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Case Report

Emery Dreifuss muscular dystrophy masquerading as limb girdle muscular dystrophy type 2 due to a novel mutation in emerin gene

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Abstract

Emery-Dreifuss muscular dystrophy (EDMD) is a rare muscular dystrophy with frequent life-threatening cardiac complications. It classically presents with muscle weakness, early contractures, cardiac conduction abnormalities and cardiomyopathy. Atrial and ventricular tachyarrhythmias, atrial standstill and cardiomyopathy are the common cardiac manifestations and can precede significant skeletal muscle weakness. Here we describe a case of EDMD, initially misdiagnosed as limb girdle muscular dystrophy due to absence of elbow contracture. Our case is unique in that it is due to a novel mutation in exon 6 of EMD gene which is so far not reported from India.

Keywords: Emery dreifuss muscular dystrophy, Emerin, Limb girdle muscular dystrophy.

Received: 26-06-2025; **Accepted:** 24-09-2025; **Available Online**: 28-10-2025

1. Introduction

Emery-Dreifuss muscular dystrophy (EDMD) (OMIM#310300) is a rare but clinically significant form of muscular dystrophy due to its frequent and potentially life-threatening cardiac complications. The classic presentation of EDMD can be described as a "triad within a triad." The main triad includes early-onset joint contractures, progressive muscle weakness and atrophy, and cardiac abnormalities. A secondary triad highlights the typical pattern of contractures, affecting neck extensors, elbow flexors, and Achilles tendons.[1] Muscle weakness in EDMD follows a characteristic humero-peroneal distribution and progresses slowly over time. Rarely do they present as limb girdle muscular dystrophy without prominent contractures.[2,3] Cardiac involvement, often manifesting as conduction defects and dilated cardiomyopathy, is the most critical aspect of the disease. While cardiac symptoms typically appear after the onset of muscle weakness, they may occasionally precede significant muscular involvement. By the age of 30, nearly all individuals with EDMD show some degree of cardiac involvement. Initially ECG may show low amplitude P waves with first degree heart block and subsequently, they develop atrial fibrillation or flutter. However, the most characteristic ECG finding is junctional rhythm without P waves due to atrial standstill. Generally, the cardiomyopathy of EDMD affects the atria first, later ventricles are affected leading to ventricular dilatation and dilated cardiomyopathy.[4] Mutation of EMD can underlie X-linked familial AF in the absence of skeletal muscle disease.[5]

2. Case Report

A 15-year-old boy born of a non-consanguineous marriage presented to a tertiary care center with progressive difficulty in getting up from squatting posture and difficulty in climbing stairs since the age of 4 years. Evaluation at that time showed proximal lower limb >upper limb weakness. There was bilateral Achilles tendon contracture (**Figure 1**c).

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https://doi.org/10.18231/j.ijn.12018.1759739242

Table 1: Electromyography findings

Muscle	Spontaneous activity	MUAP	Interference pattern
Tibialis anterior L	Nil	Small, polyphasic	Early, complete
Gastrocnemius L	Nil	Small, polyphasic	Early, complete
Quadriceps L	Nil	Small, Polyphasic	Early, complete
Deltoid L	Nil	Normal, Polyphasic	Early, complete
Biceps L	Nil	Small, Polyphasic	Early, complete

There was no elbow flexor or neck extensor contracture. There was exaggerated lumbar lordosis with a waddling gait. Deep tendon reflexes were absent except ankle jerks. There was no calf hypertrophy (**Figure 1**b). There was no family history of similar illness or sudden death. Nerve conduction study was normal. Electromyography showed low amplitude polyphasics with early recruitment suggestive of myopathy (**Table 1**).

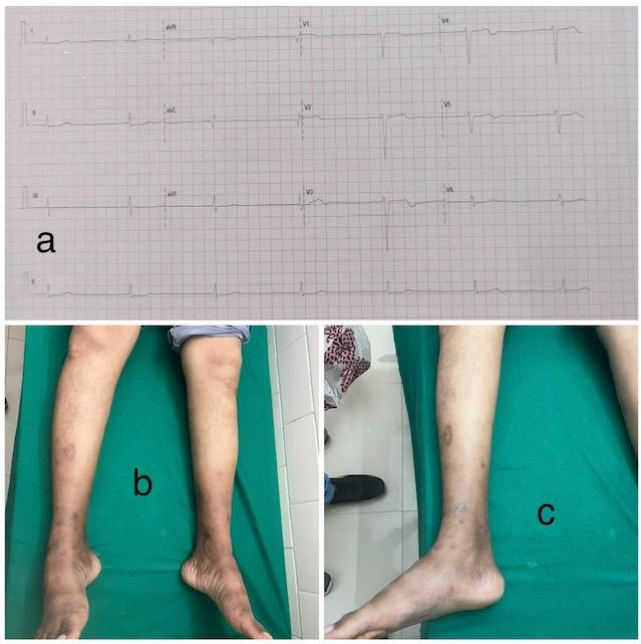

Figure 1: a: Electrocardiogram showing junctional rhythm; **b:** Bilateral calf atrophy; **c:** Ankle contracture

His creatine phosphokinase was 2230 IU/L (Normal <190 IU/L). Muscle biopsy was done from quadriceps femoris in 1998 and was reported as dystrophy. He was labelled as Limb girdle muscular dystrophy Type 2. Immunostaining was not available at time and was not done. At the age of 23, he presented with dyspnoea on exertion and evaluation showed junctional rhythm and dilated cardiomyopathy (**Figure 1**a). He had an episode of stroke-right middle cerebral artery infarct, at the age of 40 years and recurrence of stroke in same territory one year later. He presented to our institution with an episode of transient ischemic attack. In view of muscular dystrophy, junctional rhythm and dilated cardiomyopathy blood was sent for clinical exome sequencing. A hemizygous nonsense variant in exon 4 of the *EMD* gene (chrX:g.154380282dup; Depth: 77x) that results in a stop codon and premature truncation of the protein at codon 105 (p.Tyr105Ter; ENST00000369842.9) was detected. This variant is reported as likely pathogenic. The same mutation at the same location was detected in his 64-year-old asymptomatic mother. He has a son who is asymptomatic. The p.Tyr105Ter variant has not been reported in the 1000 genomes, gnomAD (v3.1), gnomAD (v2.1), topmed and Medgenome databases.

3. Discussion

In 1966, Alan H Emery and F. E Dreifuss described a family with proximal muscle weakness with early elbow and Achilles tendon contracture without calf hypertrophy and a benign course with X linked inheritance.[6] The prevalence of EDMD is around 1/100 000 for the X-linked form and autosomal dominant and autosomal recessive variants are extremely rare. The gene responsible for the X-linked form was identified in 1994 as *Emerin* (*EMD* gene or STA gene). It is located on chromosome Xq28. The *STA* gene encodes a protein, 'Emerin'. The major role of the emerin-nuclear protein complex is to stabilize the nuclear membrane against the mechanical forces that are generated in muscle cells during contraction. EDMD is a nuclear envelopathy. Several genes have been implicated in the pathogenesis of EDMD. There are 7 EDMD subtypes. EDMD1 (gene: *EMD*, protein Emerin), EDMD2 (gene *LMNA*, protein Lamin A/C, autosomal dominant), EDMD3 (gene *LMNA*, protein-Lamin A/C, autosomal recessive inheritance), EDMD4 (gene *SYNE1*, protein- nesprin-1), EDMD 5 (gene SYNE2, protein-nesprin-2), EDMD6(gene *FHL1*, protein- FHL1) and EDMD 7(gene *TMEM43*, protein-LUMA). Other genes implicated in EDMD are *SUN1*, *SUN2* and *TTN* encoding proteins SUN domain containing protein 1, SUN domain containing protein 2 and Titin respectively. Our patient had EDMD type 1 due to a novel mutation in exon 4 of *Emerin* gene. There are only very few reports of EDMD from Indian subcontinent and most common mutation was in exon 6.[6-9]

Cardiac involvement is a common feature of EDMD and is strongly associated with an increased risk of sudden death. Importantly, the severity of cardiomyopathy does not correlate with the extent of skeletal muscle involvement. Female carriers are also at elevated risk of sudden cardiac events, and the likelihood of arrhythmias increases with age. In patients presenting with a limb-girdle muscular dystrophy phenotype, EDMD should be considered—even in the absence of classic elbow contractures—particularly when cardiac rhythm abnormalities or cardiomyopathy are present.

4. Conclusion

Emery Dreifuss muscular dystrophy can present as limb girdle muscular dystrophy and genetic analysis is important as it is often associated with cardiac arrythmias and cardiomyopathy with potentially grave consequences.

5. Author Contributions

1. Somarajan Anandan: Concept, Design, Work up, Manuscript writing
2. Sajeesh Rajendran: Editing, Design
3. Joesni Joy: Literature search
4. Sisira Sree Rajan: Literature search, Editing

6. Source of Funding

None.

7. Conflicts of Interest

None.

8. Acknowledgement

None.

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Cite this article: Anandan S, Rajendran S, Joy J, Rajan SS. Emery Dreifuss muscular dystrophy masquerading as limb girdle muscular dystrophy type 2 due to a novel mutation in emerin gene. *IP Indian J Neurosci*. 2025;11(3):193-195.