

Multimodal Evaluation of Bethlem Myopathy with the c.788G > A Variant in the COL6A1 Gene: a case report with genetic, ultrasonographic, and structural-functional discordance correlations

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Introduction. Bethlem myopathy (BM) is a collagen-VI-related myopathy caused by mutations in the COL6A1, COL6A2, and COL6A3 genes. It is characterized by proximal muscle weakness, distal joint laxity, and contractures, with symptoms appearing during childhood and progressing slowly. Muscle ultrasound, using tools like the Heckmatt scale, complements genetic analysis and provides noninvasive insights into muscle pathology, particularly in atypical presentations.

Case Report. An 8-year-old male presented with muscle weakness since birth, delayed motor milestones, toe walking, and frequent falls. Family history revealed maternal-line neuromuscular disorders. Clinical examination showed hyporeflexia, thoracic hypotrophy, and decreased proximal muscle strength, alongside joint hypermobility and keratosis pilaris. Electromyography indicated a myopathic pattern in proximal upper limb muscles. Genetic analysis confirmed a pathogenic COL6A1 variant (c.788G > A, p.Gly263Asp). Ultrasound findings revealed advanced structural compromise with Heckmatt grade IV echogenicity in the deltoid, iliopsoas, and rectus femoris, indicating fatty infiltration and fibrosis. Functional tests, including Motor Function Measurement (MFM), showed adequate performance despite significant structural abnormalities.

Discussion. This case illustrates the diagnostic challenges of BM, characterized by phenotypic variability and the complexity of correlating structural and functional findings. Muscle ultrasound findings demonstrated advanced echogenic changes, but functional performance remained preserved, highlighting a mismatch between structural changes and functional outcomes.

Conclusion. This case highlights the diagnostic challenges of BM, where a patient with a COL6A1 gene mutation exhibited significant muscle abnormalities on ultrasound but maintained relatively preserved motor function according to the MFM scale. This discrepancy emphasizes the limitations of functional assessments like MFM in capturing the extent of muscle weakness. Ultrasound and dynamometry provided a more comprehensive evaluation, underscoring the importance of integrating structural and functional assessments for accurate diagnosis and management. This case stresses the need for an individualized approach in managing BM, considering both genetic and clinical findings.

Key words: Bethlem myopathy, Muscle ultrasound, COL6A1 gene, muscular dystrophy, Hypermobility

Introduction

Bethlem myopathy (BM) is a collagen-VI-related myopathy caused by mutations in the COL6A1, COL6A2, and COL6A3 genes. Collagen VI is a ubiquitous extracellular matrix

protein that forms a microfibrillar network closely associated with the basement membrane in various tissues, including muscle, cartilage, and skin ^{1,2}. BM is characterized by mild proximal muscle weakness, distal joint laxity, and contractures, with symptoms typically appearing during childhood and progressing slowly. Unlike the more severe Ullrich congenital muscular dystrophy (UCMD), BM represents the mildest phenotype within the spectrum of collagen VI-related myopathies. The classification of phenotypes related to collagen VI-related myopathies (COL6-RM) is primarily based on ambulation ability. According to the consensus reached at the 166th International Workshop of the European Neuromuscular Centre (ENMC), three clinical forms are identified: UCMD (Ullrich Congenital Muscular Dystrophy), which includes patients who have never walked or who lost ambulation before the age of 12; the intermediate form (INTM), referring to those who lose ambulation during adolescence; and BM (Bethlem Myopathy), which applies to patients who retain the ability to walk into adulthood ³. Laboratory findings often reveal slightly elevated creatine kinase (CK) levels, while imaging studies, including MRI and muscle ultrasound, demonstrate fatty infiltration and structural alterations in affected muscles ^{2,4}.

Muscle ultrasound has emerged as an indispensable tool for evaluating neuromuscular diseases, offering valuable insights into muscle architecture and pathology in a noninvasive and efficient manner. In BM, distinct echogenicity patterns, such as the “central shadow sign,” have been reported, reflecting unique myopathic processes ⁵. The semiquantitative Heckmatt scale is commonly employed to grade muscle involvement, aiding in the differentiation of BM from other neuromuscular disorders ⁵. Additionally, ultrasound findings can complement genetic analysis, particularly in atypical presentations or when invasive methods, such as muscle biopsy, are not feasible ⁵. This case report presents an 8-year-old male with a pathogenic variant in the COL6A1 gene (c.788G > A, p.Gly263Asp). This mutation was previously reported by Morel et al. in a case of Bethlem myopathy with loss of ambulation at 57 years of age, highlighting the phenotypic variability of this variant ⁶.

This case illustrates the discrepancy between severe structural muscle involvement and seemingly adequate functional performance in a pediatric patient with Bethlem myopathy, highlighting the limitations of functional scales like the MFM when used in isolation. The literature lacks studies that systematically integrate ultrasound findings, objective strength measured by dynamometry, and functional performance, particularly in children. It provides useful evidence to better understand the value of multimodal assessment in this spectrum of myopathies. The objective of this case is to contribute to the understanding of the relationship between structural changes and functional outcomes in Bethlem myopathy, emphasizing the importance of integrating various diagnostic tools for a more comprehensive clinical evaluation.

Case report

An 8-year-old male from Colombia presented with muscle weakness since birth and delayed motor milestones. At 2 years of age, he began toe walking and experienced frequent falls. Laboratory tests revealed elevated creatine kinase (CPK) levels of 814 U/L, consistent

with muscle pathology. The family history revealed a maternal lineage of neuromuscular disorders, including progressive weakness, motor disability, respiratory complications, and premature deaths affecting his maternal grandmother, mother, six uncles, and cousins. At the time of evaluation, the patient walked independently but was unable to run or jump. He reported difficulty climbing stairs and performing fine motor tasks such as buttoning clothes, although his handwriting was legible. Episodes of coughing and choking while swallowing solid foods were also reported, suggesting oropharyngeal involvement. On physical examination, notable findings included a high palate, thoracic hypotrophy, hyporeflexia in the upper limbs, areflexia in the lower limbs, and decreased proximal muscle strength. Additional observations included keratosis pilaris and joint hypermobility in the extremities (Fig. 1).



Figure 1. Ligamentous hyperlaxity in Bethlem myopathy. Demonstration of ligamentous hyperlaxity in the fingers, characterized by excessive extension of the interphalangeal joints, a common clinical feature associated with Bethlem myopathy.

Electromyographic studies demonstrated a recruitment pattern of early filling, compound muscle action potentials of low amplitude and short duration, and unstable polyphasic units. These findings were consistent with a primary myopathic process, predominantly involving the proximal muscles of the upper limbs, such as the biceps and deltoids. Quantitative interference pattern analysis (IPA) revealed an increased number of turns per second and a decreased average amplitude of turns, further supporting the diagnosis of myopathy. Functional evaluations were performed to complement the imaging and genetic findings. As shown in Table I, the Motor Function Measurement (MFM) scores indicated adequate performance for standing, axial, and distal motor tasks, despite significant muscle weakness demonstrated by dynamometry, where deltoid strength was only 16.3% of the expected mean value for children of the same age,

Table 1. Functional Testing and Dynamometry Results in an 8-Year-Old Male with Bethlem Myopathy.

Functional Testing			
Test	Measured Value (Right)	Measured Value (Left)	Performance
Standing (MFM)	89	89	Adequate
Axial Motor (MFM)	97	97	Adequate
Distal Motor (MFM)	80	95	Adequate
Total MFM Score	90	62	Adequate
Up & Go (Seconds)	5	8	Minimal fall risk
Dynamometry Results			
Muscle Group	Measured Strength (Newtons)		Percentage of Normal
Deltoid	14 (R), 16 (L)		16.3%
Biceps	20 (R), 18 (L)		14.5%
Psoas	48 (R), 49 (L)		21.8%
Quadriceps	46 (R), 48 (L)		25.9%
Tibialis Anterior	21 (R), 28 (L)		20.4%

Abbreviations: MFM: Motor Function Measurement; R: Right; L: Left; Up & Go: Timed Up and Go test.

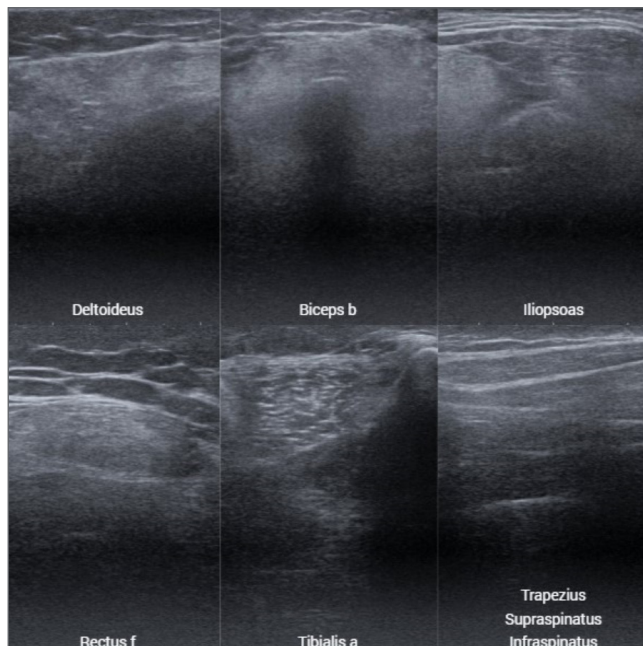


Figure 2. Ultrasonographic findings in Bethlem myopathy. Composite ultrasound images showing increased echogenicity and architectural disruption in multiple muscle groups, graded using the Heckmatt scale. Findings include: Deltoid (Heckmatt IV), Biceps (Heckmatt III), Iliopsoas (Heckmatt IV), Rectus femoris (Heckmatt IV), Tibialis anterior (Heckmatt III), and Supraspinatus (Heckmatt III). These abnormalities indicate significant fatty infiltration and fibrosis, characteristic of advanced muscle involvement in Bethlem myopathy.

based on normative data reported by Beenakker et al.

Genetic testing through clinical exome sequencing confirmed a pathogenic heterozygous variant in the COL6A1 gene (c.788G > A, p.Gly263Asp), consistent with the autosomal dominant Bethlem myopathy 1 phenotype.

Muscle ultrasound findings revealed significant abnormalities, graded using the semiquantitative Heckmatt scale. Increased echogenicity and granular hyperechoic foci were observed in multiple muscle groups, including the deltoid, biceps, iliopsoas, rectus femoris, and tibialis anterior. These findings produced a homogeneous “ground glass” appearance, indicating extensive replacement of muscle fibers by fat and fibrosis as the disease progressed (Fig. 2).

Discussion

Bethlem myopathy (BM) represents the mildest phenotype within the spectrum of type VI collagen-related myopathies. This case of an 8-year-old male with a confirmed heterozygous pathogenic variant in the COL6A1 gene (c.788G > A, p.Gly263Asp) highlights the phenotypic variability of BM and its diagnostic challenges. The patient exhibited classic clinical features, including mild proximal weakness, delayed motor development, and joint hypermobility, alongside less typical findings such as severe upper limb involvement. Muscle ultrasound findings demonstrated advanced echogenic changes consistent with Heckmatt grades III and IV, reflecting significant structural compromise. Despite these findings, functional assessments such as the Motor Function Measurement (MFM) revealed preserved motor performance, highlighting a mismatch between structural and functional evaluations.

BM typically manifests in childhood with proximal weakness, distal joint laxity, and joint contractures developing by the end of the first decade ². Although primarily inherited in an autosomal dominant manner, rare autosomal recessive cases have been reported ¹. Laboratory findings often include mildly elevated creatine kinase (CK) levels, while imaging studies, such as MRI, demonstrate characteristic fatty infiltration, particularly in the anterior thigh muscles. The clinical variability observed in this case, particularly the severe upper limb involvement, aligns with previous reports, such as a Korean case series, which documented differences in symptom onset, muscle involvement, and joint contractures ⁴. These findings underscore the phenotypic heterogeneity of BM and its overlap with other collagen VI-related myopathies.

Muscle ultrasound has proven invaluable in evaluating neuromuscular diseases, offering both semiquantitative and quantitative assessments of muscle architecture. Healthy muscle typically appears anechoic with scattered hyperechoic foci, creating a “starry night” pattern on ultrasound ⁷. In BM, the Heckmatt scale is widely used to grade echogenicity, with higher grades indicating more extensive fatty infiltration and fibrosis ⁸. In this case, grade IV echogenicity in muscles such as the deltoid and iliopsoas indicated advanced structural compromise. Quantitative grayscale analysis complements this by providing objective metrics that correlate with disease severity ⁹. These techniques, when used together, demonstrate moderate correlation, with higher Heckmatt grades typically associated with increased grayscale values ¹⁰.

The ultrasonographic findings in BM are distinct from neurogenic changes, which often present with a heterogeneous “moth-eaten” pattern reflecting areas of denervation and fibrosis¹⁰. In contrast, BM is characterized by a fine granular echogenic pattern or the “ground glass” appearance observed in this case. A unique “central shadow sign” has also been described in BM, attributed to echo density around the central fascia of the rectus femoris muscle, further distinguishing it from other neuromuscular disorders⁵. These imaging features enhance the diagnostic specificity of muscle ultrasound, particularly when used in conjunction with genetic testing.

Functional tests, such as the MFM and up-and-go, revealed preserved motor performance in this patient, despite significant structural abnormalities detected by ultrasound.

Although the patient is still able to walk independently, he presents with marked weakness in the knee extensors, with quadriceps strength measured at 46 N on the right and 48 N on the left – approximately 26% of the normal value for his age and sex. He also exhibits significant motor limitations, including the inability to run, jump, or climb stairs with ease. This pattern of weakness has been observed in adults with COL6-RM who have lost ambulation, whereas ambulatory patients typically show higher strength values. While these findings may suggest a progression toward a more severe form within the COL6-RM spectrum, it is important to consider that Bethlem myopathy is also characterized by variable progression, and many patients retain the ability to walk into adulthood despite significant weakness¹¹.

In this case, a notable discrepancy was observed between functional performance and objective muscle strength. Although the Motor Function Measurement (MFM) scale indicated adequate performance across all three domains – standing (89/89), axial (97/97), and distal motor function (80 right, 95 left), with a total score of 90 – the dynamometry results revealed markedly reduced muscle strength: deltoid 14–16 N (16.3%), biceps 18–20 N (14.5%), psoas 48–49 N (21.8%), quadriceps 46–48 N (25.9%), and tibialis anterior 21–28 N (20.4%). This mismatch likely stems from the ordinal nature of the MFM, which assigns equivalent scores to movements that demand significantly different levels of force. Consequently, the scale may obscure the actual severity of muscle weakness. This case underscores the value of combining functional assessments with objective measures such as dynamometry and muscle ultrasound to achieve a more accurate and comprehensive clinical evaluation.

This finding aligns with prior studies that suggest a mismatch between structural and functional evaluations in BM and other neuromuscular diseases¹². Quantitative dynamometry, however, revealed suboptimal muscle strength, correlating directly with the severity of ultrasound abnormalities. This observation emphasizes the need for integrating structural and functional assessments to fully understand the clinical impact of BM.

Conclusion

Bethlem Myopathy is a rare and genetically heterogeneous disorder, presenting with a range of clinical features, including proximal muscle weakness, delayed motor milestones, joint hypermobility, and, in some cases, severe upper limb involvement. The phenotypic

variability and diagnostic challenges of BM are highlighted in this case, where a patient with a heterozygous COL6A1 gene mutation displayed significant structural muscle abnormalities detected by ultrasound, yet maintained relatively preserved motor function based on the MFM scale. This discrepancy underscores the limitations of functional assessments like the MFM, which may not fully capture the extent of muscle weakness. Muscle ultrasound and dynamometry proved essential in offering a more comprehensive evaluation, emphasizing the importance of integrating structural and functional assessments for accurate diagnosis and clinical management. This case illustrates the need for an individualized approach in managing BM, considering both genetic and objective clinical findings.

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Conflict of interest statement

The authors declare that they have no competing interests.

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Authors contribution

WSHM and JCGG contributed to the conceptualization of the study and the development of the methodology. WSHM, FOC, and PVMH were responsible for data acquisition, while data analysis and interpretation were carried out by WSHM, FOC, and CCA. The original draft of the manuscript was prepared by WSHM, with critical review and editing performed by JCGG and PVMH. FOC supervised the overall project. All authors reviewed and approved the final version of the manuscript for publication.

Ethical consideration

This study was approved by the Ethics Committee of the Roosevelt Institute, Bogota, Colombia. Written informed consent was obtained from the patient's legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of Data and Materials

The data sets analysed in the current study are available from the corresponding author upon reasonable request.

References

- Kutluk MG, Kadem N, Bektas O, et al. Genotype-Phenotype Correlation of the Childhood-Onset Bethlem Myopathy in the Mediterranean Region of Turkey. *Ann Indian Acad Neurol*. 2021;24(4):547-551 https://doi.org/10.4103/aianAIAN_1182_20.
- Caria F, Cescon M, Gualandi F et al. Autosomal recessive Bethlem myopathy: A clinical, genetic and functional study. *Neuromuscul Disord*. 2019;29(9):657-663 <https://doi.org/10.1016/j.nmd.2019.07.007>.

- 3 Allamand V, Merlini L, Bushby K, Consortium for Collagen VIRM. 166th ENMC International Workshop on Collagen 22-24 May 2009, Naarden, The Netherlands. *Neuromuscul Disord.* 2010;20 5:346-54; <https://doi.org/10.1016/j.nmd.2010.02.012>.
- 4 Lee JH, Shin HY, Park HJ, et al. Clinical, Pathologic, and Genetic Features of Collagen VI-Related Myopathy in Korea. *J Clin Neurol.* 2017;13(4)331-339. <https://doi.org/10.3988/jcn.2017.13.4.331>.
- 5 Bönnemann CG, Brockmann K HF. Muscle ultrasound in Bethlem myopathy. *Neuropediatr.* 2003;34(6)335-336. <https://doi.org/10.1055/s-2003-44665>.
- 6 Morel V, Audic F, Tardy C, et al. Retrospective clinical and genetic analysis of COL6-RD patients with a long-term follow-up at a single French center. *Front Genet.* 2023;14:1242277. <https://doi.org/10.3389/fgene.2023.1242277>
- 7 Albayda J van AN. Diagnostic Value of Muscle Ultrasound for Myopathies and Myositis. *Curr Rheumatol Rep.* 2020;22(11)82 <https://doi.org/10.1007/s11926-020-00947-y>.
- 8 Heckmatt JZ, Leeman SDV. Ultrasound imaging in the diagnosis of muscle disease. *J Pediatr.* 1982;101(5)656-60 [https://doi.org/10.1016/s0022-3476\(82\)80286-2](https://doi.org/10.1016/s0022-3476(82)80286-2).
- 9 Pillen S, Verrips A, van Alfen N, et al. Quantitative skeletal muscle ultrasound: diagnostic value in childhood neuromuscular disease. *Neuromuscul Disord.* 2007;17(7)509-16. <https://doi.org/10.1016/j.nmd.2007.03.008>.
- 10 Brockmann K, Becker P, Schreiber G, et al. Sensitivity and specificity of qualitative muscle ultrasound in assessment of suspected neuromuscular disease in childhood. *Neuromuscul Disord.* 2007;17(7)517-23. <https://doi.org/10.1016/j.nmd.2007.03.015>.
- 11 Merlini L, Sabatelli P, Gualandi F, et al. New Clinical and Immunofluorescence Data of Collagen VI-Related Myopathy: A Single Center Cohort of 69 Patients. *Int J Mol Sci.* 2023;24(15):12474. <https://doi.org/10.3390/ijms241512474>.
- 12 Beenakker EA, van der Hoeven JH, Fock JM MN. Reference values of maximum isometric muscle force obtained in 270 children aged 4-16 years by hand-held dynamometry. *Neuromuscul Disord.* 2001;11(5)441-6. [https://doi.org/10.1016/s0960-8966\(01\)00193-6](https://doi.org/10.1016/s0960-8966(01)00193-6).