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Autosomal Recessive COL6A2-Related Bethlem Myopathy in Two Libyan Siblings: A Case Report

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Abstract

Background

Bethlem myopathy (BTHLM) is a rare collagen VI-related muscular dystrophy caused by pathogenic variants in COL6A1, COL6A2, or COL6A3. Although the disease is typically inherited in an autosomal dominant manner, autosomal recessive forms have been increasingly recognized and often demonstrate variable clinical severity (1).

Case Presentation

We report two affected siblings from a Libyan family with no reported parental consanguinity, harboring the same homozygous pathogenic splice-site variant in COL6A2 (NM_001849.4: c.1970-9G>A), confirmed by whole-exome sequencing and segregation analysis. Two additional siblings (one male, one female) were clinically unaffected.

Case 1 (16-year-old male): presented with delayed motor milestones (independent walking at 20 months), progressive lower-limb weakness since early childhood, a partial Gowers' sign, exercise-induced calf pain, and proximal muscle weakness. Serum creatine kinase (CK) and tendon reflexes were normal. Examination showed mild elbow flexion weakness (MRC 4/5), pes cavus deformity, and mild gluteal and left calf muscle atrophy, without scoliosis. Respiratory function was preserved.

Case 2 (7-year-old female, younger sibling): exhibited a similar but milder phenotype, with proximal muscle weakness, delayed motor performance, calf discomfort after prolonged walking, and preserved ambulation. Segregation analysis confirmed the identical homozygous COL6A2 variant.

Conclusion

These cases highlight the phenotypic variability of recessive COL6A2-related Bethlem myopathy and emphasize that a normal serum CK does not exclude collagen VI-related dystrophy. Recognition of the characteristic clinical features, combined with molecular confirmation, facilitates accurate diagnosis, multidisciplinary management, and genetic counseling.

Keywords: Bethlem myopathy; COL6A2; collagen VI; congenital muscular dystrophy; autosomal recessive.

Introduction

Bethlem myopathy is the mildest phenotype within the spectrum of collagen VI-related dystrophies. The disorder results from pathogenic variants in COL6A1, COL6A2, or COL6A3, producing abnormalities of the extracellular matrix surrounding skeletal muscle fibers (1,2). Patients usually present with slowly progressive proximal muscle weakness, distal joint hyperlaxity, contractures, pes cavus, and preserved or only mildly elevated serum creatine kinase levels (3).

Although dominant inheritance predominates, recessive COL6-related myopathies have been increasingly reported and may overlap clinically with Ullrich congenital muscular dystrophy (4,5).

Case Presentation

Case 1

A 16-year-old boy presented with progressive lower-limb weakness beginning in early childhood. His history included delayed independent walking (20 months), progressive proximal muscle weakness, a partial Gowers' sign, difficulty climbing stairs, calf pain after prolonged walking, and distal upper-limb weakness particularly during prolonged activity and at night. There was no cognitive impairment.

On examination, his anthropometric measurements were: height 176 cm (50th–75th percentile), weight 50 kg (5th–10th percentile), and BMI 16.1 kg/m² (15th percentile) for age and sex. Neurological examination showed normal muscle tone and normal deep tendon reflexes, elbow flexion power of 4/5 bilaterally, mild proximal lower-limb weakness, mild gluteal muscle wasting, mild left calf atrophy, pes cavus deformity, and no scoliosis.

Serum CK was within normal limits. Whole-exome sequencing identified a homozygous pathogenic COL6A2 splice-site variant (c.1970-9G>A), and segregation analysis confirmed the molecular diagnosis.

Case 2

The patient's younger sister, aged 7 years, presented with a similar but less severe phenotype. Her anthropometric measurements were within the expected range for age and sex: height 123 cm (50th–75th percentile), weight 25 kg (50th percentile), and BMI 16.5 kg/m² (50th percentile).

Clinical findings included mild proximal muscle weakness (hip flexion power 4/5), exercise intolerance, calf pain after prolonged walking, and preserved independent ambulation. Serum CK was normal.

Genetic testing confirmed the identical homozygous pathogenic COL6A2 splice-site variant (NM_001849.4: c.1970-9G>A), consistent with autosomal recessive collagen VI-related Bethlem myopathy.

Molecular characteristics: homozygous state; classified as pathogenic; predicted to disrupt normal mRNA splicing; consistent with the autosomal recessive Bethlem myopathy/Ullrich spectrum.

Table 1. Clinical Characteristics of the Two Patients with Autosomal Recessive COL6A2-Related Bethlem Myopathy

Feature	Case 1 (Male, 16 years)	Case 2 (Female, 7 years)
Family history	Affected sibling	Affected sibling
Parental consanguinity	Not reported	Not reported
Age at independent walking	20 months	Mildly delayed
Disease onset	Early childhood	Early childhood
Motor progression	Slowly progressive	Mild, slowly progressive
Proximal muscle weakness	Present	Present (mild)
Gowers' sign	Partial, positive	Negative
Difficulty climbing stairs	Present	Present (mild)
Exercise intolerance	Present	Present
Calf pain after walking	Present	Present
Ambulation	Preserved	Preserved
Cognitive impairment	Absent	Absent
Respiratory involvement	None	None

Feature	Case 1 (Male, 16 years)	Case 2 (Female, 7 years)
Scoliosis	Absent	Absent
Pes cavus	Present	Absent
Muscle atrophy	Mild gluteal and left calf wasting	Absent

Table 2. Neurological Examination Findings

Parameter	Case 1	Case 2
Muscle tone	Normal	Normal
Deep tendon reflexes	Normal	Normal
Proximal lower-limb strength	Mild weakness	Mild weakness
Upper-limb weakness	Elbow flexion 4/5 bilaterally	Not significant
Distal weakness	Mild, during prolonged activity	Absent
Contractures	None	None significant
Pes cavus	Present	Absent
Mobility status	Independent walking	Independent walking

Table 3. Laboratory Investigations

Investigation	Case 1	Case 2	Interpretation
Serum CK	Normal	Normal	Normal CK does not exclude collagen VI myopathy
Muscle enzymes	No elevation	No elevation	Consistent with Bethlem phenotype
Muscle biopsy	Not performed	Not performed	—
MRI (lower limb muscles)	Not performed	Not performed	—
Pulmonary function test	Preserved	Not performed	—
Other routine biochemistry	Normal	Normal	No evidence of metabolic myopathy

Table 4. Anthropometric Data

Parameter	Case 1	Case 2
Height	176 cm (50th–75th percentile)	123 cm (50th–75th percentile)
Weight	50 kg (5th–10th percentile)	25 kg (50th percentile)
BMI	16.1 kg/m² (15th percentile)	16.5 kg/m² (50th percentile)
Nutritional status	Within acceptable range for age	Good build
Growth pattern	Within expected range	Within expected range

Table 5. Molecular Genetic Findings

Parameter	Result
Testing method	Whole-exome sequencing
Gene identified	COL6A2

Parameter	Result
Transcript	NM_001849.4
Variant	c.1970-9G>A
Variant type	Splice-site variant
Zygosity	Homozygous
Classification	Pathogenic
Inheritance pattern	Autosomal recessive
Segregation analysis	Confirmed in affected siblings
Predicted effect	Abnormal mRNA splicing
Clinical correlation	Consistent with COL6A2-related Bethlem myopathy

Table 6. Differential Diagnosis Considered

Disorder	Overlapping Features	Findings Favoring COL6A2-Related Bethlem Myopathy
Myotonia congenita (Thomsen disease) — initial working diagnosis	Muscle symptoms, familial occurrence	Absence of myotonia; genetic confirmation of COL6A2
Duchenne muscular dystrophy	Proximal weakness, Gowers' sign	Normal CK, slow progression, preserved ambulation
Limb-girdle muscular dystrophy	Proximal weakness	Collagen VI molecular diagnosis
Ullrich congenital muscular dystrophy	Collagen VI spectrum	Mild phenotype consistent with Bethlem myopathy

Table 7. Key Diagnostic and Management Points

Domain	Findings
Diagnostic clues	Childhood onset, proximal weakness, pes cavus, normal CK
Confirmatory test	Whole-exome sequencing
Main diagnosis	Autosomal recessive COL6A2-related Bethlem myopathy
Recommended follow-up	Physiotherapy, contracture monitoring, respiratory assessment, standardized functional measures (e.g., 6-minute walk test)
Genetic counseling	Recommended for parents, to clarify carrier status given the absence of known consanguinity

Discussion

These two siblings illustrate the clinical spectrum of recessive COL6A2-related Bethlem myopathy. Several features support this diagnosis: early motor delay, slowly progressive proximal weakness, a partial Gowers' sign, normal serum CK, preserved tendon reflexes, pes cavus deformity, mild muscle atrophy, and positive molecular confirmation. Unlike dystrophinopathies, disease progression is slow, and ambulation is generally maintained into adulthood. The

occurrence of affected siblings born to clinically unaffected, reportedly non-consanguineous parents is consistent with autosomal recessive inheritance, although it also raises a question that merits explicit discussion.

A homozygous pathogenic variant occurring in two siblings from a reportedly non-consanguineous family is uncommon and warrants comment. Several explanations should be considered. First, distant or unrecognized consanguinity cannot be entirely excluded on history alone. Second, the variant may represent a regional founder allele with a higher-than-expected carrier frequency in the local population; homozygous COL6A2 variants have similarly been reported in other Middle Eastern and North African families, including a consanguineous Saudi family carrying a different COL6A2 splice-site variant (c.1817-3C>G), in which the authors specifically highlighted the high consanguinity rate and the previously unrecognized burden of collagen VI-related myopathy in the region (6). Third, rarer mechanisms such as uniparental disomy can produce an apparently homozygous genotype in the absence of consanguinity, as documented for a COL6A2 variant in a recent Chinese multicenter cohort (8). In the present family, parental carrier testing was not performed, which limits our ability to distinguish between these possibilities; this is noted as a limitation, and parental and sibling carrier testing is recommended going forward.

Recognition of collagen VI disorders is clinically important, as affected patients benefit from regular physiotherapy, stretching exercises, respiratory surveillance, orthopedic monitoring, and genetic counseling.

Conclusion

This case report expands the phenotypic spectrum of autosomal recessive COL6A2-related Bethlem myopathy in a Libyan family. Despite carrying the same homozygous pathogenic variant, both siblings demonstrated variable disease severity while preserving ambulation. Early molecular diagnosis enables appropriate rehabilitation, anticipatory monitoring for respiratory and orthopedic complications, and accurate genetic counseling. Normal CK does not exclude collagen VI-related myopathies, and pes cavus with proximal weakness should raise suspicion for a collagen VI disorder. COL6A2-related disease demonstrates marked intrafamilial phenotypic variability, and whole-exome sequencing is valuable in diagnosing unexplained congenital or childhood-onset myopathies.

Limitations

This study has several limitations. Muscle MRI and muscle biopsy were not performed because of resource constraints, and the diagnostic evaluation relied on genetic analysis of peripheral blood samples. Parental and sibling carrier testing was not performed because of cost constraints, which limits interpretation of the homozygous genotype in the absence of reported consanguinity. In the absence of a national genetic disease registry in Libya, data on other potentially affected individuals in the region remain unavailable. Finally, the findings are limited to a single family without long-term follow-up.

Declarations

Consent for publication

Written informed consent for publication of this report was obtained from the parents and assent from the 16-year-old patient. Verbal assent was obtained for the 7-year-old patient.

Conflicts of interest

[Authors to state: e.g., "The authors declare no conflicts of interest."]

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