

CASE REPORT

A rare case of late-onset limb-girdle muscular dystrophy: Calpainopathy

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1 | INTRODUCTION

Calpainopathy is the most common limb-girdle muscular dystrophy subtype (40%) worldwide.¹ Its usual presentation is in patients between 5 and 20 years of age (75% of cases).² Here, we present a case of late-onset calpainopathy presenting at an age of 65 years, which is extremely rare and has been previously described only in a couple of case reports.³⁻⁵

2 | CASE PRESENTATION

A 65-year-old man, presented with a history of bilateral, proximal lower limb weakness for the past 1 year. It started with difficulty in climbing upstairs and gradually progressed such that he required support for walking on level ground. He also developed difficulty turning from side to side and proximal muscle weakness in bilateral arms for the last 8 months. He also complained of occasional muscle cramps, although he had no associated tenderness, stiffness, or joint pain. Distal muscle, and sensory and cranial nerve involvement were absent and there was no fever or weight loss history. He had a history of pulmonary tuberculosis, but no other comorbidities. There was no similar illness in the family members.

On examination, there was hypertrophy of calf muscles in both the lower limbs and bilaterally symmetrical winging of the scapula (Figure 1). Power was reduced bilaterally, around the shoulder joints (4/5) and hip joints (4/5) in all ranges of motion, as well as the trunk muscle (3/5). Beevor's sign was absent. Deep tendon reflexes, sensory examination, and cranial nerve examination were normal. There

was a lordotic posture and a waddling, broad-based gait. The rest of the systems were normal on examination.

Blood investigations showed only mildly raised creatine kinase (CK) levels (Table 1). Electromyography was suggestive of a "myopathic pattern." Polyphasic MUAPs with short duration and small amplitude were seen in the right biceps and right vastus lateralis.

The patient underwent a muscle biopsy from the right vastus lateralis muscle. Histopathology showed loss of fascicular architecture and variation in fiber size, with few regenerating and degenerating fibers. There was perimysial and endomysial adipose tissue infiltration (Figure 2). NADHTR revealed few lobulated fibers (Figure 3). Immunohistochemistry showed normal staining patterns for alpha, beta, and gamma sarcoglycan and dysferlin. Immunoblot was suggestive of an absent calpain band, suggesting calpainopathy as a likely diagnosis (Figure 4).

Thus, based on clinical, electromyogram, and histopathology reports, a diagnosis of late-onset calpainopathy was made.

The patient was prescribed muscle strengthening exercises, namely high sitting-hip flexion, adductor squeeze with knee flexion and extension, static and dynamic quadriceps, side-lying shoulder exercises, and scapular protraction and retraction. He was discharged with a home exercise program. On follow-up after 6 weeks, he reported improvement in the symptoms.

3 | DISCUSSION

Calpainopathies are of two types: LGMD R1, calpain-3-related (previously LGMD2A) is an autosomal recessive disease and LGMD D4,

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FIGURE 1 Calf muscle hypertrophy (A) and winging of the scapula (B)

TABLE 1 Laboratory parameters

Tests	Values	Normal range	Remarks
Hemoglobin	13.7 g/dl	12–15	WNL
Total leukocyte counts	6590/cu mm	4000–11,000	WNL
Differential leukocyte counts (N/L/M/E)	58.8/29.4/5.9/0.6	N-40-80 L-20-40 M-2-10 E-1-6	WNL
Platelets	216,000/ μ l	150,000–400,000	WNL
Hematocrit	44.0%	36–46	WNL
Urea	13 mg/dl	17–49	WNL
Creatinine	0.4 mg/dl	0.5–0.9	WNL
Uric acid	4.1 mg/dl	2.4–5.7	WNL
Calcium	8.0 mg/dl	8.6–10.0	WNL
Phosphorus	2.8 mg/dl	2.5–4.5	WNL
Sodium	141 mmol/L	135–145	WNL
Potassium	4.8 mmol/L	3.5–5.1	WNL
Erythrocyte sedimentation rate	22 mm/h		WNL
C-reactive protein	<0.5		WNL
Aspartate aminotransferase	29 U/L	\leq 32	WNL
Alanine aminotransferase	44 U/L	\leq 33	WNL
Total protein	8.0 g/dl	6.4–8.3	WNL
Total bilirubin	0.91 mg/dl	0–1.2	WNL
Alkaline phosphatase	64 mg/dl	35–104	WNL
Albumin	4.7 g/dl	4.0–4.9	WNL
HbA1c	5.6%	Non-diabetic range: 4.8–5.6 Prediabetic range: 5.7%–6.4% Diabetes range: \geq 6.5% High risk: >7.0%	WNL
Creatine kinase	600 U/L	39–308	Raised
Vitamin D	22.8 U/L	10–44	WNL
iPTH	18.2 pg/ml	15–65	WNL
TSH	3.20 μ lU/ml	0.27–4.20	WNL
T3	72 ng/dl	80–200	WNL
T4	7.4 μ g/dl	5.1–14.1	WNL
Sr Cortisol	8 mcg/dl	(5–23)	WNL
Myositis profile	Negative		
ANA, ANCA, RF	Negative		

Abbreviation: WNL, within normal limits.

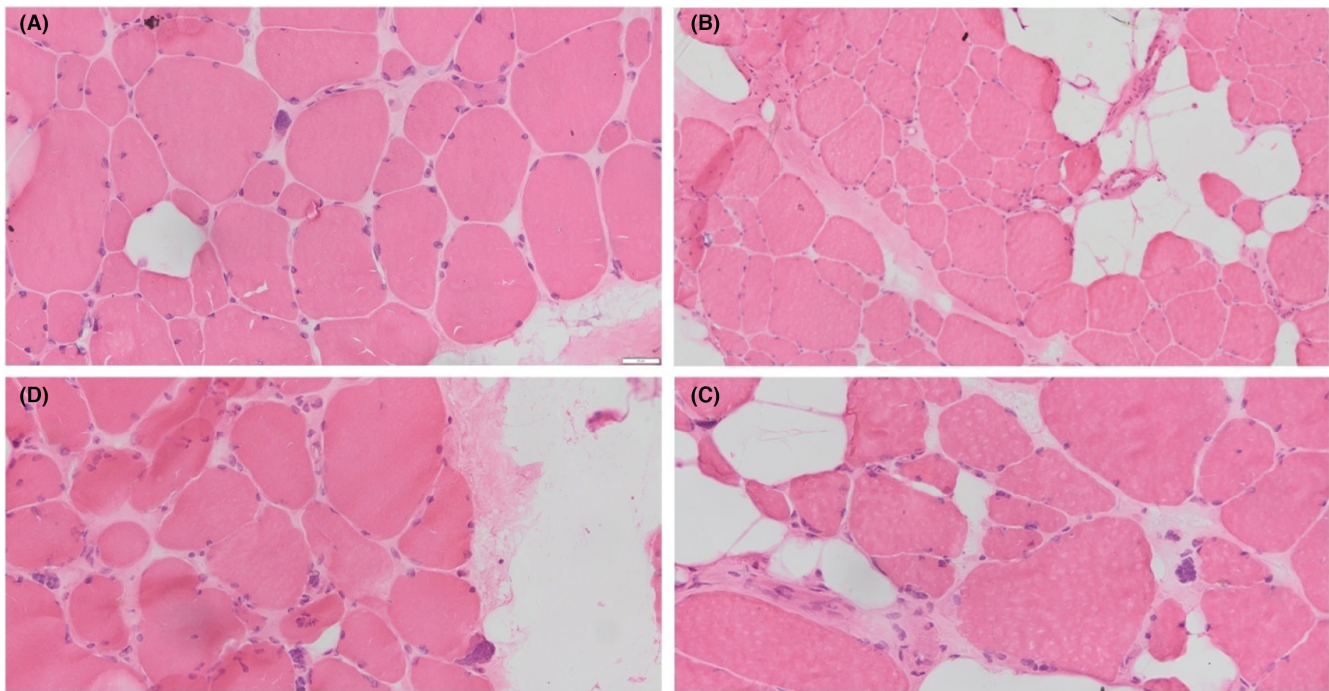


FIGURE 2 Histopathology of right vastus lateralis muscle

calpain-3-related (previously LGMDD4) is an autosomal dominant disease.

Calpain-3, a calcium-dependent cysteine protease, helps regulate calcium outflow from the sarcoplasmic reticulum, interacts with cytoskeletal proteins, such as titin and dysferlin, and plays an important role in sarcomere assembly, remodeling, and repair.^{6,7} Possibly, loss-of-function pathogenic calpain-3 variants lead to recessive disease with abnormal muscle sarcomeres and eventual muscle fibers death.⁸ The autosomal dominant disease is due to certain single pathogenic *CAPN3* variants that exert a dominant-negative deleterious effect on protein function.⁹

Autosomal recessive calpainopathy (LGMD R1) is considered the most common type of LGMD worldwide,¹⁰ with variation depending in part on the geographic region.^{8,11} The phenotype is variable,

ranging from pelvic and shoulder girdle muscle weakness to asymptomatic disease with elevated serum CK levels (hyperCKemia).⁸ The severe disease significantly involves the parascapular muscles, biceps, gluteus maximus, adductors, and hamstrings. Hip girdle muscles are weaker than shoulder girdle muscles, with severe weakness involving hip extension, adduction, and knee flexion. Scapular winging, abdominal laxity, hyperlordosis, and a waddling gait are common, as was observed in our patient. Contractures are extensive and tend to develop early. Facial weakness may occur in cases with early-onset or severe disease.⁶ CK levels range from 500 to 20,000 units/L. In our patient, the CK level was 600 units/L. Muscle biopsy often shows lobulated fibers, as seen in our case. Cardiac and pulmonary involvement is unusual.⁷

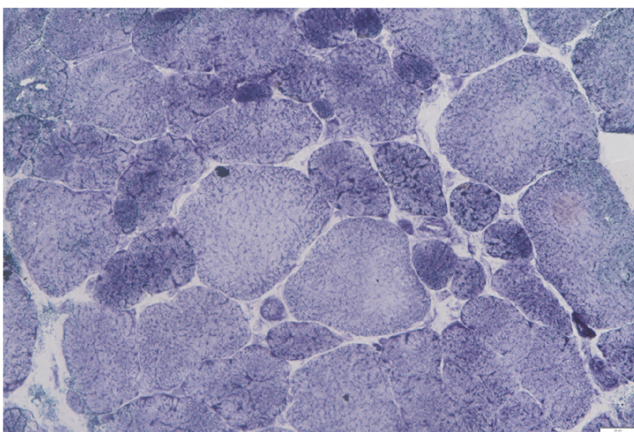


FIGURE 3 NADHTR staining shows lobulated fibers

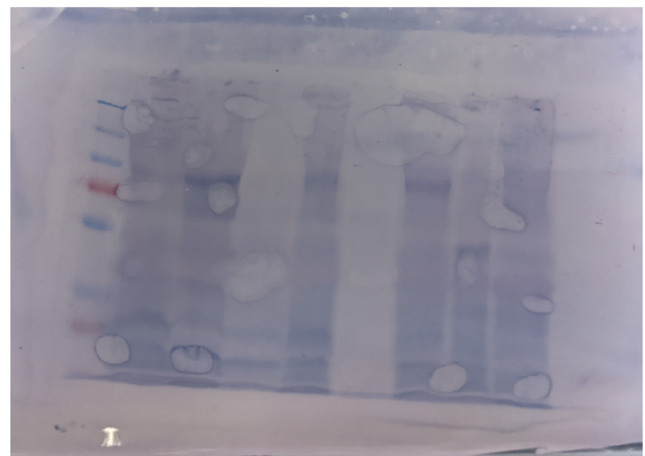


FIGURE 4 Immunoblot showing partial loss of calpain band in first line

Although course and severity are variable, the requirement for a wheelchair occurs between the ages of 21 and 40 years in ~80%.¹² The autosomal dominant calpainopathy (LGMD D4) has a phenotype that resembles but is generally milder than the recessive form. As an extremely rare presentation, the patient in this case report had an onset of weakness above 60 years of age and was walking independently with minimal support at an age of 65 years. Single-gene genetic diseases are now being reported in elderly patients more often. Some of the possible explanations for this phenomenon can be the overall increasing lifespan, increasing awareness about such disease entities, and the recent advent of DNA-based genetic testing.⁴ Our patient denied genetic analysis, and a probable diagnosis of calpainopathy was made based on biopsy and immunoblot reports.

The role of exercise in limb-girdle muscular dystrophy has been reported in previous studies which showed improvement after exercise.^{13,14} The above patient also showed a good response to physiotherapy.

In conclusion, older adults may rarely present with genetic disorders which have the usual age of onset at a young age, and such diagnoses should not be dismissed merely based on the age of the patient. A high index of suspicion and systematic approach may help to make such rare diagnoses and provide optimum therapy.

AUTHOR CONTRIBUTIONS

Bhawana Painkra, Richa Mallick, Pramod Kumar, and Prasun Chatterjee were directly involved in patient evaluation and management; and case report manuscript planning, writing and review. Sumanta Das was involved in evaluation and reporting of biopsy slides.

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CONFLICT OF INTEREST

Nothing to disclose.

INFORMED CONSENT

Written informed consent was taken from the patient.

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