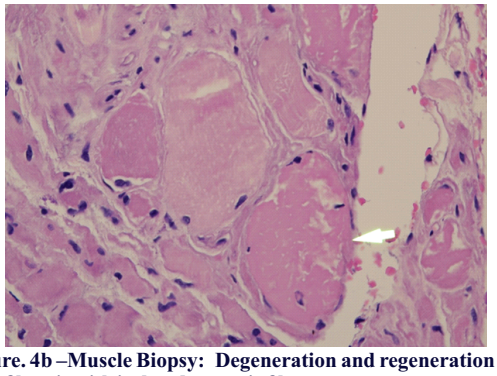

Figure. 4b –Muscle Biopsy: Degeneration and regeneration along with fibrosis with isolated necrotic fibres.

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