ORIGINAL ARTICLE

BAG3-Related Myofibrillar Myopathy Presenting as Hypercapnia: A Case Report and Literature Review

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Objective *BAG3*-related myopathy is a rare condition so far reported in twenty patients worldwide. The purpose of this study was to draw attention to this rare disease and to the fact that *BAG3*-related myopathy should be considered as a rare differential diagnosis of hypercapnia.

Methods We report a sporadic case of a 14-year-old Chinese girl with a *de novo* p.Pro209Leu mutation in *BAG3* and reviewed the literatures for reported cases related to this mutation.

Results We described a 14-year-old Chinese girl who presented with gradually appearing symptoms of hypercapnia that required assisted ventilation. The muscle biopsy and the blood whole-exome sequencing results confirmed the diagnosis of myofibrillar myopathy with a *de novo* p.Pro209Leu mutation in *BAG3*. Totally twenty-one patients from twenty families with a confirmed diagnosis of *BAG3*-related myopathy were reported to date, including this patient and literature review. The male to female ratio was 11:10 and most showed initial symptoms in the first decade of life. Most patients presented toe/clumsy walking or running as the onset symptom, followed by muscle weakness or atrophy. Creatine kinase levels were elevated in fourteen patients and were normal in three. Eighteen patients developed respiratory insufficiency during the disease course and thirteen (one could not tolerate non-invasive assisted ventilation) required non-invasive assisted ventilation for treatment. Except for one not reported, heart involvement was found in seventeen patients during the disease course and seven underwent heart transplantation. Z-disk streaming and aggregation could be observed in most of the patients' muscle histology. In the long-term follow-up, five patients died of cardiac or respiratory failure.

Conclusion *BAG3*-associated myopathy is a rare type of myofibrillar myopathy. It should be considered as a rare differential diagnosis of hypercapnia.

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MYOFIBRILLAR myopathies (MFMs) are a group of genetically heterogeneous but morphologically distinct muscular dystrophies.^[1, 2] The clinical features of MFMs are variable, including rapidly progressive limb and axial muscle weakness, rigid spine, cardiomyopathy, and respiratory insufficiency. The diagnosis of MFMs is based on clinical characteristics, electromyography (EMG), nerve conduction study (NCS), and, importantly, muscle histology.^[3] The main histological characteristics observed on optical microscopy include amorphous granular or hyaline deposits, fibre deformity and disorganisation, fibre-size variation, vacuole presence, and ectopic accumulation of various proteins; the most common feature on electron microscopy is Z-disc streaming, accompanied by progressive destruction of its structure.^[1, 4]

MFMs follow an autosomal dominant inheritance pattern, although infrequently, X-linked or autosomal recessive inheritance patterns can be observed.^[4] The following nine gene types related to proteins located at the Z-disks are reportedly related to MFM: desmin (*DES*), α B-crystallin (*CRYAB*), myotilin (*MYOT*, also *TTID*), filamin C (*FLNC*), Z-band alternatively spliced PDZ motif-containing protein (*ZASP*, also *LDB3*), four and a half LIM domains protein 1 (*FHL1*), Bcl-2-associated anthanogene-3 (*BAG3*), dnaJ homolog subfamily B member 6 (*DNAJB6*) and titin (*TTN*).^[2] *BAG3* is a stress-inducible, 61-kDa protein that appears in various cell types, including cardiomyocytes and skeletal muscle cells as well as in cancer cells to modulate major biological processes to mediate cell adaptive responses to stressful stimuli.^[5, 6] *BAG3* is a member of the *BAG* family of co-chaperones (*BAG* 1–5), which are characterised by a conserved *BAG* domain that is well known to bind the nucleotide-binding domain of members of the Hsp70 family.^[7] *BAG3*-related myopathy is a rare condition; it was first reported by Selcen *et al.*,^[8] and then the same mutation was found in other patients worldwide with variable clinical characteristics.^[8–14]

In this report, we present a novel case of myopathy due to *BAG3* mutation caused by the known p.Pro209Leu mutation with symptoms of skeletal muscle weakness preceding symptoms of hypercapnia along with a comprehensive literature review. We aimed to summarise the clinical characteristics, respiratory function, laboratory and histology findings, and clinical outcomes of patients with *BAG3*-related myopathy to draw attention to this rare condition.

PATIENTS AND METHODS

Patient

A 14-year-old Chinese girl was diagnosed as *BAG3*-related myopathy with respiratory insufficiency. Medical information was collected, muscle biopsy of the girl's quadriceps was performed, and peripheral venous blood was extracted from the proband and her family members for examination of whole-exome sequencing. Informed consent was obtained from the patient and all family members.

Literature review

We searched PubMed using the terms '*myofibrillar myopathy*' or '*BAG3*' or '*BAG3-related myopathy*' to identify all articles in English. We summarised the clinical characteristics, laboratory findings, involvement of lungs and heart, treatment, and clinical outcome of all patients whose cases have been reported so far.

Data collection and statistical analysis

The descriptive results were presented as percentages or ranges. Two authors extracted the medical information of the patients whose data were reported in the selected articles using standardised forms. The data from the selected articles were primarily descriptive.

RESULTS

Case presentation

On May 17, 2017, a 14-year-old Chinese girl presented to the respiratory clinic with a 3-month history of shortness of breath after activity and dyspnoea in the supine position that gradually progressed. Simultaneously, she complained of drowsiness, dizziness, and headache during the day. She was born to non-consanguineous parents of Chinese ethnicity without remarkable antenatal and perinatal history. The patient's history was notable for scoliosis diagnosis at 4 years old, and she gradually developed clumsy walking, inability to run, difficulty getting up from squatting, and talipes equinus. At 8 years of age, she underwent surgery for talipes equinus, but claudication remained. She had no history of contact with special drugs, chemicals, or radioactive substances. Her parents and younger brother had no similar symptoms.

Physical examination findings

On physical examination, the patient was in a good

general condition, and showed no signs of respiratory distress. The thorax was asymmetric, and the thoracic range of motion decreased, without clubbed fingers and chest auscultation abnormalities. The results of cardiac and abdominal examinations were normal. The neurologic examination revealed partial atrophy of the lower limbs and absent tendon reflexes for both the upper and lower extremities. The muscle strength measured with the Medical Research Council scale was 5- in the proximal upper extremities and 5 in the distal upper extremities; it was 3 in both the proximal and distal lower extremities. Gowers' sign was positive. She had a flexor plantar reflex. Regarding the spine and bones, there were deficiencies in the lumbar curve, over-bending of the thoracic curve, and high foot arches.

Laboratory and neurological examination findings

The general laboratory examinations were near normal, except creatine kinase (CK) was elevated to almost twice the upper limit [307 IU/L (normal range: 24–170 IU/L)]. Arterial blood gas on room air of waking time revealed hypercapnic respiratory failure (pH of 7.385, PaCO₂ of 52.5 mm Hg, PaO₂ of 74.3 mm Hg, HCO_3^- of 30.6 mmol/L). The pulmonary function examination showed severe restrictive ventilation dysfunction, with maximum expiratory and inspiratory pressure remarkably decreased. Forced vital capacity of 26.0% predicted was decreased to 15.4% predicted in the supine position. Polysomnography could not be tolerated. Chest radiography revealed mild scoliosis (**Fig. 1**). Chest computed tomography imaging was normal. Brain and spine magnetic resonance imaging revealed no space-occupying lesions or apparent neurodegenerative disease. The NCS indicated that both the motor and sensory nerves were impaired. The lower-extremity nerves were more severely impaired than the upper-extremity nerves, and there was no wave on the peroneus nerve test. Needle EMG showed a neurogenic damage pattern combined with evidence of myogenic damage (**Fig. 2** and **Table 1**). Echocardiographic and electrocardiographic findings were almost unremarkable, except for QTc (461 ms) slightly extended on electrocardiography.

Morphological study

She then underwent left quadriceps femoris muscle biopsy. Under light microscopy, muscle haematoxylin/eosin staining (**Fig. 3A**) showed transverse sections, with greater variability in muscle-fibre size and some scattered angular muscle fibres. Several degenerated

Figure 1. Posteroanterior (A) and lateral (B) chest radiographs reveal scoliosis.

Figure 2. The electromyographic result of the patient showed a neurogenic damage pattern combined with evidence of myogenic damage.

fibres were seen, and a few fibres contained cytoplasmic aggregates. There was no peri-fascicular atrophy, necrosis, or phagocytosis. Modified Gomori trichrome staining (**Fig. 3B**) showed dark stained cytoplasmic aggregates in some fibres. Nicotinamide adenine dinucleotide staining (**Fig. 3C**) indicated irregular internal architecture in a few muscle fibres. Acid phosphatase staining (**Fig. 3D**) revealed deep stained positive particles in a few individual muscle fibres. Immunohistochemical staining with anti Spectrin, anti Dys-2 and anti Dys-3, and anti α -sarcoglycan and β -sarcoglycan antibodies were generally normal. Regrettably, electron microscopy examination was not performed.

Genetic defect identification

The patient's blood sample was subjected to whole-ex-

Table 1. Results of nerve conduction study

Nerve stimulated	Recording site	Distal or peak latency (ms)	Amplitude (mv)	Conduction velocity (m/s)
Medianus Motor Left	Wrist-APB	3.91 (30% ↑)	10.5	
	Elbow-Wrist	9.34	9.9	44.2 (32% ↓)
Medianus Motor Right	Wrist-APB	3.96 (32% ↑)	7.1 (68% ↓)	
	Elbow-Wrist	8.96	5.8 (68% ↓)	44.0 (32% ↓)
Ulnaris Motor Left	Wrist-ADM	2.42	8.9	
	Above Elbow-Wrist	8.34	8.2	43.1 (34% ↓)
Ulnaris Motor Right	Wrist-ADM	2.6	8.3	
	Above Elbow-Wrist	8.56	8.5	41.1 (37% ↓)
Tibialis Motor Left	Ankle-AH	NR	NR	
Peroneus Motor Left	Ankle-EDB	NR	NR	
	Fibula Head-Ankle	NR	NR	
Peroneus Motor Right	Ankle-EDB	NR	NR	NR
	Fibula Head-Ankle	NR	NR	NR

APB: abductor pollicis brevis; ADM: abductor digiti minimi; AH: abductor hallucis; EDB: extensor digitorum brevis; NR: no response.

ome sequencing, which revealed that the patient was heterozygous for a canonical missense mutation in the third exon of *bcl-2* associated athanogene protein 3 (*BAG3*) (c.626C>T; p. Pro209Leu). Then, the blood samples of her family underwent Sanger-sequencing

validation for the heterozygous mutation. The results confirmed that the proband had a *de novo* heterozygous missense mutation (**Fig. 4A**), while her father (**Fig. 4B**), mother (**Fig. 4C**), and younger brother (**Fig. 4D**) did not carry this mutation and did not present any clinical manifestations.

Figure 3. Pathological evaluation of the left quadriceps femoris muscle. A. Hematoxylin/eosin staining showed transverse sections, with greater variability in muscle-fiber size and some scattered angular muscle fibers ($\times 200$). Several degenerated fibers are seen, and a few fibers contained cytoplasmic aggregates. There was no peri-fascicular atrophy, necrosis, or phagocytosis. B. Modified Gomori trichrome staining shows dark stained cytoplasmic aggregates in some fibers ($\times 400$). C. Nicotinamide adenine dinucleotide staining indicates irregular internal architecture in a few muscle fibers ($\times 200$). D. Acid phosphatase staining reveals deep stained positive particles in a few individual muscle fibers ($\times 200$).

Diagnosis and treatment

She was diagnosed with MFM with a missense *de novo* mutation in *BAG3*. Before a precise diagnosis could be reached, empirical non-invasive ventilation during sleep (inhaled positive airway pressure, 16 cmH₂O; exhaled positive airway pressure, 6 cmH₂O) was initiated to alleviate CO₂ retention and improve diurnal quality of life. After support with non-invasive ventilation, the PaCO₂ at awakening in the morning gradually decreased to the diurnal level, from 64.6 to 52.2 mm Hg. She continued receiving non-invasive ventilation support after discharge, and reported improvement of drowsiness, chest tightness, and shortness of breath.

Literature review

In total, 21 patients from 20 families with a confirmed diagnosis of *BAG3*-related myopathy have been reported to date, including this patient and literature review. (**Table 2**).^[2, 3, 8-16] The male to female ratio was 11:10, and most showed initial features in the first decade of life. Most patients presented toe/clumsy walking or running ($n=11$) as the onset symptom followed by muscle weakness or atrophy ($n=5$) and cardiomyopathy ($n=4$) (**Fig. 5A**). The most common phenotype was muscle weakness ($n=18$), followed by toe/clumsy

Figure 4. Sanger-sequencing validation for the heterozygous mutation in the *BAG3* gene with a c.626C>T (red arrow). The genetic testing confirmed a mutation of c.626C>T (Pro209Leu) in the proband (A), while her father (B), mother (C), and younger brother (D) did not carry this mutation.

walking or running ($n=12$), rigid spine ($n=11$), scoliosis ($n=10$), muscle atrophy ($n=9$), and contractures ($n=7$) (**Fig. 5B**). CK levels were elevated in 14 patients and were normal in three patients. Eighteen patients developed respiratory insufficiency during the disease course and 13 (one could not tolerate non-invasive assisted ventilation) required non-invasive assisted ventilation for treatment. Except for one not reported, heart involvement was found in 17 patients during the disease course and seven underwent heart transplantation. As for the muscle histology (**Table 3**), Z-disk streaming and aggregation could be observed in most of the patients, which is the most important characteristic of this class of disease, and other features, including fibre-size variation, protein accumulation, granulomatous material, atrophic fibres, and disorganisation of myofibrils and fibres, could also be seen in different patients. In the long-term follow-up, five patients died of cardiac or respiratory failure. Twelve patients' family members did not present similar symptoms and did not carry this mutation; affected family members were only found in two families.

DISCUSSION

We reported the case of a patient who presented

Figure 5. Clinical characteristics of the current patient and of the patients in the literature review. Symptoms at onset of *BAG3*-related myopathy of the patients whose cases were reported in the articles (A). Phenotypes of *BAG3*-related myopathy in these patients (B).

Table 2. Summary of the characteristics of the current patient and of the patients in the literature review

Patient number	References	Sex (age at onset)	Symptoms at onset	Skeletal myopathy	Other features	CK levels	Electromyography	Neuropathy	Electroneurography	Respiratory function	Cardio-myopathy [QTc (ms)]	Treatment	Parents	Outcome
1	Kostera-Pruszyk <i>et al.</i> ^[13]	Female (8 years old)	Toe-walking and foot deformity	Subclinical	Rigidity of cervical and thoracic spine, contractures at hips, knees, and ankles; bilateral pes cavus deformity, and absence of deep tendon reflexes in the lower extremities	1.5-fold above normal	NR	Axonal-demyelinating sensory-motor polyneuropathy	Conduction velocity in the median/ulnar motor nerves, 38 m/s	Normal (FVC 87%)	Restrictive cardiomyopathy (mean 478 ms, max 574 ms)	NR	Unaffected	NR
2	Jaffer <i>et al.</i> ^[11]	Female (1.5 years old)	Toe-walking	Proximal weakness, proximal muscle atrophy, and weakness of neck flexion	Rigid spine, Achilles tendon tightness, elbow/finger atrophy, and flexion contractures of tures neck flexion	NR	Chronic neurogenic changes, absent responses on stimulation of the phrenic nerves, and chronic denervation of the diaphragm	Giant axonal neuropathy (neuropathological axonal loss and giant thin myelinated axons)	Some intermediate slowing of conduction velocity	NR	Restrictive cardiomyopathy (NR)	Heart transplantation at 13 years of age	Unaffected	NR
3	Jaffer <i>et al.</i> ^[11]	Male (early childhood)	Toe-walking and high step-gait	Proximal and distal muscle weakness and atrophy	Rigid spine, pectus carinatum, distal contractures and scoliosis	NR	Chronic neurogenic changes	Giant axonal neuropathy (giant thin myelinated axons)	Some intermediate slowing of conduction velocity	FVC 63% → 53%; nocturnal hypoventilation	Restrictive cardiomyopathy (NR)	Non-invasive ventilatory support	Unaffected	NR

Continued Table 2. Summary of the characteristics of the current patient and of the patients in the literature review

Patient number	References	Sex (age at onset)	Symptoms at onset	Skeletal myopathy	Other features	CK levels	Electromyography	Neuropathy	Electroneurography	Respiratory function	Cardio-myopathy [QTc (ms)]	Treatment	Parents	Outcome
4	Jaffer <i>et al.</i> [11]	Male (11 months)	Toe-walking, clumsy, and frequent falls	Severe proximal and distal weakness	Rigid spine, scoliosis, Achilles tendon tightness, and lower limb deformities	1054–2500 IU/L	NR	NR	NR	FVC 50% when standing, 39% when lying	Restrictive cardiomyopathy (NR)	Nocturnal non-invasive ventilatory support after the 9th month	Unaffected	Died of cardiorespiratory failure at age 12 years and 9 months
5	Jaffer <i>et al.</i> [11]	Female (first decade)	Toe-walking and progressive mobility impairment	Minimal distal upper limb weakness and proximal weakness of the hip extensors and adductors	Pectus carinatum, tight Achilles tendons, and scoliosis (Cobb angle 104 °)	154 IU/L	Chronic neurogenic changes	Axonal neuropathy	Some intermediate slowing of conduction velocity	FVC 46%	Restrictive cardiomyopathy (NR)	Nocturnal non-invasive ventilatory support	Her older sister and father similarly affected	NR
6 (older sister of patient No. 5)	Jaffer <i>et al.</i> [11]	Female (8 years old)	Bilateral pes cavus and progressively impaired mobility	NR	NR	NR	NR	NR	NR	Respiratory weakness	NR	Nocturnal non-invasive ventilatory support in her 20s	As above	NR
7	Odgerel <i>et al.</i> [10]	Male (12 years old)	Neck, proximal muscles of upper and lower extremities involved, and cardiomyopathy	Generalized muscle weakness and atrophy	Skeletal deformity	Normal	Neurogenic/myopathic changes	Giant axonal neuropathy	Axonal neuropathy	Respiratory weakness at 15 years of age	Restrictive/hypertrophic cardiomyopathy (NR)	Heart transplantation at 14 years of age; ventilator dependency at age 29 years	Unaffected	Alive

Continued Table 2. Summary of the characteristics of the current patient and of the patients in the literature review

Patient number	References	Sex (age at onset)	Symptoms at onset	Skeletal myopathy	Other features	CK levels	Electromyography	Neuropathy	Electroneurography	Respiratory function	Cardio-myopathy [QTc (ms)]	Treatment	Parents	Outcome
8	Odgerel <i>et al.</i> [10]	Male (9 years old)	Proximal muscles of upper and lower extremities involved, and cardiomyopathy	Generalized muscle weakness and atrophy	NR	NR	NR	NR	NR	Respiratory weakness at 19 years of age	Restrictive/hypertrophic cardiomyopathy (NR)	NR	Unaffected	Sudden death at 9 years
9	Odgerel <i>et al.</i> [10]	Female (12 years old)	Neck and distal lower extremity muscle weakness, bilateral pes cavus, and slight dorsal scoliosis	Neck and distal muscle weakness	Bilateral pes cavus and slight dorsal scoliosis	2–3 times above normal	Myopathic changes	Giant axonal neuropathy	Axonal neuropathy	Respiratory weakness at 20 years of age	Restrictive/hypertrophic cardiomyopathy (NR)	NR	Unaffected	Died at the age of 20 years of cardiac and respiratory failure
10	Odgerel <i>et al.</i> [10]	Male (5 years old)	Problem running	Proximal muscle weakness	NR	Normal	Neurogenic/myopathic changes	Giant axonal neuropathy	Axonal neuropathy	Respiratory weakness at 10 years of age	Restrictive/hypertrophic cardiomyopathy (NR)	Heart transplantation at 13 years of age; ventilator dependent at 13 years of age	Unaffected	Died at 15 years of age
11	Lee <i>et al.</i> [9]	Female (6 years old)	Progressive clumsy walking and easy falling during exercise	Mild proximal muscle weakness of both legs and later both arms	Rigid spine and scoliosis, contractures, and foot deformity	991 IU/L (normal range < 154)	Increase in duration of the action potential with normal amplitude	Axonal neuropathy	Decreased motor (tibial and peroneal) amplitudes and latencies	Restrictive lung disease	Restrictive hypertrophic cardiomyopathy (450–570 ms)	NR	Her father was a carrier of c.772C>T (p. Arg258 Trp)	NR

Continued Table 2. Summary of the characteristics of the current patient and of the patients in the literature review

Patient number	References	Sex (age at onset)	Age at Symptoms onset	Skeletal myopathy	Other features	CK levels	Electromyography	Neuropathy	Electroneurography	Respiratory function	Cardio-myopathy [QTc (ms)]	Treatment	Parents	Outcome
12	Konerman <i>et al.</i> ^[14]	Male (8 years old)	Restrictive cardiomyopathy	Severe diffuse muscle atrophy and weakness (distal > proximal), and mild bilateral lower facial weakness	Toe walking, imbalance, foot deformity, spinal rigidity	669 to 1099 IU/L (normal range: 55–170)	Fibrillation potentials in the proximal and distal muscles; giant motor unit potentials (> 10 mV) in the distal muscles; and reduced recruitment in all muscles	Sensorimotor axonal and demyelinating features and indolent primarily axonal neuropathy with second-ary demyelination/remyelination	Upper extremity motor conduction velocities were in the “intermediate” range	Difficulty breathing with hypercapnic respiratory insufficiency of neuromuscular etiology; intermittent ventilation throughout the day and continuous ventilation during the day and continuous at night	Restrictive cardiomyopathy	Orthotopic heart transplant at 8 years of age, intermittent ventilation throughout the day and continuous ventilation at night via tracheostomy	Unaffected	NR
13	Noury <i>et al.</i> ^[12]	Female (10 years old)	Inability to run and maintain prolonged standing	Proximal and distal lower limb weakness; neck flexion; winging, and was impossible	Rigid spine, varus foot deformity, bilateral scapular winging, and hypophonia	Normal	Mild myogenic changes in the upper limb proximal muscles	Severe sensory-motor axonal neuropathy predominant in the lower limbs with mild myogenic changes in the upper limb proximal muscles	NR	FVC 42%	Normal (NR)	No	NR	NR
14	Selcen <i>et al.</i> ^[8]	Male (early childhood)	Toe-walking	Severe diffuse muscle weakness and atrophy	Contractures at the knees and ankles and bilateral diaphragm paralysis	3-fold above normal	NR	NR	NR	Respiratory insufficiency	Restrictive cardiomyopathy (NR)	Heart transplantation at 13 years of age	NR	NR

Continued Table 2. Summary of the characteristics of the current patient and of the patients in the literature review

Patient number	Reference	Sex (age at onset)	Symptoms at onset	Skeletal myopathy	Other features	CK levels	Electromyography	Neuropathy	Electroneurography	Respiratory function	Cardio-myopathy [QTc (ms)]	Treatment	Parents	Outcome
15	Selcen <i>et al.</i> ^[8]	Female	(13 years old)	Scoliosis, rigid spine, and moderately easy fatigability	Axial, moderate-severe proximal and distal muscle weakness	Spinal stiffness, 6-fold above normal speech	Myopathic motor unit potentials	Axonal and demyelinating peripheral neuropathy	Axonal and demyelinating peripheral neuropathy	Restrictive respiratory insufficiency	Hypertrophic cardiomyopathy (NR)	Nocturnal non-invasive ventilatory support	NR	NR
16	Selcen <i>et al.</i> ^[8]	Male	(7 years old)	Toe-walking	Weakness of the axial and proximal limb muscles	Valgus ankle deformity, thoracic scoliosis, scapular winging, and rigid spine	15-fold above normal	NR	NR	Reduced FVC and respiratory insufficiency	Restrictive cardiomyopathy (NR)	Did not tolerate nocturnal ventilatory support	NR	Died following a chest infection
17	Schänzer <i>et al.</i> ^[15]	Male	(4 years old)	Restrictive cardiomyopathy	Proximal muscle weakness	Mild scoliosis	Slightly increased (227 IU/L; normal range < 180)	Myopathic pattern	Combined demyelinating and axonal polyneuropathy	VC 53% and nocturnal hypoxemia and hypercapnia	Restrictive cardiomyopathy	Heart transplantation, non-invasive ventilatory support	Unaffected	NR
18	D'Avila <i>et al.</i> ^[3]	Female	(11 years old to 14 years old)	Spinal contractures causing rigidity, scapular winging, and later postural muscle atrophy	Postural muscle atrophy and proximal weakness in a limb girdle distribution pattern with loss of ambulation	Spinal contractures causing spinal rigidity, scapular winging, and later postural muscle atrophy	Normal to 1.500 U/L	Axonal neuropathy	NR	Respiratory insufficiency	Impaired conduction, arrhythmia, and cardiac hypertrophy	Ventilatory support on a continuous basis or overnight.	Unaffected	NR

Continued Table 2. Summary of the characteristics of the current patient and of the patients in the literature review

Patient number	Reference	Sex (age at onset)	Symptoms at onset	Skeletal myopathy	Other features	CK levels	Electromyography	Neuropathy	Electroneurography	Respiratory function	Cardio-myopathy [QTc (ms)]	Treatment	Parents	Outcome
19	Latham <i>et al.</i> ^[16]	Male (2 years old)	Toe walking and progressive decreased fine motor range of motion of the neck and lower extremities	Loss of gross and fine motor control	Severe contractures of the lower extremities, scoliosis, rigid spine, and neck extension contracture	110 to 510 IU/L (normal range: 35–230)	NR	NR	NR	Obstructive sleep apnea and severe restrictive lung disease	Restrictive cardiomyopathy	Cardiac transplantation, nighttime noninvasive ventilation	NR	NR
20	Semmler <i>et al.</i> ^[2]	Male (34 years old)	Distal lower limb weakness and symmetrical calve atrophy	Skeletal muscle weakness	Scapular winging	1050 IU/L	Mixed pattern	Axonal sensorimotor polyneuropathy	NR	Normal	Normal	NR	NR	NR
21	Current patient	Female (14 years old)	Scoliosis	Axial, both upper and lower extremity muscle weakness and atrophy	Clumsy walking, difficulty in squatting, unstable gait	2-fold above normal	Neurogenic damage pattern combined with evidence of myogenic damage	Demyelinating and axonal neuropathy	Both motor and sensory nerves were impaired; the condition of the nerves in the lower extremities was more severe than that of nerves of the upper extremities and there was no wave on the peroneus nerve test	Severe restrictive ventilation dysfunction	Normal (461 ms)	Non-invasive ventilatory support	Unaffected	Alive

CK: creatine kinase; NR: not report; FVC: forced vital capacity; VC: vital capacity.

Table 3. Summary of the histology of the muscle biopsy of the current patient and of the patients in the literature review

Patient number	Histology of the muscle biopsy
1	Large deposits in fibers, Z-disc streaming, disorganization of myofibrils, and sarcomeric disorganization with accumulation of polymorphic dense structures; focal changes containing granulomatous material.
2	NR
3-4	Accumulation of myotilin and desmin, small atrophic fibers consistent with denervation, granulomatous material, myofibrillar loss, Z-line streaming.
5	NR
6	NR
7-8	Myofibrillar breakdown, presence of desmin-reactive inclusions, Z-line streaming.
9	Accumulation of dark dense material, increment of intermyofibrillar spaces, and multiple core areas, desmin positive inclusions, electron dense filamentous and granular material disrupting the Z-lines
10	Atrophic fibers, focal myofibrillar disorganization, and dark inclusions with prominence of desmin
11	Atrophic fibers, focal myofibrillar disorganization, accumulation of electron-dense granulo-filamentous materials, myofibrillar degeneration with minicores
12	Fiber size variation with atrophic and hypertrophic fibers, myofibrillar disruption, scattered fibers with inclusions and vacuoles
13	Accumulation of granulo-filamentous material originating from the Z-disk disrupting the sarcomeres, accumulation of dense granulomatous material
14-16	Fiber size variation, protein accumulation, Z disk streaming and accumulation of electron dense structures, disarray of myofibrils, mitochondrial cluster, and apoptotic nuclei
17	Myofibrillar disintegration, intracytoplasmic inclusions containing different proteins, myofibrillar disintegration, and Z-disk streaming
18	Z disk aggregates and atrophic type I fibers, whereas type II fibers were hypertrophic
19	Myofibril dissolution and accumulation of degradation products at the Z-disk
20	Z-disk streaming and accumulation of granulo-filamentous material
21	Variability in muscle-fiber size, some scattered angular muscle fibers and several degenerated fibres. Dark stained cytoplasmic, irregular internal architecture, deep stained positive particles could be seen in fibers.

to the hospital with dyspnoea, and additional laboratory testing led to a diagnosis of hypercapnia and severe restrictive ventilation dysfunction. The combination of medical history, physical examination, and chest imaging helped exclude pulmonary and airway diseases and pointed towards neuromuscular disease, later confirmed with EMG and NCS. The electrophysiological testing and muscle biopsy revealed features of MFM, and the genetic testing results confirmed MFM with a *de novo* missense *BAG3* mutation.

Respiratory failure can arise from an abnormality in any of the 'effector' components of the respiratory system—central nervous system, peripheral nervous system, respiratory muscles and chest wall, airways, or alveoli. Brain and spine MRI could help to exclude inherited or acquired central nervous system disease and disorder of respiratory control centre. The normal chest CT, combined with normal pulmonary auscultation and normal forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) ratio, helped exclude the possibility of intrinsic lung diseases, airway occlusion, and pleural disease.

Respiratory-muscle weakness can directly lead to respiratory insufficiency resulting from respiratory-pump failure. The process is usually insidious, accompanied by elevated arterial-CO₂ concentration. Respiratory insufficiency caused by respiratory-muscle weakness occurring in multiple types of neuromuscular disease, should be made a careful differential diagnosis. Hereditary motor sensory neuropathy (HMSN, also known as Charcot-Marie-Tooth disease) should be considered as those patients often presented with pronounced distal leg weakness, pes cavus, inverted champagne bottle shaped legs, and absence of tendon reflex, however, early-onset respiratory insufficiency is very rare in HMSN and involvement of the proximal muscles of the lower limbs is infrequent. The EMG and NCS results revealed demyelinating and axonal neuropathy in both the motor and sensory nerves, supporting a diagnosis of peripheral neuropathy, whereas the myogenic damage could not be explained by HMSN. As hypercapnia due to respiratory muscle weakness is not a common complication in inflammatory myopathy, these diseases were unlikely. Metabolic diseases, such as late-onset acid maltase deficiency, can also cause musculoskeletal or peripheral nervous system dysplasia with respiratory insufficiency as the main clinical manifestation, which also had to be evaluated. Inherited muscle diseases, such as myotonic dystrophy type 1, limb-girdle muscu-

lar dystrophy, MFM, hereditary myopathy with early respiratory failure, tropomyosin 3-based myopathy, could only be completely distinguished by muscle biopsy and gene testing. The patient was diagnosed with MFM by the electrophysiological testing, muscle biopsy and gene testing.

MFM symptoms vary across subtypes. *DES* mutations more commonly involve the facial, neck flexor, and trunk muscles, in contrast to *MYOT* or *ZASP* mutations.^[17] *DES* and *BAG3* mutations more likely involve the heart.^[18] Reportedly, patients with genetic variants in *TTN*, *FHL1*, *DES*, *CRYAB*, *FLNC*, and *BAG3* could present with respiratory insufficiency during the disease course.^[4, 19]

BAG3-related myopathy is a rare MFM subtype associated with the common heterozygous c.626C>T, p.Pro209Leu, mutation in exon 3. *BAG3* mutation results in myofibril dissolution and deposits of degradation products at the Z-disk, which is pathognomonic for MFM.^[16] Homma *et al.*^[20] found that mouse knockouts of *BAG3* had obviously limited growth within 12 weeks after birth and died within 4 weeks, which proved the key role of *BAG3* in promoting skeletomuscular maturation. Patients develop symptoms during childhood, initiating with muscle weakness that, with a variable proximal, proximodistal, or distal pattern, are mostly accompanied by rigid spine, contractures, peripheral neuropathy, possible nasal speech, and respiratory insufficiency and cardiomyopathy, which may precede muscle weakness.^[21] The disease course is severe, with respiratory and cardiac insufficiency leading to premature death in some patients.^[4] Summarising the clinical characteristics of patients with *BAG3*-related myopathy reported to date, we found that most showed initial features during childhood, with toe/clumsy walking or running, and muscle weakness or atrophy; other features involving the musculoskeletal system including rigid spine, contractures, and skeletal deformity could also be observed. Increase in CK levels was observed in 82.4% (14/17) of patients with CK levels reported in our study; according to previous evidence, CK levels are reported to be generally higher in *BAG3*-related myopathy than in most other MFM types.^[18]

Respiratory insufficiency in *BAG*-related MFM usually presents with nocturnal hypoxaemia and hypercapnia, severe restrictive ventilation dysfunction with reduced forced vital capacity. The symptoms are nonspecific; patients usually complain of shortness of breath, which gradually progresses to dyspnoea espe-

cially in the supine position, sometimes combined with sleep-related symptoms, including sleep disruption, headache, and diurnal hypersomnolence, which could be attributed to lack of sleep, nocturnal hypoventilation, or hypercapnia. Some other factors in myopathies, such as scoliosis, chest wall deformity, or muscle contractures, may aggravate respiratory insufficiency by interfering with airway clearance and increasing the risk of pneumonia.^[19] Therefore, for patients of hypercapnia, the diagnosis of MFM should be considered if the patient accompanied by multiple muscles involved, skeletal deformity or elevated CK level. Almost all patients progress to require non-invasive assisted ventilation support. Excepting for one not reported, 90% (18/20) of patients presented with respiratory insufficiency, which is a markedly high proportion, and 13 (one could not tolerate non-invasive assisted ventilation) required non-invasive assisted ventilation for treatment.

Cardiac involvement is also common in this disease, and some patients even have restrictive cardiomyopathy at the onset. Cardiac involvement should be carefully evaluated because of the risk of sudden death caused by cardiomyopathy or long QT syndrome. Among the 21 patients summarized in our study, excepting for one not reported, 85.0% (17/20) presented with heart disease including restrictive cardiomyopathy, hypertrophic cardiomyopathy, and arrhythmia. The cardiac function of our patient was still normal, whereas there should be close monitoring of cardiac function in the long-term follow-up, given that *BAG3*-related myopathy is commonly accompanied by cardiomyopathy and heart failure.

Supportive treatment remains the main therapy for this disease. For patients with impaired conduction or arrhythmia, a pacemaker or cardioversion defibrillator could be considered as well as heart transplantation in severe cardiomyopathy. For patients with respiratory failure, non-invasive assisted ventilator should be applied. Other supportive means include physical rehabilitation and orthopaedic surgery or nutrition medicine including adenosine triphosphate, inosine, and vitamin E supplementation. Therapeutic options that target the pathogenesis have been recently preclinically explored, such as regulating the protein quality control system and heat shock protein function, protecting the mitochondria, preventing oxidative stress or apoptosis, and inhibiting aggregation. Therefore, more in-depth studies on the pathogenesis of MFM may promote new therapeutic solutions in the future.^[4]

In conclusion, we described the sporadic case of

a 14-year-old Chinese girl with a *de novo* p.Pro209Leu mutation in *BAG3* who presented with skeletomuscular and peripheral nerve dysfunction in childhood and gradually appearing symptoms of hypercapnia that required assisted ventilation, suggesting that *BAG3*-associated MFM should be considered as a rare differential diagnosis of hypercapnia.

Declaration of Conflicts of Interest

The authors have no competing interests to declare.

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中文摘要

临床表现为高碳酸血症的 BAG3 相关肌原纤维性肌病： 一例病例报告及文献回顾

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摘要

目的 BAG3 相关肌病是一种罕见疾病，目前在世界范围内仅报道 20 例患者。本研究旨在引起对这一罕见疾病的关注，以及强调将 BAG3 相关性肌病视为呼吸功能不全所致高碳酸血症的罕见鉴别诊断。

方法 报告一例 14 岁中国女性患者因 BAG3 p.Pro209Leu 新发突变所致肌原纤维性肌病病例，并回顾总结该基因缺陷所致病例文献报道。

结果 本文报道了一例 14 岁中国女性患者，临床表现为逐渐出现的高碳酸血症，需要无创通气辅助呼吸。依靠肌肉活检病理及外周血全外显子组检测，诊断为 BAG3 p.Pro209Leu 突变所致肌原纤维性肌病。结合本例患者及文献回顾，共有 20 个家庭的 21 例患者确诊为 BAG3 相关性肌病。男女比例为 11:10，大多数患者在 10 岁以前就表现出临床症状。大多数患者首发症状为踮脚走路跑步或步态笨拙，其次是肌肉无力萎缩。14 例患者血肌酸激酶水平升高，3 例患者血肌酸激酶水平正常。18 例患者在病程中出现呼吸功能不全，13 例患者（1 例患者不能耐受无创辅助通气）需要无创辅助通气治疗。除 1 例未报告外，17 例患者在病程中出现心脏受累，7 例患者接受了心脏移植。大多数患者的肌肉病理可以观察到 Z-盘聚集现象。在长期随访中，5 例患者死于心衰或呼吸衰竭。

结论 BAG3 相关肌病为肌原纤维性肌病的罕见类型，应被视为高碳酸血症的罕见鉴别诊断。

关键词：肌原纤维性肌病；BAG3；呼吸功能不全；高碳酸血症