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CASE REPORT

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Adult late-onset limb-girdle muscular dystrophy R1/2A complicated by parathyroid adenoma and sick sinus syndrome: a case report and literature review

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Abstract

Background Limb-girdle muscular dystrophy (LGMD) is a group of hereditary myopathies. This group of diseases is highly heterogeneous in terms of genetic mode, age at onset, and disease progression; therefore, they are easily misdiagnosed and missed in clinical practice.

Case presentation We describe a case of adult late-onset LGMD R1/2A in a 56-year-old female patient. The patient experienced elevated creatine kinase levels lasting 5 years, muscle soreness of the limbs lasting 4 years, and exacerbation of limb fatigue lasting 1 month. Early in the course of the disease, the patient experienced severe bradycardia and was later diagnosed with sick sinus syndrome. In addition to cardiac involvement, our patient also had primary hyperparathyroidism during the disease course, which was confirmed pathologically as a parathyroid adenoma. A biopsy of the left biceps showed pathological manifestations of mild myogenic damage. All-exon gene sequencing confirmed the diagnosis of LGMD R1/2A, and she was treated with vitamin E, vitamin B2, and coenzyme Q. Due to atrial fibrillation secondary to sick sinus syndrome, a pacemaker was implanted.

Conclusion The patient in this case study had adult late-onset LGMD R1/2A with cardiac involvement and functional parathyroid adenoma, which is rare and clinically significant. Therefore, early clinical identification, diagnosis, as well as targeted and active treatments can improve the prognosis of such patients.

Keywords Limb-girdle muscular dystrophy R1/2A, Functional parathyroid adenoma, Primary hyperparathyroidism, Sick sinus syndrome

Background

Limb-girdle muscular dystrophy (LGMD) is a group of hereditary myopathies exhibiting different degrees of weakness and atrophy of the scapular girdle and pelvic girdle muscles and is accompanied by normal to significantly increased serum creatine kinase (CK) levels. It is typically an adult-onset disease. However, this group of diseases is highly heterogeneous in terms of genetic mode, age at onset, and disease progression; therefore, they are easily misdiagnosed and missed in clinical practice. Here, we report a case of adult late-onset LGMD R1/2A. The patient experienced a lengthy

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disease duration and slow disease progression. Additionally, her condition was complicated by parathyroid adenoma and sick sinus syndrome, which is a clinically rare combination.

Case presentation

A 56-year-old female patient was admitted to the hospital in February 2023 because of "elevated CK levels lasting 5 years, muscle soreness of the limbs lasting 4 years, and exacerbation of limb fatigue lasting 1 month." A physical examination 5 years ago revealed elevated CK levels. In August 2018, a cardiovascular examination revealed "lactic dehydrogenase (LDH) and CK levels at 264.1 and 665.0 U/L, respectively. Additionally, esophageal ultrasound showed abnormal sinus node function; electrocardiography (ECG) showed significant bradycardia (44 beats/min); and troponin, cardiac ultrasound, and coronary computed tomography (CT) angiography were normal. The patient was diagnosed with "sick sinus syndrome." She refused surgery and was treated long-term with trimetazidine and coenzyme Q. Four years prior to presentation, she experienced soreness and swollen limbs, mainly in the lower extremities; however, the symptoms remained unnoticed by the patient. Subsequently, the patient was hospitalized in our department in July 2021. The examination results were as follows: aspartate aminotransferase (AST), 40.9 U/L; LDH, 266.0 U/L; CK, 661.0 U/L; creatine kinase MB isoenzyme (CK-MB), 25.3 U/L; myoglobin, 306.9 ng/mL; calcium, 3.21 mmol/L; phosphorus, 0.7 mmol/L; parathyroid hormone (PTH), 280.1 pg/mL; and 24 h urine calcium, 11.52 mmol/L. Test results for complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), human leucocyte antigen B27, rheumatoid factor, anticyclic citrullinated peptide antibody, anti-streptolysin O, immunoglobulin, complement, anti-nuclear antibody spectrum, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis antibody spectrum, myositis antibody spectrum, thyroid function, and tumor markers were normal. Additionally, lung CT, nerve electromyography, thigh muscle magnetic resonance imaging (MRI), and bone emission CT results were normal. The patient was diagnosed with "hyperparathyroidism" and "right parathyroid adenoma" in July 2021 at the Shanghai Sixth People's Hospital affiliated with Shanghai Jiaotong University. Next, the right inferior parathyroid lesion was excised under general anesthesia. Pathological examination (Pathology number F2021-5384) confirmed a right lower parathyroid adenoma, and immunohistochemistry revealed Ki-67 (3%), PTH (+), GATA3 (+), and Syn (+). After the surgery, the levels of blood calcium, phosphorus, PTH, thyroid function, and myocardial enzymes all returned to normal range. Soreness and swelling of the limbs significantly improved, without any myalgia or muscle weakness. In January 2023, the patient experienced proximal muscle soreness again with obvious lower-extremity fatigue. No abnormal rashes were observed. At that time, the proximal muscles of the limbs were mildly tender, the muscle strength of the limbs was grade V, and the muscular tone was normal. An examination on February 14, 2023, revealed the following: alanine aminotransferase, 67.0 U/L; AST, 61.8 U/L; LDH, 414.0 U/L; CK, 1635.0 U/L; and CK-MB, 40.0 U/L. Nerve electromyography was performed on February 17, 2023, and it showed myogenic damage involving the proximal and distal muscles of the upper extremity and the proximal muscles of both lower extremities. Results for PTH, troponin I, complete blood count, ESR, ultrasensitive CRP, calcium, phosphorus, immunoglobulin, complement, anti-nuclear antibody spectrum, ANCA-associated vasculitis antibody spectrum, thyroid function, tumor markers, lung CT, and the MRI of the right thigh and right calf were normal. A biopsy of the left biceps conducted on March 13, 2023, showed pathological manifestations of mild myogenic damage (Fig. 1). All-exon gene sequencing revealed the following: (1). Gene/transcript CAPN3 NM_000070.3; physical location: chr15:42702630; gene subregion: exon 20; mutation information: c.2120A > G p.Asp707Gly; mutation type: heterozygous; pathogenicity: pathogenic; disease/phenotype: LGMD types IV (autosomal dominant inheritance) and I (autosomal recessive inheritance); RS number: rs200379491; (Fig. 2A). (2). Gene/transcript CAPN3 NM_000070.3; physical location: chr15:42702167; gene subregion: exon 19; mutation information: c.2089T > C p.Cys697Arg; mutation type: heterozygous; suspected pathogenicity; disease/phenotype: LGMD types IV (autosomal dominant inheritance) and I (autosomal recessive inheritance); (Fig. 2C). (3). Gene/transcript MYH2 NM-001100112.2; physical location: chr17:0427913; gene subregion: exon 35; mutation information: c.5045G > A p.Arg1682His; mutation type: heterozygous; disease/phenotype: congenital myopathy type VI with eye muscle paralysis; RS number: rs145099248 (Fig. 2E). The patient was diagnosed with "LGMD R1/2A" and was treated with vitamin E and vitamin B2 combined with coenzyme Q. Due to atrial fibrillation secondary to sick sinus syndrome, pacemaker implantation was performed at Ruijin Hospital, Shanghai, on May 24, 2023.

Previous history: she has a history of bradycardia lasting more than 17 years, a cesarean section, and breast fibroidectomy. Personal history: the patient had a daughter and a husband, both of them were healthy. Family history: the patient's parents were not consanguineously married; her mother is still alive and has Alzheimer's disease. Her father is deceased and also had a history

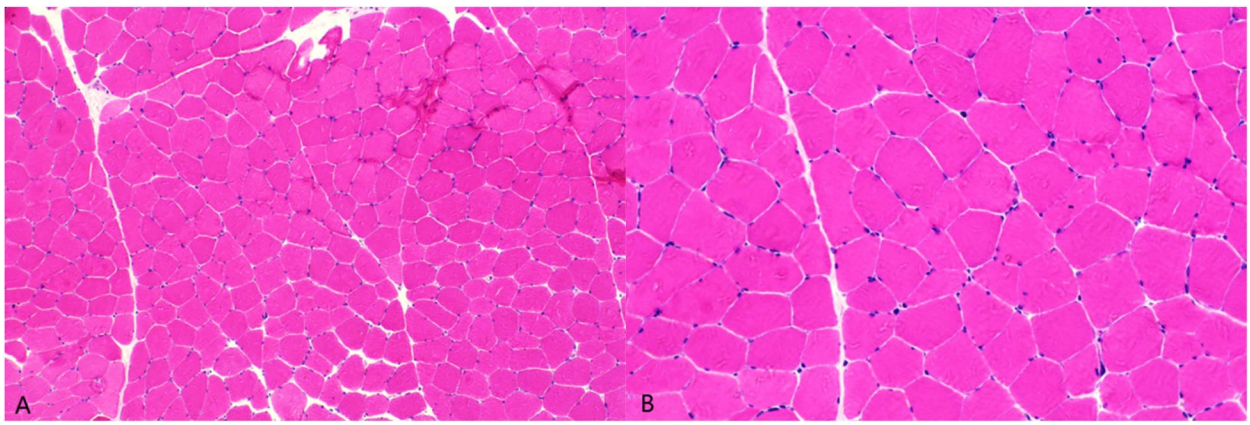

Fig. 1 Left biceps muscle biopsy and cryostat sections. Hematoxylin–eosin staining: Myofibers appear mildly variable in size, exhibiting no necrotic or regenerating fibers, no obvious perifascicular atrophy, and no significant inflammatory cell infiltration in the interstitium

of arrhythmias (bradycardia and atrial fibrillation) and underwent pacemaker implantation.

Whole-exon gene testing of relatives was performed. The patient's mother carried the heterozygous mutation NM_000070.3 (CAPN3) c.2120A > G p.Asp707Gly (Fig. 2B) but did not develop into LGMD. Her daughter carried the heterozygous mutations NM_000070.2 (CAPN3) c.2120A > G (D707G) (Table 1) and NM-147127.4 (EVC2) c.2320C > T (Q774) (Table 2), but also did not develop into LGMD.

Patient status: she currently has sore limbs; her fatigue symptoms have been alleviated, and she experiences no limb movement limitations, allowing her to walk normally.

Discussion and conclusions

LGMD was initially described by Walton and Nattrass [1] in 1954 as a group of muscle diseases with limb-girdle muscle weakness as the main clinical manifestation. This group of diseases has common clinical characteristics: onset occurs mostly during teenage and adult years, manifesting in different degrees of weakness and atrophy of the shoulder girdle and pelvic girdle muscles, with normal to significantly increased serum CK levels. The 1995 European Neuromyopathy Center Working Group [2] categorized LGMD into LGMD types I (AD) and II (AR) based on inheritance mode, and the subtypes were further classified according to the order of discovery of the disease-causing genes and differences in defective proteins. By 2017, the number of LGMD subtypes had increased to 34 (8 and 26 subtypes of LGMD types I and II, respectively) [3]. LGMD R1/2A is associated with mutations in the gene encoding muscle-specific calcium-activated calpain on chromosome 15, the vast majority of which are single-nucleotide mutations (60%–70%), with the remaining 30%–40% being small fragment insertion or deletion mutations. Mutations were distributed throughout each exon, but some hot spots were observed, with exon 21 containing the most mutations. CAPN3 encodes a skeletal muscle enzyme named calpain 3 [4, 5]. Currently, over 450 unique pathological mutations have been identified. They affect all protein domains and, in most cases, impair the autolytic and proteolytic activities of enzymes. Pathogenic CAPN3 mutations disrupt various homeostatic mechanisms in the skeletal muscles, resulting in LGMD 2A.

LGMD mainly affects the skeletal muscle but may also involve myocardial tissue. A recent German study that assessed cardiac involvement in different muscular dystrophies using MRI found that the hearts of patients with LGMD are commonly involved, with regional wall motion abnormalities (prevalence in patients with LGMD: 55%) and late enhancement (prevalence in patients with LGMD: 82%) [6]. Among the many subtypes of LGMD, cardiac lesions in LGMD R3-6 [7], LGMD R9 [8, 9] and LGMD 1E [10] are more common and typically manifest as conduction defects and/or dilated cardiomyopathy. Patients with such manifestations are at risk of severe or fatal cardiac events and have a poor prognosis. However, cardiac involvement is rarely reported in LGMD R1/2A, even in older individuals and those with more severe symptoms [11]. A multicenter study that investigated the clinical manifestations and disease progression of 85 genetically confirmed patients with LGMD 2A for up to 4 years also found that patients with this subtype rarely had life-threatening cardiac abnormalities; 94% of those patients had a mean left ventricular ejection fraction of 67.5%, and only one patient had myocardial hypertrophy [12]. The patient in our case report experienced severe bradycardia relatively early

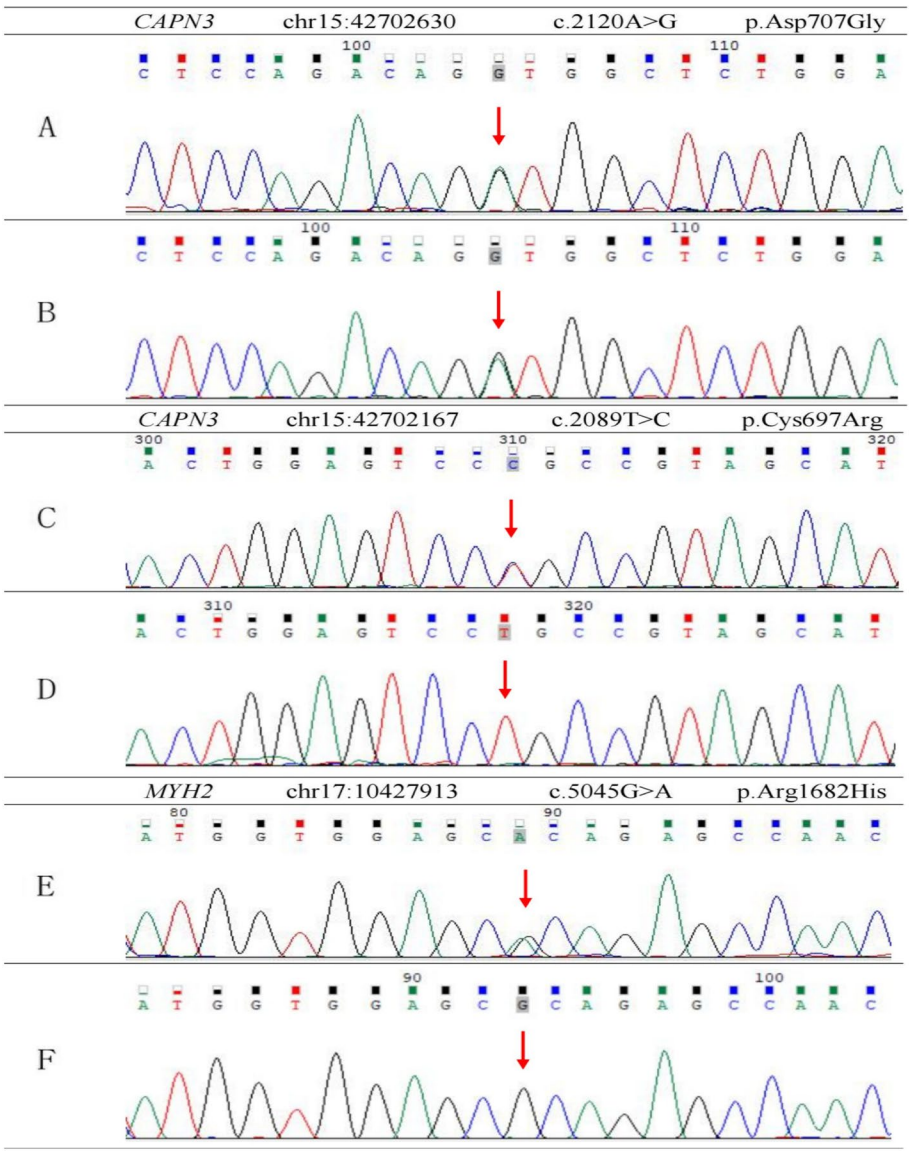

Fig. 2 All-exon gene sequencing revealed the following: **A** Patients: CAPN3, NM_000070.3; c.2120A > G: p.Asp707Gly, heterozygous mutations (Het). **B**. Patient's mother: CAPN3, NM_000070.3; c.2120A > G: p.Asp707Gly, Het. **C**. Patients: CAPN3, NM_000070.3; c.2089T > C: p.Cys697Arg, Het. **D**. Patient's mother: No mutation. **E**. Patients: MYH2, NM_001100112.2; c.5045G > A: p.Arg1682His, Het. **F**. Patient's mother: No mutation

Table 1 Patient's daughter: NM_000070.2 (CAPN3) c.2120A > G (D707G), Het

Result	Carrier
Variant(s)	NM_000070.2(CAPN3):c.2120A>G(D707G) heterozygote
Methodology	Sequencing with copy number analysis
Interpretation	This individual is a carrier of calpainopathy. Carriers generally do not experience symptoms.
Detection rate	>99%
Exons tested	NM_000070:1-24.

Table 2 Patient's daughter: NM-147127.4 (EVC2) c.2320C>T (Q774), Het

Result	Carrier
Variant(s)	NM_147127.4(EVC2):c.2320C>T(Q774*) heterozygote †
Methodology	Sequencing with copy number analysis
Interpretation	This individual is a carrier of EVC2-related Ellis-van Creveld syndrome. Carriers generally do not experience symptoms.
Detection rate	>99%
Exons tested	NM_147127:1-22.

and was diagnosed with sick sinus syndrome after examination, while atrial fibrillation and atrial septal aneurysm developed during disease progression, suggesting a risk of cardiac involvement in LGMD R1/2A. A study from the United Kingdom found that 2 of 85 patients with LGMD R1/2A experienced atrial fibrillation and left ventricular dysfunction [13]. Additionally, an autopsy of two patients with LGMD R1/2A in Japan confirmed our findings; both patients had right bundle branch blocks: one patient had myocardial hypertrophy, and histological examination of the sinus node in the other patient showed fatty infiltration with ischemic changes [14]. Severe cardiac lesions in LGMD R1/2A are rare, which may be related to the fact that the orthologous human gene CAPN3 is expressed only in the heart during early embryogenesis and subsequently disappears. CAPN3 mRNA can be found in the heart, although no protein can be detected. Patients diagnosed with LGMD R1/2A should be made aware of cardiac lesions, such as conduction defects. During the disease course, ECG and cardiac color Doppler ultrasound should be dynamically monitored, and if necessary, further examinations, such as cardiac-enhanced MRI, should be performed for early identification and intervention to improve patient prognosis.

In addition to cardiac involvement, our patient also had primary hyperparathyroidism (PHPT) during the disease course, which was confirmed pathologically as a parathyroid adenoma. PHPT is an endocrine disease characterized by hypercalcemia and abnormally increased PTH levels. Calcium ions are the main regulatory and signaling molecules of muscle fibers, and they can activate myosin through the actin filament-associated troponin-tropomyosin system or calmodulin or by directly binding to myosin and exerting an effect on the muscular system. Changes in serum calcium concentration affect skeletal muscle tissue, and functional changes in calcium ions processing appear to cause muscular dystrophy [15]. Furthermore, excessive PTH has been shown to adversely affect skeletal muscle metabolism, and PHPT has been associated with muscle dysfunction, such as muscle weakness, myopathy, postural stability [16], muscle atrophy, and fatigue [17, 18], with the pathogenesis involving the expression of the PTH receptors PTHR1 and PTHR2 in the skeletal muscle [19, 20]. During the concomitant period of parathyroid adenoma, our patient experienced significant muscle soreness and weakness with elevated CK level, hypercalcemia, and elevated PTH level. When the parathyroid tumor was removed, the patient's blood calcium and PTH levels returned to normal, her muscle soreness and weakness subsequently improved, and the CK levels progressively decreased simultaneously. We hypothesized that some subtle link might exist between functional parathyroid adenomas and LGMD. The function of calpain 3 protein may be affected by changes in calcium ion concentration, and LGMD R1/2A is caused by abnormalities in the function of calpain 3 protein due to mutations in the CAPN3 gene. Therefore, parathyroid adenomas, by affecting blood calcium levels, may indirectly affect the function of calpain 3 protein, thereby influencing the course of LGMD R1/2A. To this end, we searched the Chinese and international literature and no direct relationship was found between parathyroid adenoma and LGMD R1/2A. Coincidentally, our patient had a functional parathyroid adenoma with hypercalcemia, which may have contributed to the exacerbation. Besides, previous studies have confirmed that some parathyroid adenomas may be associated with genetic mutations [21–23]. Unfortunately, our patient did not undergo genetic testing of the parathyroid gland. In this case report, conclusive evidence is lacking for establishing a correlation between parathyroid adenoma or hyperparathyroidism and LGMD R1/2A, and their concurrent occurrence may be merely coincidental. However, this unique and uncommon instance warrants clinical attention and merits further in-depth investigation. To date, no specific treatment exists for LGMD. Treatment is mainly supportive, including rehabilitation and prevention of complications in other organs. Patients with heart involvement should be closely followed up with ECG or echocardiography, and some patients require a cardiac pacemaker. Heart transplantation is an option for patients with heart failure if conditions permit [24, 25]. Recently, small molecules, gene replacement, gene editing, and cell replacement therapy have been investigated at different research stages [26] with favorable application prospects in animal experiments [27, 28], bringing renewed hope for the treatment of patients with LGMD. Additionally, the preferred treatment for symptomatic PHPT is parathyroidectomy [29, 30]. Surgical treatment can significantly relieve clinical symptoms, correct abnormal serological indicators, and reduce damage to important systems and organs such as the bones and kidneys. Our study has several limitations. First, the study is based on a single case, which limits the generalizability and external validity of the results. Additionally, findings from a single case may not be applicable to all patients with LGMD R1/2A. The patient did not undergo genetic testing for the parathyroid adenoma, which limits the understanding of the possible link between parathyroid adenoma and LGMD R1/2A. Furthermore, no direct evidence in the study exists to suggest a causal relationship between the two conditions. The patient in this case study had adult late-onset LGMD R1/2A with cardiac involvement and

functional parathyroid adenoma, which is rare and clinically significant. Therefore, early clinical identification, diagnosis, as well as targeted and active treatments can improve the prognosis of such patients.

Abbreviations

ANCA	Antineutrophil cytoplasmic antibody
AST	Aspartate aminotransferase
CK	Creatine kinase
CRP	C-reactive protein
CT	Computed tomography
ECG	Electrocardiography
ESR	Erythrocyte sedimentation rate
LDH	Lactic dehydrogenase
LGMD	Limb-girdle muscular dystrophy
CK-MB	Creatine kinase MB isoenzyme
MRI	Magnetic resonance imaging
PTH	Parathyroid hormone
PHPT	Primary hyperparathyroidism

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Authors' contributions
XLH wrote the original manuscript. Writing review and editing was done by LQW. Data curation was performed by XLH and FFJ. All authors read and approved the final manuscript.

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Data availability
Data is provided within the manuscript.

Declarations

Ethics approval and consent to participate
The study was approved by the local ethics committee, and written informed consent was obtained from all participants. Ethics approval number: (2021) Ethics approval No.(96).

Consent for publication
The participant gave written informed consent for their personal or clinical details along with any identifying images to be published in this study.

Competing interests
The authors declare no competing interests.

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