DOI: 10.33470/2379-9536.1328

CASE REPORT Volume 7 Issue 3

Bethlem myopathy demonstrated in three generations of a rural West Virginia family carrying an autosomal dominant COL6A3 mutation

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ABSTRACT

Mutations in the genes that code for type VI collagen can lead to collagenopathies (collagen VI myopathies), such as Bethlem myopathy (BTHLM1), which affect structural tissues like muscles and tendons. We present the case of a young female and her two relatives who were discovered to share the autosomal dominant COL6A3 mutation and whose presentation to the clinic varied from mild to severe. Type VI collagenopathies represent a clinically and genetically heterogeneous spectrum of disorders generally characterized by muscle weakness and joint contractures. We highlight the importance of examining close relatives whenever possible and documenting a pedigree prior to proceeding with further electromyography (EMG) and lab workup, which includes obtaining genetic testing in order to reach a unifying diagnosis. The proband (L.C.) reported challenges with activities of daily living due to distal hand weakness, had significant findings on neuromuscular exam, and had abnormalities on needle EMG testing. Five of her relatives were reported to have weakness and trouble with day-to-day function. Her mother (M.C.) and maternal grandfather (W.C.) were able to be examined in person and had the condition genetically confirmed.

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KEYWORDS

Bethlem myopathy, collagenopathy, COL6A3, weakness, genetics

ABBREVIATIONS

Bethlem myopathy (BTHLM1), Ullrich myopathy (UCMD1), Collagen VI (COL6), electromyography (EMG), nerve conduction study (NCS)

CASE REPORT

L.C. (the proband) was a 21-year-old female who presented to the neurology clinic with complaints of numbness and paresthesias in distal extremities, spasms in the calves, 4 years of progressive finger and ankle weakness, and 2 years of difficulty with finger contractures and losing her grip, making feeding difficult. She was a product of a nonconsanguineous marriage, with a history of hepatitis C and substance abuse. The patient's sister was diagnosed with hepatitis C after a history of IV drug use with the proband's now ex-boyfriend; subsequently, L.C. was tested and diagnosed with hepatitis C but has yet to receive treatment. L.C. reported normal educational progress with appropriate early childhood milestones and swallowing function. She denied autonomic symptoms, demonstrated no fragile hyper-extensible skin, and was not hypermobile in her joints but did report inability to whistle. Pertinent negatives include no ataxia, ptosis, or fatigable weakness. She was medically managed with gabapentin 800mg TID for paresthesias and baclofen for leg spasms that were discontinued when she became pregnant. Relevant social history included being unemployed and a mother to a toddler. Physical examination was pertinent for weakness of neck flexion, eye closure, and cheek puffing, significant finger contractures and lesser elbow, knee, and ankle contractures, and scapular winging. There was no grip or percussion myotonia. There was generalized weakness involving deltoids, biceps, and wrists sparing finger flexors, quadriceps, hamstrings, and plantar flexion muscles. She was unable to kneel down, perform a squat, or get up off the floor. Reflexes were intact. Temperature sensation, light touch, vibration, and proprioception were diminished distal to the mid-shins. She toe-walked due to ankle contractures. Lab testing showed normal CPK, B12, TSH/Free T4, glucose, and HbA1c. Vitamin D was insufficient at 26.5 ng/ml. Ankle foot orthotics (AFO) were prescribed which she chose not to utilize. Normal nerve conduction study (NCS) of the arms and legs

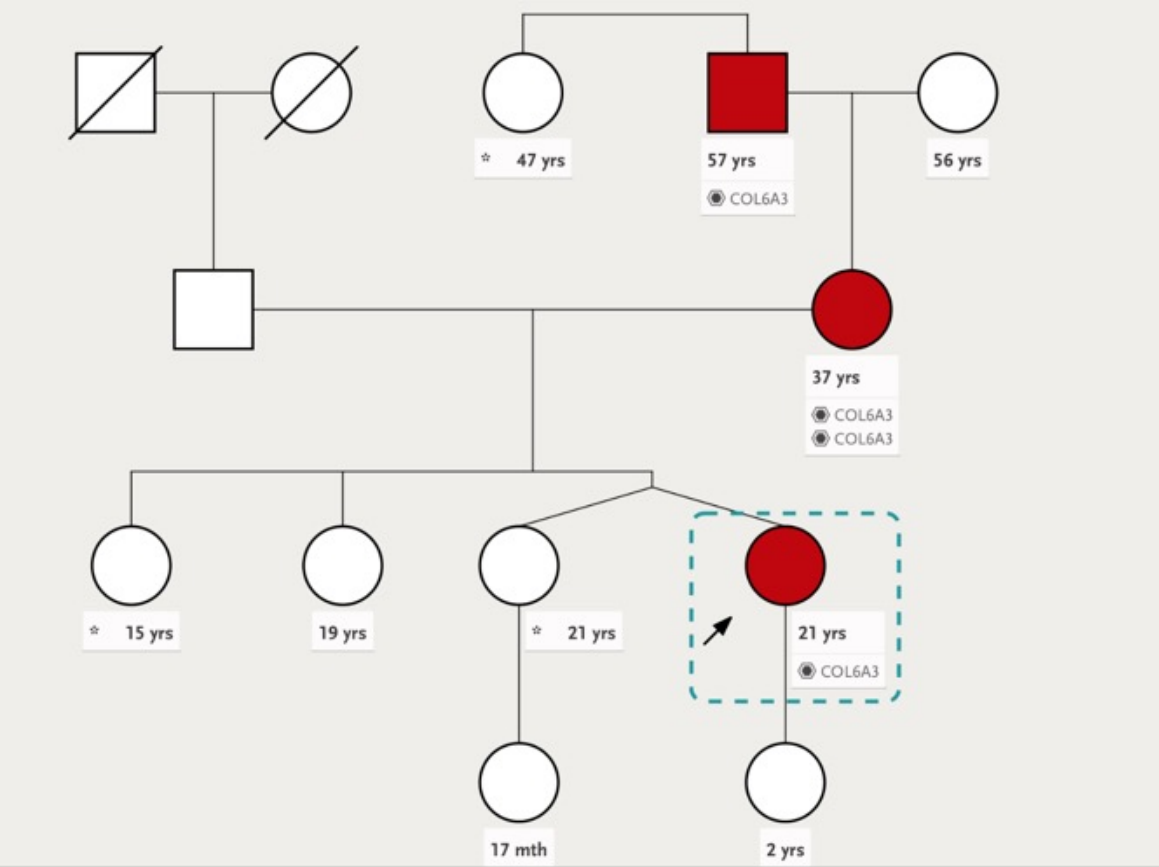

FIGURE 1. Family pedigree. The arrow indicates the proband, L.C. The asterisk indicates other affected individuals with distal weakness and/or tendon surgery who were not genetically tested. The red color indicates individuals with a confirmed COL6A3 mutation (c.6354+1G>A).

ruled out large fiber peripheral neuropathy. EMG (Figure 2) revealed a lack of myotonic discharges, but there were myopathic units in the left biceps brachii and tibialis anterior muscles. The patient declined a muscle biopsy. Invitae genetic testing revealed a mutation in the COL6A3 gene at c.6354+1G>A. She was referred for genetic counseling, but her insurance did not cover it.

The family tree (Figure 1) indicated multiple relatives who had distal hand weakness including two (37-year-old M.C. and 57-year-old W. C.) who were affected in an autosomal dominant fashion who were able to be examined (shown in red in Figure 1). M.C., the proband's mother, was a 37-year-old woman with a medical history of depression and smoking, who was invited for saliva genetic testing and found to carry the same mutation as L.C. In the clinic, she complained of paresthesias in distal extremities and reported having had multiple tendon and Achilles lengthening surgeries. She took Lyrica and Neurontin in the past. Pertinent exam findings were hammertoes, high arches, areflexia at the ankles, and mild weakness of finger abduction and extension. NCS/EMG study showed a right common peroneal mononeuropathy with acute and chronic denervation in the right tibialis anterior and extensor hallucis longus. She was more mildly affected than L.C., as she felt well enough to not medicate her paresthesias and was not limited in her activities of daily living. W.C., the proband's maternal 57-year-old grandfather, presented to the clinic in need of evaluation for disability benefits due to inability to work as a maintenance worker. His medical history included smoking, hypertension, and gastritis. He reported being slower to walk and run than his peers. In the last 10 years, he deteriorated and developed more cramps and an inability to climb stairs. Examination showed weakness of multiple muscle groups: biceps and triceps in the arms, finger extensors, finger

Figure 2. Table of nerve conduction results for the proband L.C. showed that nerve conduction study results were entirely normal in all four extremities, which rules out any mononeuropathy or polyneuropathy. (The electromyography data records for the proband L.C. could not be uploaded due to technical difficulties with resolution but are available upon request by contacting the corresponding author. The needling of her four extremities was significant for early recruitment, short duration, and small amplitude units in the left biceps brachii and left tibialis anterior muscles, which indicates myopathic changes that can occur in various muscle diseases but excludes diseases of nerve roots or motor neuron disease.)

Motor Nerve Conduction:

Nerve and Site	Latency ms	Latency NI ≤ ms	Amplitude mV	Amplitude NI ≥ mV	Lat Diff ms	Dist mm	Velocity m/s	Velocity NI ≥ m/s
Median.L to Abductor pollicis brevis.L								
Wrist	3.0	4.4	7.2	4.00	3.0	70		
Elbow	6.6		6.9		3.6	200	56	49.0
Ulnar.L to Abductor digiti minimi (manus).L								
Wrist	2.3	3.3	8.7	6.00	2.3	70		
Below elbow	6.0		8.1		3.7	210	57	49.0
Above elbow	7.6		8.0		1.6	100	63	49.0
Median.R to Abductor pollicis brevis.R								
Wrist	3.2	4.4	11.1	4.00	3.2	70		
Elbow	6.9		8.6		3.7	220	59	49.0
Ulnar.R to Abductor digiti minimi (manus).R								
Wrist	2.5	3.3	8.1	6.00	2.5	70		
Below elbow	6.0		7.3		3.5	200	57	49.0
Above elbow	7.7		7.2		1.7	100	59	49.0

Sensory and Mixed Nerve Conduction:

Nerve and Site	Onset Latency ms	Peak Latency ms	Peak Latency NI ≤ ms	Amplitude mV	Amplitude NI ≥ mV	Lat Diff ms	Dist mm	Velocity m/s	Velocity NI ≥ m/s
Median.L to Digit II (index finger).L									
Wrist	2.1	2.7	3.5	38	20.0	2.1	130	62	50.0
Ulnar.L to Digit V (little finger).L									
Wrist	1.9	2.5	3.1	33	17.0	1.9	110	58	50.0
Radial.L to Anatomical snuff box.L									
Forearm	1.7	2.1	2.9	36	15.0	1.7	100	59	50.0
Median & Ulnar.L to Wrist.L									
Digit IV (Median)	2.4	2.9	3.3	9*	9.20				
Digit IV (Ulnar)	2.2	2.8	3.3	11	5.80	0.1			

Motor Nerve Conduction:

Nerve and Site	Latency ms	Latency NI ≤ ms	Amplitude mV	Amplitude NI ≥ mV	Lat Diff ms	Dist mm	Velocity m/s	Velocity NI ≥ m/s
Peroneal.L to Extensor digitorum brevis.L								
Ankle	4.8	6.5	6.5	2.00	4.8	90		
Fibula (head)	11.4		6.0		6.6	315	48	44.0
Popliteal fossa	13.2		5.9		1.8	90	50	40.0
Tibial.L to Abductor hallucis.L								
Ankle	4.5	5.8	11.1	4.00	4.5	70		
Popliteal fossa	13.0		10.2		8.5	385	45	41.0
Peroneal.R to Extensor digitorum brevis.R								
Ankle	4.6	6.5	9.3	2.00	4.6	90		
Fibula (head)	11.0		8.6		6.4	295	46	44.0
Popliteal fossa	12.6		8.5		1.6	90	56	40.0
Tibial.R to Abductor hallucis.R								
Ankle	4.6	5.8	11.4	4.00	4.6	70		
Popliteal fossa	12.6		10.5		8.0	360	45	41.0

Sensory and Mixed Nerve Conduction:

Nerve and Site	Onset Latency ms	Peak Latency ms	Peak Latency NI ≤ ms	Amplitude mV	Amplitude NI ≥ mV	Lat Diff ms	Dist mm	Velocity m/s	Velocity NI ≥ m/s
Superficial peroneal.L to Ankle.L									
Lower leg	2.4	3.1	4.4	7	6.00	2.4	120	50	40.0
Sural.L to Ankle.L									
Lower leg	2.7	3.5	4.4	14	6.00	2.7	120	44	40.0
Superficial peroneal.R to Ankle.R									
Lower leg	2.5	3.1	4.4	18	6.00	2.5	120	48	40.0
Sural.R to Ankle.R									
Lower leg	2.6	3.4	4.4	15	6.00	2.6	120	46	40.0

flexors, thumb abductors, knee contractions causing knee extension weakness, quadriceps weakness with difficulty arising from a chair, and ankle dorsiflexion weakness with steppage gait. Reflexes were intact except absent at the ankles. Pinprick sensation was normal. His labs showed A1c 5.6%, LDL 152, CK 454, and a negative celiac panel. Ankle foot orthotics were prescribed for him. W.C. submitted a blood sample for an Invitae collagenopathy panel, and the same pathogenic variant was found as in L.C. and M.C. It affected a donor splice site in intron 19 of the COL6A3 gene and disrupted RNA splicing, likely resulting in absent or disrupted protein.

The finding of a c.6354+1G>A mutation in these relatives was previously reported in other individuals with Bethlem myopathy. Splice site variants typically lead to loss of protein function. This variant was not present in population databases (ExAC no frequency), but ClinVar contained an entry for this variant. The proband's twin, younger sister, and maternal aunt who were all affected to variable degrees were not available to be tested genetically or examined in person. According to L.C., M.C., and W.C.'s recollection, the proband's maternal great aunt suffered from many contractures and needed tendon surgeries. The proband's twin sister and her 15-year-old sister (who also had tendon transfers) were both affected with similar distal hand weakness.

DISCUSSION

The family pedigree (Figure 1) obtained in the clinic showed an autosomal dominant inheritance pattern over three generations. The proband's history, exam, and EMG suggested a presumably neuromuscular disease localized to the distal skeletal muscles. Collagen VI is a ubiquitously expressed microfibrillar protein found in skeletal muscles; when mutant ColVI-null mice deficient in it were studied, they exhibited myopathic features including decreased muscle mass and contractile force.[1] Contractures of Achilles tendons, which were repaired surgically in members of L.C.'s family, are a feature commonly described in Bethlem myopathy cases. Collagen VI has many other roles in the body including inhibition of apoptosis and oxidative damage, the promotion of tumor growth, and the regulation of cell differentiation and the autophagic machinery.[2] Informed consent was obtained, and genetic counseling was recommended to discuss the implications of these results because they may affect subsequent offspring and close relatives, especially those of child-bearing age.

L.C.'s paresthesias were presumed to be from a hepatitis C-related small fiber neuropathy, but this was not confirmed with a skin biopsy. Alternate investigations described in the literature in similar cases include muscle biopsy to check for increased connective tissue and fatty replacement with or without fiber necrosis, MRI imaging that shows concentric patterns in vastus lateralis and central high signal in rectus femoris, and Collagen VI Immunolabeling on cultured skin fibroblasts.3 These methods were not pursued due to the reliability of genetic testing. The three individuals presented here greatly benefited from pursuing a definitive genetic diagnosis because it gave them access to necessary resources such as genetic counseling and encouraged autonomy through family planning. Proactively, the proband chose to have her daughter examined by a pediatric neurologist at Nationwide Children's Hospital. It is possible that L.C.'s daughter will need special classroom accommodations, and she may possibly need an individualized education program. L.C. expressed an interest in having more children and that this spurred her to seek neurologic consultation. W.C. was able to get economic assistance by applying his specific diagnosis to the disability application.

The COL6A3 gene is associated not only with autosomal dominant and recessive Bethlem myopathy 1 (BTHLM1) but with Ullrich congenital muscular dystrophy 1 (UCMD1). The phenotype associated with UCMD1 is typically toward the more severe end of the spectrum and is characterized by congenital muscle weakness, proximal joint contractures, and significant hyperlaxity of distal joints. BTHLM1 patients experience progressive muscle weakness and joint stiffness (contractures) in their fingers, wrists, elbows, and ankles. During childhood, a developmental delay may be noted, however, the L.C. family cohort did not report lagging behind in education. By the age of 50-years-old, approximately two-thirds (66%) of people with BTHLM1 will need to use a walker, cane, or wheelchair. Some people with Bethlem myopathy have skin abnormalities such as follicular hyperkeratosis, but this was not seen in the individuals presented here. Rarely, individuals with BTHLM1 may develop breathing problems as

the disease progresses. Age of onset varies from the prenatal period to adulthood. Close relatives have up to a 50% chance of being a carrier. This condition has a differential diagnosis consisting of other rare diseases including congenital myopathies, facioscapulohumeral muscular dystrophy, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, and Ehlers-Danlos connective tissue syndrome,[4] indicating the benefit of genetic testing. A targeted genetic test can offer cost-effective, safe, and fairly rapid turnaround time, which can improve the quality of care for patients.[5]

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