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CASE REPORT

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A Sri Lankan boy with Emery-Dreifuss muscular dystrophy 5 presenting during infancy with persistent transaminitis

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Abstract

Background Emery-Dreifuss muscular dystrophy is a rare muscular dystrophy characterised by muscle weakness, joint contractures, and cardiac involvement. Among its subtypes, Emery-Dreifuss muscular dystrophy 5 typically presents with muscle weakness and cardiomyopathy during late childhood. Here, we report a Sri Lankan boy with Emery-Dreifuss muscular dystrophy 5 presenting with an unusual manifestation of persistent transaminitis detected during infancy.

Case presentation A 21-month-old boy is admitted for further evaluation of high transaminases detected at nine months of age. He was the first-born child of healthy, non-consanguineous parents with an uncomplicated perinatal period. At nine months, he was found to have high transaminases (aspartate transaminase- 230IU/L and alanine transaminase- 234IU/L), which had persisted. He had marginal isolated gross motor developmental delay; however, he could walk unaided at 18 months. Examination revealed pseudohypertrophy of the calf and positive Gower's sign. Lower limb tone and tendon reflexes were normal, and there were no joint contractions. He did not have dysmorphic features or peripheral stigmata of chronic liver disease.

Investigations revealed persistently high aspartate and alanine transaminases and very high creatine phosphokinase of 15625 U/L. Abdominal ultrasonography and other liver function tests were normal. Based on normal liver function tests and high creatine phosphokinase, a muscular dystrophy was suspected. The electromyogram showed features of myopathy, and the muscle biopsy was compatible with congenital muscular dystrophy. The genetic analysis of the dystrophin gene by PCR-based amplification of 19 deletion-prone exons and copy number variation analysis did not reveal deletions in the dystrophin gene. The whole exome sequencing detected a missense splice region heterozygous variant of the *SYNE2* gene, confirming Emery-Dreifuss muscular dystrophy 5.

Conclusions Here, we report an extremely rare presentation of Emery-Dreifuss muscular dystrophy 5 during infancy with transaminitis. This case report highlights the importance of evaluating non-hepatic causes for elevated

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transaminases and the usefulness of whole exome sequencing in establishing an accurate diagnosis when relatively uncommon diseases are suspected.

Keywords Emery-Dreifuss muscular dystrophy, Muscular dystrophy, Myopathy, Transaminitis, Creatine phosphokinase

Background

Emery-Dreifuss muscular dystrophy (EDMD) is a rare form of muscular dystrophy with a prevalence of 0.3 per 100,000 [1]. It comprises several subtypes that show variable inheritance patterns. The classic clinical triad is muscle weakness, joint contractures, and cardiac involvement [2]. However, not all subtypes demonstrate all these features. Of note, joint contractures are not a feature of EDMD5. The typical manifestations of EDMD5 are muscle weakness and cardiomyopathy during late childhood. Here, we report a Sri Lankan boy with EDMD5 presenting with an unusual manifestation of persistent transaminitis detected during infancy.

Case presentation

A 21-month-old boy presented for further evaluation of high transaminases detected at nine months of age. He was the first-born child, born at term with a birth weight of 3.5 kg to healthy, non-consanguineous parents following an uncomplicated antenatal period. His neonatal period was uncomplicated except for penoscrotal hypospadias, which was corrected at 11 months.

At nine months, he was treated for acute dysentery with intravenous cefotaxime, at which point he was found to have high transaminases. Aspartate transaminase (AST) was 230 IU/L and the alanine transaminase (ALT) was 234 IU/L. The rest of the liver function tests, including alkaline phosphatase, gamma-glutamyl transferase, bilirubin, albumin, and prothrombin time, were normal. Since then, he has had elevated AST and ALT in the range of 200-800IU/L.

His development history revealed a marginal delay in achieving gross motor milestones. He had sat with support at eight months, stood with support at 15 months and walked unaided at 18 months. His fine motor skills, vision, hearing, language, and social development were age appropriate.

On examination at 21 months of age, he weighed 11.3 kg (median to −1SD), and his height was 86.5 cm (median to +1SD). He did not have dysmorphic features or peripheral stigmata of chronic liver disease. The abdominal examination did not reveal hepatomegaly or splenomegaly. The examination of lower limbs revealed pseudohypertrophy of the calves (Fig. 1) and positive Gowers sign. Lower limb muscle tone and deep tendon reflexes were normal. However, there was hip girdle muscle weakness. There were no joint contractions. Cardiovascular and respiratory systems were clinically normal.

Investigations revealed AST of 204 IU/L, ALT of 286 IU/L, and creatine phosphokinase (CPK) of 15,625 U/L. Abdominal ultrasonography, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin were normal. Based on normal liver function tests, normal abdominal ultrasonography and very high CPK, non-hepatic origin for high transaminases, possibly due to myopathy, was suspected. Further investigations revealed high lactate dehydrogenase (2713 U/L) and evidence of myopathy in the electromyogram. Muscle biopsy showed skeletal muscle fibres with variation in fibre size, atrophic fibres, basophilic regeneration of myotubules and markedly increased endomysial connective tissue suggestive of congenital muscular dystrophy. Immunohistochemical studies were not performed due to unavailability. His electrocardiogram and echocardiogram were normal, and his mother's CPK level was within normal range.

The genetic analysis of the dystrophin gene by Multiplex Ligation-dependent Probe Amplification (MLPA) of 19 deletion-prone exons (mutational hot spots) did not reveal deletions in the dystrophin gene, making Duchene muscular dystrophy unlikely. Then, we proceeded with the whole exome sequencing (WES) of the index case, looking for any pathogenic or likely pathogenic single nucleotide polymorphisms and small indels in protein-coding regions (done at Credence Genomics (Pvt) Ltd, Sri Lanka). A separate Copy Number Variation analysis was carried out to exclude large deletions and duplications on the rest of the dystrophin gene. WES revealed a missense splice region heterozygous variant of the *SYNE2* gene (NC_000014.9:g64122426 A>T [p. Gln-4474Leu]); NM_015180.6:c.13421 A>T) corresponding to the cDNA position chr14:64122434. According to the American College of Medical Genetics and Genomics (ACMG) mutation classification guidelines, the mutation was a variant of uncertain significance. However, in silico analysis by mutation tester and SIFT tools predicted the mutation is deleterious with a significant protein change (Table 1). Based on the classical clinical presentation and laboratory evidence of muscular dystrophy, identification of a variant in the *SYNE2* gene and the in silicoprediction of the deleterious variant, the diagnosis of Emery-Dreifuss muscular dystrophy 5 was made. Parental testing was advised but not done due to economic constraints.

Discussion

EDMD are a group of inherited muscular dystrophies characterized by muscle weakness, joint contractures, and cardiac involvement with arrhythmias, conduction

Fig. 1 Photographs showing calf pseudohypertrophy

Table 1 In Silico analysis of the identified variant of the *SYNE2* gene

Tool	Prediction
Aggregated	
Aggregated Prediction	Deleterious (0.8)
Functional Coding	
Revel	Benign (Moderate) (0.15)
AlphaMissense	Benign (Supporting) (0.153)
Eve	(N/A)
Varity	(N/A)
MUT Assesor	Med (2.3)
SIFT	Deleterious (Supporting) (0)
Polyphen2	(N/A)
MT	Deleterious (1)
FATHMM	Uncertain (0.57)
DANN	Deleterious (0.99)
MetaLR	Benign (low) (0.29)
PrimateAI	Benign (Moderate) (0.32)
BayesDel	Uncertain (−0.03)
CardioBoost ARM	(N/A)
CardioBoost CM	(N/A)
Splice Altering	
SpliceAI	Splice-Altering/strong (0.55)
dbscSNV Ada	Deleterious (1)
dbscSNV RF	N/A (1)
Conservation	
GERP	Uncertain (5.37)
Functional Whole Genome	
GenoCanyon	Deleterious (1)
fitCons	Deleterious (0.71)
Mitochondrial	
MitoTip	(N/A)
APOGEE	(N/A)

block, and cardiomyopathy [1]. Molecular pathology involves the defective structure or function of proteins forming the cell nuclear envelope. The clinical manifestations are more evident in tissues constantly under stress, such as skeletal and cardiac muscle [3].

Pathogenic variants in several genes, including *EMD*, *LMNA*, *SYNE1*, *SYNE2*, *TMEM43*, *SUN1*, and *SUN2*, which encodes for emerin, lamin A, nesprin-1, nesprin-2, transmembrane protein 43, SUN domain-containing protein 1 and SUN domain-containing protein 2 respectively are recognized to cause EDMD. Our patient had a variant in the *SYNE2* gene, causing aberrant nesprin-2 protein, giving rise to the clinical phenotype of EDMD5.

The nuclear envelope contains a protein bridge known as the linker of nucleoskeleton and cytoskeleton complex (LINC) that connects the nucleus and cytoskeleton through the nuclear envelope. The LINC is made up of emerin, lamin A, nesprin-1, nesprin-2 and SUN domain-containing proteins 1 and 2. Nesprins support the structural integrity and localisation of the nuclear envelope by functioning as connecting partners for lamin A and

emerin [4]. Pathogenic variants in the *SYNE2* gene result in variable clinical presentations, including asymptomatic elevation of CPK, EDMD5, and severe dilated cardiomyopathy [1].

The few previously published case reports of EDMD5 describe patients presenting with mild symptomatic muscle weakness or cardiac involvement during late childhood or adulthood [3, 4]. In contrast, our patient presented at an unusually early age of nine months. The most unusual feature of our patient is the initial presentation with high transaminases during infancy before the development of features of muscular dystrophy. His other liver function tests, including alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin, were normal, suggesting transaminitis is of non-hepatic origin. Skeletal muscle tissue contains both AST and ALT, and elevation of transaminases (predominantly AST) is reported in myopathies and muscular dystrophies [5]. We could not find any previous reports of EDMD5 presenting with transaminitis during infancy.

The diagnosis of EDMD5 is established by genetic testing; therefore, it is recommended as the first line in children presenting with classical clinical features. Muscle biopsy histology with immunofluorescence studies of SYNE2 expression in the nuclear envelope would support the diagnosis; however, in the presence of confirmatory genetic testing, these are less commonly performed [6].

The management of EDMD5 consists of multidisciplinary care; however, no disease-modifying medication has been identified yet [1]. The cardiac manifestations arise years after skeletal muscle involvement; therefore, cardiac screening is mandatory during the follow-up. It includes clinical examination, electrocardiogram, echocardiogram, and Holter monitoring at the diagnosis, followed by regular monitoring [7]. The prognosis of EDMD5 is related to the severity of cardiac involvement.

In conclusion, we have reported an extremely rare presentation of EDMD5 during infancy as transaminitis. This case report highlights the importance of evaluating non-hepatic causes for transaminitis and the usefulness of whole exome sequencing in establishing an accurate diagnosis when relatively common diseases are excluded.

Abbreviations

EDMD	Emery-Dreifuss muscular dystrophy
AST	Aspartate transaminase
ALT	Alanine transaminase
CPK	Creatine phosphokinase
WES	Whole exome sequencing
LINC	Linker of nucleoskeleton and cytoskeleton complex

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SM, TV, GD, TS, MR, and PP participated in making the diagnosis and managing the child. SM and TS wrote the manuscript. All authors read and approved the final manuscript.

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Data availability
The data that support the findings of this study are not openly available due to sensitivity reasons and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Informed written consent was obtained from the mother of the patient. Ethics committee approval was not obtained as this is a case report, and the hospital where the patient was managed does not require ethical approval to publish case reports.

Consent for publication
Written informed consent was obtained from the patient's mother for the publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare no competing interests.

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