Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Childhood-onset Emery-Dreifuss muscular dystrophy type 2 due to an LMNA c.98A>G (p.Glu33Gly) variant: a longitudinal case report from childhood to adulthood

Farah Mohamed Ramzy Hasan Mohamed
farah.mohamed@msc.mil.ae
Zayed Military Hospital
Esraa Mohamed Abdullah Elameen
Zayed Military Hospital
Amani Ali Saif Alzaabi
Zayed Military Hospital
Asmaa Ismail Elballat
Zayed Military Hospital
Mahfoud Elbashari
Zayed Military Hospital

Case Report

Keywords: Emery-Dreifuss muscular dystrophy, LMNA, laminopathy, cardiac surveillance, case report

Posted Date: November 10th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11265916/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Childhood-onset Emery-Dreifuss muscular dystrophy type 2 due to an LMNA c.98A>G (p.Glu33Gly) variant: a longitudinal case report from childhood to adulthood

Farah Mohamed Ramzy Hasan Mohamed; Esraa Mohamed Abdullah Elameen; Amani Ali Saif Alzaabi; Asmaa Ismail Elballat; Mahfoud Elbashari

Zayed Military Hospital, Abu Dhabi, United Arab Emirates

Author email addresses

Farah Mohamed Ramzy Hasan Mohamed: farahdarwish5@hotmail.com
Esraa Mohamed Abdullah Elameen: essrajaber@gmail.com
Amani Ali Saif Alzaabi: aalzaabi757@gmail.com
Asmaa Ismail Elballat: Dr.asmaa07@yahoo.com
Mahfoud Elbashari: dr_mahfoud@yahoo.co.uk

Corresponding author: Farah Mohamed Ramzy Hasan Mohamed, farah.mohamed@msc.mil.ae, Zayed Military Hospital, Abu Dhabi, United Arab Emirates

Abstract

Background

Emery-Dreifuss muscular dystrophy type 2 (EDMD2) is an autosomal dominant laminopathy caused by pathogenic Lamin A/C (LMNA) gene variants and characterized by early joint contractures, slowly progressive skeletal-muscle weakness, and potentially life-threatening cardiac disease. Detailed longitudinal descriptions extending from childhood into adulthood are uncommon, particularly for individual LMNA variants.

Case presentation

We describe a boy whose limb weakness began at 6-7 years of age and who was referred at age 10 years for progressive proximal weakness and bilateral elbow flexion contractures. Examination showed proximal upper- and lower-limb weakness, depressed or absent deep tendon reflexes, mild pes cavus, and approximately 20-degree bilateral elbow contractures. Serum creatine kinase was mildly elevated (approximately 430 IU/L), nerve conduction studies were normal, electromyography was myopathic, and muscle biopsy showed changes consistent with muscular dystrophy. Over the next four years, weakness and contractures progressed, and by age 14 years, he required a wheelchair for community mobility. At age 23 years, fixed elbow contractures and muscle wasting persisted. Echocardiography and exercise stress testing were unremarkable; 24-hour Holter monitoring showed frequent premature atrial contractions and rare

premature ventricular contractions without sustained arrhythmia. Molecular testing identified a heterozygous pathogenic LMNA variant, c.98A>G (p.Glu33Gly), confirming EDMD2.

Conclusions
This case illustrates the diagnostic value of early contractures in a child with relatively modest creatine kinase elevation and a myopathic electrophysiologic pattern, and it documents the evolution of genetically confirmed LMNA-related EDMD from childhood into adulthood. The preserved cardiac structure at adult assessment does not eliminate future risk; lifelong rhythm and structural cardiac surveillance remain essential. Molecular confirmation also enables appropriate counselling and targeted evaluation of at-risk relatives.

Keywords
Emery-Dreifuss muscular dystrophy; LMNA; laminopathy; cardiac surveillance; case report

Background

Emery-Dreifuss muscular dystrophy (EDMD) is a rare inherited neuromuscular disorder characterized by the triad of early joint contractures, slowly progressive skeletal-muscle weakness and wasting, and cardiac involvement [1-5]. Several genes can cause an EDMD phenotype; autosomal dominant EDMD type 2 (EDMD2) is most commonly associated with pathogenic variants in LMNA, which encodes the nuclear-envelope proteins lamin A and lamin C [1-4]. Because LMNA variants can affect multiple tissues, LMNA-related disease encompasses a broad spectrum of laminopathies involving skeletal muscle, cardiac muscle, adipose tissue, and, in some genotypes, peripheral nerves [1,2].

The neuromuscular phenotype of EDMD is often recognizable clinically. Contractures of the elbows, Achilles tendons, and posterior cervical muscles may precede substantial weakness and can therefore provide an early diagnostic clue [1,4,5,11]. Skeletal-muscle progression is usually gradual, but the cardiac phenotype may evolve independently. Atrial and ventricular arrhythmias, conduction-system disease, and dilated cardiomyopathy are major determinants of morbidity and mortality in LMNA-related disease [1,69]. Consequently, a normal initial cardiac evaluation does not remove the need for lifelong surveillance.

Genetic confirmation is increasingly central to diagnosis because LMNA-related muscular dystrophy overlaps phenotypically with other inherited myopathies and because family histories may be misleading or

incomplete [1,4,12]. The LMNA c.98A>G (p.Glu33Gly) variant has previously been reported in individuals with LMNA-related disease and is listed as pathogenic in ClinVar [12]. Accordingly, the value of the present report is not the identification of a previously unreported variant, but the detailed childhood-to-adult clinical trajectory of a patient with this genotype, including the evolution of contractures, mobility limitations, and early rhythm findings in the setting of preserved cardiac structure. We report a longitudinal case of childhood-onset EDMD2 associated with the heterozygous LMNA c.98A>G (p.Glu33Gly) variant, emphasizing clinical recognition, molecular confirmation, multidisciplinary management, and continued cardiac surveillance.

Case presentation

A 10-year-old boy was referred from the orthopedic service to pediatric neurology because of progressive muscle weakness and bilateral elbow contractures. His parents had first noticed weakness between 6 and 7 years of age. Initially, the weakness predominantly affected the lower limbs, with greater functional difficulty on the left. He fatigued after walking short distances and was unable to keep pace with his siblings during physical activity. Although he was able to climb stairs, he increasingly used forward trunk flexion as a compensatory strategy, and his endurance and balance gradually worsened during prolonged walking.

During the same period, his father noticed progressive limitation of elbow extension. Passive stretching initially permitted full extension, but the elbows gradually became fixed in flexion despite regular stretching exercises. There was no history of developmental delay, perinatal complications, birth asphyxia, seizures, dysphagia, respiratory symptoms, or cognitive impairment. His past medical history was otherwise unremarkable.

The patient had two healthy younger sisters. His parents were non-consanguineous. His mother reportedly developed lower-limb weakness after a febrile illness during childhood and had previously been diagnosed with poliomyelitis. Because her weakness was described as progressive, an alternative inherited neuromuscular disorder was considered possible in retrospect; however, genetic testing of the mother was not available, and familial segregation of the LMNA variant therefore could not be established.

At age 10 years, the patient walked independently with a mildly abnormal gait. He could walk on his toes but had difficulty walking on his heels. He rose from the floor without a Gowers' sign. Cranial nerve examination was normal, with no facial weakness or ophthalmoplegia. Manual muscle testing showed symmetrical proximal weakness in the upper and lower limbs. Neck flexion and shoulder movements were Medical Research Council (MRC) grade 4/5; elbow flexion and extension were MRC grade 3/5 bilaterally; wrist and hand strength were preserved. Hip flexion, knee extension, and ankle dorsiflexion were mildly reduced (MRC grade 4/5), whereas plantar flexion was preserved. Deep tendon reflexes were absent at the knees, ankles, and biceps. Mild bilateral pes cavus and approximately 20-degree flexion contractures of both elbows were present. There was no calf hypertrophy, scoliosis, dysmorphism, organomegaly, or neurocutaneous abnormality.

Serum creatine kinase was mildly elevated at approximately 430 IU/L. Motor and sensory nerve conduction studies were normal. Needle electromyography showed a myopathic pattern. A muscle biopsy performed overseas demonstrated myopathic changes consistent with muscular dystrophy. The patient continued regular pediatric neurology follow-up. During the next four years, proximal weakness in the upper and lower limbs progressed. By age 14 years, he was unable to walk long distances, required a wheelchair for community mobility, and had increasing difficulty climbing stairs. Upper-limb weakness also progressed, and the elbow contractures became more pronounced. Spinal alignment remained preserved without clinically evident scoliosis. Multidisciplinary management included pediatric neurology, physiotherapy, occupational therapy, orthopedic surgery, seating services, and rehabilitation.

At age 23 years, he reported further progressive weakness accompanied by pain in both the upper and lower extremities. He was alert and cognitively intact. Cranial nerve examination remained unremarkable, with full extraocular movements and preserved orbicularis oculi strength. In the upper limbs there was mild bilateral triceps weakness, bilateral fixed elbow flexion contractures, and muscle wasting with relative prominence of the brachioradialis muscles. The lower limbs showed generalized muscle wasting, while strength was largely preserved on manual testing. Deep tendon reflexes remained depressed in the upper and lower limbs, plantar responses were flexor bilaterally, and sensation was normal. Repeat nerve

conduction studies were normal and needle electromyography again showed a myopathic process. Given the established risk of cardiac involvement in EDMD, a comprehensive adult cardiac evaluation was undertaken. Exercise treadmill testing was unremarkable. Transthoracic echocardiography showed normal cardiac structure and function. Twenty-four-hour Holter monitoring demonstrated frequent premature atrial contractions and rare premature ventricular contractions, with no significant pauses or sustained arrhythmias. The patient remained under cardiology follow-up for surveillance of conduction disease, arrhythmia, and cardiomyopathy.

Molecular genetic testing subsequently identified a heterozygous pathogenic missense variant in LMNA, c.98A>G (p.Glu33Gly), confirming autosomal dominant EDMD2. The molecular diagnosis was concordant with the phenotype of early fixed elbow contractures, slowly progressive proximal weakness, mild creatine kinase elevation, and myopathic electromyographic findings.

Clinical photographs obtained during adult follow-up illustrate the fixed elbow posture, lower-limb/ankle posture in the setting of Achilles tendon tightness, and the posterior cervical and upper-trunk appearance (Figs. 1-4).

{Insert Table 1 Here}

Table 1. Longitudinal clinical timeline

Age/period	Clinical domain	Key findings
6-7 years	Symptom onset	Lower-limb weakness, easy fatigability, reduced walking endurance, emerging limitation of elbow extension.
10 years	Neuromuscular evaluation	Independent ambulation; proximal weakness; approximately 20degree bilateral elbow flexion contractures; absent knee, ankle, and biceps reflexes; mild pes cavus; CK approximately 430 IU/L; normal nerve conduction; myopathic EMG; muscle biopsy consistent with muscular dystrophy.
10-14 years	Progression	Progressive proximal weakness and fixed elbow contractures; increasing difficulty with stairs and long-distance walking; wheelchair required for community mobility; no clinically evident scoliosis.
23 years	Adult neuromuscular assessment	Fixed elbow flexion contractures, upper-limb and generalized muscle wasting, mild bilateral triceps weakness, depressed reflexes, normal sensation; repeat EMG remained myopathic.
23 years/adulthood	Cardiac and genetic assessment	Normal echocardiography and exercise stress test; Holter with frequent PACs and rare PVCs without sustained arrhythmia; heterozygous LMNA c.98A>G (p.Glu33Gly) pathogenic variant identified.

Discussion and Conclusions

Phenotypic evolution and clinical diagnostic value

The earliest distinctive feature in this patient was the development of progressive elbow contractures in childhood, preceding substantial functional decline. This sequence is characteristic of EDMD and remains clinically useful in distinguishing the disorder from many other inherited myopathies [1,4,5,11]. In a child with slowly progressive weakness, modest creatine kinase elevation, and a myopathic electromyographic pattern, early elbow or Achilles tendon contractures should prompt consideration of an EDMD-spectrum disorder and timely molecular testing.

The absence of developmental delay, cognitive impairment, bulbar symptoms, and sensory loss supported a primary skeletal-muscle disorder. Normal motor and sensory nerve conduction studies, together with myopathic needle electromyography, further favored myopathy over peripheral neuropathy. Although the muscle biopsy supported muscular dystrophy, it was not etiologically specific. Molecular testing ultimately

established the diagnosis, illustrating the contemporary role of genetic testing in phenotypically overlapping neuromuscular disorders [1,4,12].

The family history is noteworthy but unresolved. The patient's mother had childhood-onset lower-limb weakness that had been attributed to poliomyelitis. Because her symptoms were reported to progress, an inherited neuromuscular disorder is possible; however, without clinical reassessment or segregation testing, the maternal history cannot be used to establish inheritance. This distinction is important when counselling families about autosomal dominant LMNA-related disease.

Natural history during longitudinal follow-up

Across more than a decade of documented follow-up, the patient showed a slowly progressive neuromuscular course. Childhood fatigue and mild lower-limb weakness evolved into greater limitations in walking distance and stair climbing, while elbow contractures became fixed despite stretching. By adolescence, a wheelchair was required for community mobility. In early adulthood, fixed contractures and muscle wasting remained prominent. The apparent preservation of strength in several lower-limb muscle groups on adult manual testing does not negate the earlier functional decline, because endurance, contractures, selective muscle involvement, pain, and compensatory strategies can substantially affect mobility beyond what is captured by a single manual strength examination.

The absence of scoliosis during the available follow-up is clinically relevant but does not reduce the need for continued musculoskeletal surveillance. Long-term management should remain multidisciplinary and individualized, with attention to stretching and contracture management, seating and mobility needs, occupational function, pain, orthotic support, and orthopedic assessment [1,4].

Clinical photographs

Clinical photographs obtained during adult follow-up illustrate the characteristic fixed elbow posture, lower-limb/ankle posture associated with Achilles tendon tightness, and posterior cervical/upper-trunk appearance (Figures 1-4).



Figure 1. Bilateral elbow flexion contractures. Frontal upper-body photograph obtained during adult follow-up, showing both upper limbs maintained in flexion because of fixed bilateral elbow contractures.



Figure 2. Lower-limb posture with Achilles tendon tightness. Posterior view of the lower legs and feet during standing. The photograph illustrates the ankle and heel posture in the clinical context of documented Achilles tendon tightness.



Figure 3. Posterior view of fixed elbow posture. Posterior upper-body photograph showing the arms maintained in flexion at the elbows, consistent with the fixed bilateral elbow contractures documented on examination.



Figure 4. Posterior cervical and upper-trunk appearance. Posterior view of the neck and upper thoracic region during adult follow-up. The photograph accompanies the clinically documented posterior cervical stiffness and limitation of neck movement.

Cardiac surveillance

Cardiac disease is a major determinant of prognosis in LMNA-related muscular dystrophy. Conduction abnormalities, atrial and ventricular arrhythmias, and dilated cardiomyopathy can occur independently of skeletal-muscle severity and may precede structural cardiac abnormalities [1,6-9]. Adult echocardiography and exercise testing were normal in this patient, while ambulatory monitoring showed frequent premature atrial contractions and rare premature ventricular contractions without sustained arrhythmia. These findings do not establish malignant arrhythmic disease, but neither does a normal echocardiogram provide durable reassurance in an LMNA carrier.

Current management principles for LMNA-related disease support serial clinical review, electrocardiography, ambulatory rhythm monitoring, and cardiac imaging, with escalation based on symptoms, conduction disease, ventricular function, arrhythmic burden, and validated risk factors [1,7-9]. This case therefore reinforces the need to maintain surveillance even when structural cardiac assessment is initially normal.

Molecular confirmation and genotype context

The heterozygous LMNA c.98A>G (p.Glu33Gly) missense variant confirmed EDMD2 in the context of a compatible phenotype. Importantly, p.Glu33Gly is not novel: it has been reported in LMNA-related disease, including cohorts highlighting the importance of early recognition of LMNA-related muscular dystrophy, and is currently classified as pathogenic in ClinVar [12]. The educational contribution of this case is therefore the longitudinal phenotype rather than discovery of a new variant.

Molecular confirmation has implications beyond diagnostic nomenclature. It identifies a patient who requires lifelong cardiac follow-up, allows genetic counseling regarding autosomal dominant inheritance and variable expression, and enables targeted testing of at-risk relatives. In this family, evaluation of the mother and other relatives could clarify segregation and identify individuals who might benefit from cardiac surveillance before symptoms develop [1,10].

Strengths and limitations

The principal strength of this report is the longitudinal observation of a genetically confirmed LMNA-related muscular dystrophy from childhood into adulthood, allowing the sequence of contracture development, functional progression, and adult cardiac findings to be described within a single patient. The report also illustrates a common diagnostic challenge in rare neuromuscular disease: a suggestive phenotype may be recognized years before molecular confirmation.

The limitations are those inherent to a single case report. Serial quantitative functional measures and standardized strength scores were not available across the entire follow-up period. Longitudinal cardiac data were limited, including the absence of serial cardiac magnetic resonance imaging and repeated ambulatory monitoring over multiple years. Genetic testing was not performed in relatives, so familial segregation and the significance of the maternal history remain unresolved. These limitations restrict genotype-phenotype inference and preclude conclusions about the frequency or predictive value of the observed cardiac findings.

Conclusions

LMNA-related EDMD should be considered in children with progressive elbow or Achilles tendon contractures, particularly when accompanied by slowly progressive proximal weakness, modest creatine kinase elevation, and myopathic electrophysiologic findings. In this patient, molecular testing established EDMD2 due to the pathogenic LMNA c.98A>G (p.Glu33Gly) variant after a clinical course beginning in early childhood. The longitudinal findings emphasize that progressive musculoskeletal disability can coexist with initially preserved cardiac structure and that lifelong cardiac surveillance remains necessary. Early molecular diagnosis also supports anticipatory multidisciplinary care, family counselling, and targeted evaluation of at-risk relatives.

List of abbreviations

CK, creatine kinase; EDMD, Emery-Dreifuss muscular dystrophy; EDMD2, Emery-Dreifuss muscular dystrophy type 2; EMG, electromyography; LMNA, lamin A/C gene; MRC, Medical Research Council; PAC, premature atrial contraction; PVC, premature ventricular contraction.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from the Ethics Committee of Zayed Military Hospital, Abu Dhabi, United Arab Emirates.

Consent for publication

Written informed consent for publication of the patient's clinical information and accompanying clinical photographs was obtained from the patient.

Availability of data and materials

The genetic testing results are documented in laboratory report LFY329S, dated 15 May 2026. Further information could not be provided by the testing laboratory due to confidentiality restrictions. The identified *LMNA* variant (NM_170707.4.98A>G; p.Glu33Gly) has been previously reported in ClinVar in association with Charcot-Marie-Tooth disease type 2 (Variation ID: 66962; https://www.ncbi.nlm.nih.gov/clinvar/variation/66962/). The variant was not observed in the gnomAD v4.1 population database (reported allele frequency: 0; https://gnomad.broadinstitute.org/variant/1-156115016-A-G?dataset=gnomad_r4). No additional causative pathogenic variants were identified. Further patient-level data are not publicly available due to confidentiality and patient privacy considerations.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for this work.

Authors' contributions

FM and EM contributed to drafting and revising the case report. ME, AA and AI contributed to the literature review and critical revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the Research and Innovation Department at Zayed Military Hospital for its support during preparation and submission of this case report. During manuscript preparation, the authors used ChatGPT (OpenAI) to assist with language editing, organization, and formatting. All clinical content, interpretation, references, and final wording were reviewed and verified by the authors, who take full responsibility for the manuscript.

References

1. Yaou RB, Leturcq F, Bonne G. Emery-Dreifuss Muscular Dystrophy. In: GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; updated 18 Sep 2025.
2. Muchir A, Worman HJ. Emery-Dreifuss muscular dystrophy: focal point nuclear envelope. Curr Opin Neurol. 2019;32(5):728-734.
3. Bonne G, Di Barletta MR, Varnous S, Bécane HM, Hammouda EH, Merlini L, et al. Mutations in the gene encoding lamin A/C cause autosomal dominant Emery-Dreifuss muscular dystrophy. Nat Genet. 1999;21(3):285-288. doi:10.1038/6799.
4. Heller SA, Shih R, Kalra R, Kang PB. Emery-Dreifuss muscular dystrophy. Muscle Nerve. 2020;61(4):436-448.
5. Emery AE, Dreifuss FE. Unusual type of benign X-linked muscular dystrophy. J Neurol Neurosurg Psychiatry. 1966;29(4):338-342.
6. Fatkin D, MacRae C, Sasaki T, Wolff MR, Porcu M, Frenneaux M, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med. 1999;341(23):1715-1724.
7. van Rijsingen IAW, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, et al. Risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers: a European cohort study. J Am Coll Cardiol. 2012;59(5):493-500.
8. Wahbi K, Ben Yaou R, Gandjbakhch E, Anselme F, Gossios T, Lakdawala NK, et al. Development and validation of a new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. Circulation. 2019;140(4):293-302.
9. Zeppenfeld K, Tfelt-Hansen J, de Riva M, Winkel BG, Behr ER, Blom NA, et al. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J. 2022;43(40):3997-4126.
10. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, et al. Genetic evaluation of cardiomyopathy-a Heart Failure Society of America practice guideline. J Card Fail. 2018;24(5):281-302.
11. Madej-Pilarczyk A. Clinical aspects of Emery-Dreifuss muscular dystrophy. Nucleus. 2018;9(1):314320.
12. Menezes MP, Waddell LB, Evesson FJ, Cooper S, Webster R, Jones K, et al. Importance and challenge of making an early diagnosis in LMNA-related muscular dystrophy. Neurology. 2012;78(16):1258-1263. doi:10.1212/WNL.0b013e318250d839.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- BMCNeurologyEDMD2CompletedCAREChecklist.docx