POMPE DISEASE, THE MUST-NOT-MISS DIAGNOSIS: A REPORT OF 3 PATIENTS

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ABSTRACT: *Introduction:* Pompe disease is a progressive and debilitating neuromuscular disorder that presents with a heterogeneous array of signs and symptoms including proximal muscle weakness, respiratory insufficiency, and/or elevated creatine kinase levels. It mimics other neuromuscular disorders, making its diagnosis challenging and often significantly delayed, thereby increasing morbidity and early mortality of the disease. *Methods:* Three Pompe disease patients are discussed to highlight the challenging path to diagnosis and the common cluster of symptoms that could lead to timely and accurate diagnosis. *Results:* After significant delays in diagnosis, Pompe disease was diagnosed on the basis of the pattern of proximal weakness. *Conclusions:* Suspicion and recognition of the characteristic symptoms of Pompe disease may improve both the timing and accuracy of the diagnosis, which will improve clinical outcomes and minimize disease progression.

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Pompe disease is a rare, progressive neuromuscular disorder (NMD)[1] characterized by the absence or marked deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA).[2] Deficiency of GAA leads to glycogen accumulation in the lysosomes and cytoplasm, and substantial accumulation of autophagic vesicles and autophagic buildup, causing tissue damage especially in cardiac, skeletal, and smooth muscles.[3] Pompe disease is a multi-system disorder presenting as a broad spectrum of clinical phenotypes with varying rates of progression, symptoms at onset, and degrees of organ involvement.[1,4,5] Infantile-onset Pompe disease the most severe form of the disease, presents within the first months of life, and is characterized by the complete absence of GAA.[6] Symptoms include cardiomegaly, hepatomegaly, profound muscle weakness and hypotonia, respiratory distress, developmental delay, and difficulty feeding. Death ensues from cardiorespiratory failure within the first year.[6]

Late-onset Pompe disease in children and adults generally presents as progressive proximal muscle weakness (most notably in the limb-girdle muscles), diaphragmatic weakness and eventual respiratory insufficiency, hypotonia, and elevation in serum creatine kinase (CK) or liver enzyme levels.[7] Late-onset Pompe disease is often misdiagnosed as other more common NMDs such as limb-girdle muscular dystrophies (LGMDs)[8] because of the overlap of proximal muscle weakness, respiratory insufficiency and other symptoms (Table 1).[9,10] The average diagnostic delay for late-onset Pompe disease is 4.1 years,[7] during which time, a patient's muscle and respiratory function will continue to decline, potentially leading to eventual wheelchair and ventilator dependency.[11,12] The rate of deterioration of pulmonary and proximal muscle strength in patients with late-onset Pompe disease is variable.[5] Studies show the incidence of progressive decline in pulmonary function and proximal muscle strength increases with time from symptom onset or disease diagnosis[13,14]; accelerated disease progression and severe disease course were noted in some patients with symptom onset in childhood.[14] Increased awareness of Pompe disease in the last decade has reduced the diagnostic delay[7,11] and spurred breakthroughs in treatment.

Pompe disease has become a "must-not-miss diagnosis" since the availability of an easy, relatively inexpensive blood-based diagnostic assay and approval in 2006 of a disease-specific enzyme replacement therapy (ERT; Alglucosidase alfa [MYOZYME®], Genzyme Corporation, Cambridge, Massachusetts, USA)[10,15,16] in the United States and Europe. Treatment of Pompe disease with ERT may reverse, stabilize, or slow disease progression and reduce mortality.[17,18] Timely diagnosis and early treatment can improve patient outcomes by reducing overall disability. To increase recognition of this disorder, we describe 3 cases of late-onset Pompe disease in adult patients that demonstrate the challenging path to diagnosis and the common presenting symptoms.

CASE 1

The first case involves a 45-year-old man with progressive proximal weakness of the lower

Table 1. Neuromuscular disorders with signs and symptoms that mimic Pompe disease.[9,10]

Disorder type	Diagnoses
Dystrophies	Limb-girdle muscular dystrophy
	Dystrophinopathies (Duchenne and Becker muscular dystrophies)
	Myofibrillar myopathy
	Myotonic dystrophy type II
	Scapuloperoneal syndromes
	Danon disease
	X-linked myopathy with excessive autophagy
	Facioscapulohumeral muscular dystrophy
Inflammatory myopathies	Polymyositis myopathies
	Inclusion body myositis
Congenital myopathies	Nemaline rod myopathy
	Central core and multiminicore myopathy
	Centronuclear myopathy
	Hyaline body myopathy
	Other congenital myopathies
Metabolic myopathies	Glycogen storage diseases
	Debranching enzyme deficiency myopathies
	Branching enzyme deficiency
	McArdle disease (late-onset)
	Mitochondrial myopathy
	Lipid disorder myopathies
Motor neuron disorders	Spinal muscular atrophy types II and III
	Kennedy disease
	Amyotrophic lateral sclerosis
Neuromuscular junction Disorders	Myasthenia gravis
	Congenital myasthenic syndromes
	Lambert-Eaton syndrome
Peripheral neuropathy	Hereditary neuropathies
	Chronic inflammatory demyelinating polyneuropathy
	Amyloid neuropathy

Note. Information was adapted from "Diagnostic criteria for late-onset (childhood and adult) Pompe disease," by American Association of Neuromuscular & Electrodiagnostic Medicine, 2009, Muscle & Nerve, volume 40, p. 150. Copyright 2009 Wiley Periodicals, Inc. Adapted with permission; and from "Pompe disease: a review of the current diagnosis and treatment recommendations in the era of enzyme replacement therapy," by Katzin LW and Amato AA, 2008, Journal of Clinical Neuromuscular Disease, volume 9, p. 421. Copyright 2008 by Lippincott Williams & Wilkins. Adapted with permission.[9,10]

limbs starting at age 24 years. He first consulted an orthopedic surgeon because of lower back pain and excessive fatigue and was referred to a neurologist, who suspected multiple sclerosis because of the patient's age and symptoms. At 26 years of age, with no diagnosis and worsening pain and fatigue, the patient started to experience excessive fatigue and difficulty walking and climbing stairs. The patient recalled he was a slow runner during his teenage years, was slower on a bicycle than his friends and could not jump very

high during volleyball games. No family history of Pompe disease or other NMDs were reported.

Neurologic and physical examinations at age 29 years showed a waddling gait, bilateral scapular winging, and lumbar hyperlordosis (Fig. 1 and Supportive Video 1 show these symptoms when the patient was age 33 years). As seen in the video, the patient kept his head in a lowered position to stabilize his gait. His Medical Research Council (MRC) scale scores (range, 4–5 out of 5) indicated mild proximal muscle weakness, most notably in the neck flexors, iliopsoas and glutei, hamstrings, and deltoid muscles, all of which had MRC scale scores less than 5. Abdominal muscle involvement was pronounced, as noted by the fact that he could not sit up or even raise his shoulders from the mat when in the supine position. He recalled difficulties performing these actions in his adolescent years. Electromyography (EMG) showed a myopathic pattern with some high-frequency discharges and normal nerve conduction findings. Laboratory results revealed moderate elevation of serum CK level (780 IU/L).

This clinical presentation raised suspicion of LGMD, and a deltoid muscle biopsy was performed when the patient was 29 years old. Pathologic examination of the specimen showed slight variations in fiber size, no necrosis or endomysial fibrosis,

FIGURE 1. A then 33-year-old man with Pompe disease (Case 1) exhibiting bilateral scapular winging (written permission to use the image was obtained from the patient). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
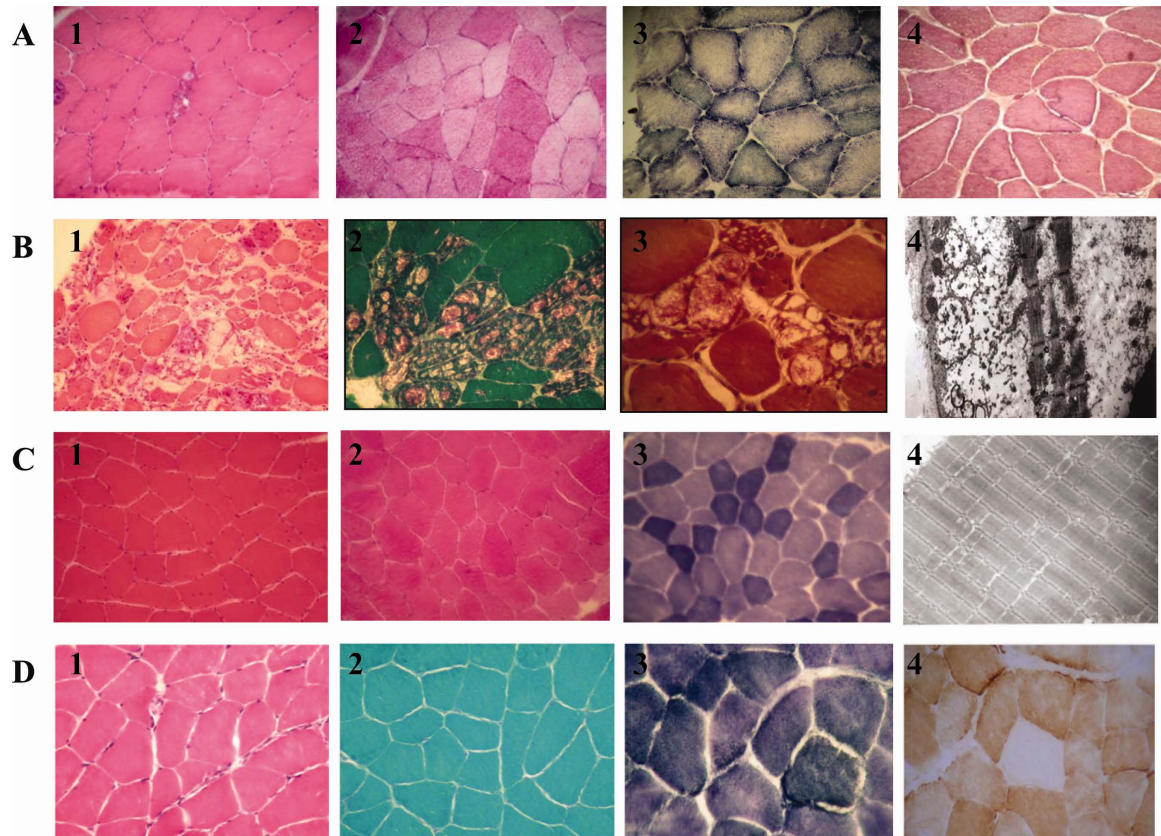
FIGURE 2. Histopathology of muscle biopsy specimens from patients in Cases 1, 2, and 3. A: First deltoid muscle biopsy specimen from Case 1 patient at age 29 years. (A.1) Hematoxylin–eosin (HE) staining shows slight fiber size variation and 1 rimmed vacuole, but no necrosis or endomysial fibrosis; (A.2) periodic acid–Schiff (PAS) staining shows no glycogen accumulation; (A.3) nicotinamide adenine dinucleotide tetrazolium reductase (NADH-TR) staining shows a slightly irregular intermyofibrillar network (all original magnifications × 400). B: Second biopsy specimen (contralateral biceps) from Case 1 patient at age 37 years. Severe vacuolar myopathy, myofibrillar loss, and glycogen accumulation seen with (B.1) HE, (B.1 a) PAS, and (B.2) Gomori trichrome (GT) staining; (B.3) acid-phosphatase positive vacuoles (all original magnifications × 400); (B.4) electron microscopy shows autophagic vacuoles and free glycogen (original magnification × 7000). C: Biceps biopsy specimen from Case 2 patient at age 29 years. (C.1) HE staining shows relatively preserved structure without vacuolar myopathy or glycogen accumulation; (C.2) PAS and (C.3) NADH-TR staining shows slight type 2 fiber hypertrophy (all original magnifications × 400); (C.4) electron microscopy shows no autophagic vacuoles (original magnification × 3000). D: Normal muscle biopsy specimen from a 68-year-old patient with Pompe disease (Case 3). (D.1) HE and (D.2) GT staining shows relatively preserved muscle structure; (D.3) succinic dehydrogenase and (D.4) cytochrome *c* oxidase staining shows a single cytochrome *c* oxidase-deficient ragged red fiber (all original magnifications × 400). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

and 1 rimmed vacuole (Fig. 2A). There was no evidence of inflammation; histochemical, ultrastructural, and immunostaining and Western blot analyses for LGMDs showed no abnormalities. Congenital myopathy, polymyositis, and motor neuron disease were ruled out. The patient received a diagnosis of unspecified LGMD and was advised to adhere to a follow-up schedule to monitor his general health, muscle strength, and pulmonary function.

The patient's condition continued to worsen, and by the age of 35 years, he was experiencing excessive tiredness after walking short distances; undue shortness of breath (dyspnea) when climbing stairs, walking briskly, or performing light exercise. He also experienced morning headaches (a sign of hypercapnia); and inability to lie flat in

bed because of worsening respiratory symptoms. Neurologic assessment showed that the patient had great difficulty climbing stairs and could not raise his arms above his head. Pulmonary function tests revealed ventilatory muscle weakness. His vital capacity (VC) was reduced to 50% (2.92 L) of predicted (5.84 L) in the sitting position and decreased to 1.74 L in the supine position, representing 30% of the predicted value. The >10% difference between sitting and supine VC values was also suggestive of diaphragm muscle weakness. The patient consequently started noninvasive ventilation (NIV) with a bilevel positive airway pressure system.

At age 37 years, 13 years after the initial symptoms of muscle weakness and fatigue presented, the patient was tested for Pompe disease because

of the rapid progression of respiratory symptoms in the presence of unspecified LGMD. A second biceps muscle biopsy was performed (8 years after the first biopsy) which revealed vacuoles with abnormal glycogen accumulation on periodic acid–Schiff staining, suggestive of Pompe disease (Fig. 2B). Reduction of GAA enzyme activity in purified lymphocytes to levels in the diagnostic range of Pompe disease confirmed the diagnosis: fraction acid, 0.01 nmol/hour/mg protein (range, 0.49–1.27); fraction neutral, 0.69 nmol/hour/mg protein (range, 0.63–1.20); and neutral: acid ratio, 69 (range, 0.60–1.30). Later, the patient underwent genetic testing, and 2 specific GAA gene mutations were identified (c-32-13T>G and c.1236+5G>A).

At age 40 years, he started ERT. He is now 45 years old and continues to receive ERT every 2 weeks. Since receiving ERT, the patient can walk longer distances and has noted an improvement in his general well-being. This case illustrates the importance of recognizing characteristic symptoms of Pompe disease: early proximal muscle weakness and elevated CK level. Although ERT was not commercially available when this patient was diagnosed, he received ERT as soon as it was approved.

CASE 2

Case 2 describes a 40-year-old man who had experienced proximal muscle weakness of the lower limbs since the age 23 years. He had no history of motor development problems and described himself as having been extremely active in sports and a very good skier. At age 24 years, he was still actively participating in sports but noticed progressive weakness of his lower limbs and sluggishness in his skiing performance. At age 26 years, he began experiencing difficulties when playing sports and running. By the age of 28 years, he noted undue tiredness and fatigue, excessive sweating and low back pain after playing sports, and symptoms of progressive proximal muscle weakness. Family history was positive for muscle weakness; he has 3 siblings, 1 of whom is similarly, but mildly affected with proximal muscle weakness. Both the patient and his brother had elevated liver enzyme levels during childhood, but no specific disorder was diagnosed. At age 29 years, the patient was admitted to the intensive care unit, where he was diagnosed and treated for pneumonia. He was advised to use NIV during sleep.

Supportive Video 2 demonstrates findings from the physical and neurologic assessments at age 32 years, which included scapular winging, abdominal and trunk muscle weakness, slight waddling gait, inability to sit upright from the supine position without assistance, and use of a "Gower-like" maneuver
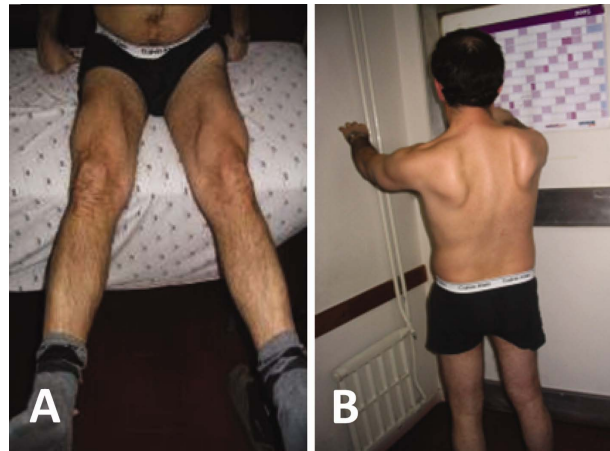
FIGURE 3. A then 32-year-old man with Pompe disease (Case 2) exhibiting prominent quadriceps muscles (A) and scapular winging (B) (written permission to use the image was obtained from the patient). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to stand from a supine position. Electromyography exhibited a myopathic pattern and high-frequency discharges, and the patient's nerve conduction studies were normal. As seen in Figure 3, prominent quadriceps muscles were also noted in this patient. Laboratory results showed a moderately elevated serum CK level (580 IU/L). Pulmonary function tests confirmed signs of respiratory insufficiency while sitting. The patient's VC was reduced to 52% (2.85 L) of predicted value (4.96 L) in the sitting position, and decreased to 1.29 L in the supine position, representing 26% of the predicted value. Lower than average maximal expiratory pressure (MEP) and maximal inspiratory pressure (MIP) results were also noted.

Pathologic examination of a biceps muscle biopsy specimen showed slight type 2 fiber hypertrophy; however, the histochemical, ultrastructural, immunostaining, and Western blot analyses for LGMDs showed no abnormalities (Fig. 2C). Polymyositis, motor neuron diseases, and neuromuscular junction disorders were ruled out. The pattern of proximal muscle weakness, respiratory symptoms, moderate elevation of serum CK level, negative results from the muscle biopsy examination, and positive family history led to a diagnosis of unspecified LGMD with respiratory involvement. A follow-up schedule was devised to monitor the patient's general health, muscle strength, VC, MIP, and MEP.

The patient's pulmonary functions continued to worsen at a faster rate than his motor functions, and by the age of 33 years, he could not lie flat and reported difficulty performing almost all physical activities. His neurologist suspected Pompe disease because of the pattern of disease progression (respiratory insufficiency progressing faster than motor insufficiency) and the patient's clinical

presentation. Ten years after symptom onset, Pompe disease was confirmed by a blood-based assay that demonstrated reduced GAA enzyme activity in purified lymphocytes within the diagnostic range for Pompe disease. Later, genetic testing revealed 2 mutations in the GAA gene (c.-32-13T>G and c.836G>A).

At age 35 years, he began ERT. He is now 40 years of age and continues to receive ERT every 2 weeks. Since starting ERT, he has reported improvement in his breathing and ability to walk longer distances. This case demonstrates the importance of including Pompe disease as a differential diagnosis in patients presenting with proximal muscle weakness, especially in those who have low VC or respiratory insufficiency while preserving relatively good muscle strength in the lower limbs.

CASE 3

Case 3 describes a 78-year-old woman who developed right eyelid ptosis without diplopia at the age 48 years. Two years later, she consulted her internist because of excessive fatigue. Neurologic assessment showed lower limb muscle weakness and waddling gait, and myasthenia gravis was suspected. Results from a laboratory test for anti-acetylcholine receptor antibody and a repetitive stimulation test were negative; the patient did not respond to anticholinesterase medication. Myasthenia gravis was ruled out, and the patient received a diagnosis of nonspecific myopathy. She continued to perform her daily activities and occasionally followed-up with her internist; however, her proximal muscle weakness continued to worsen.

At the age of 68 years, the patient consulted a neurologist because of continued fatigue. Neurologic assessments showed that she had difficulty climbing stairs and an exaggerated waddling gait. Laboratory tests revealed a normal serum CK level, the EMG showed a myopathic pattern, and nerve conduction analyses were normal. Pathological examination of muscle biopsy tissue was almost normal, with the exception of 1 cytochrome oxidase-deficient ragged red fiber (Fig. 2D), a change that is occasionally observed at this age without diagnostic significance. The patient's diagnosis remained as nonspecific myopathy or possibly mitochondrial myopathy because of eyelid ptosis, muscle weakness, and muscle biopsy results. A follow-up schedule was instituted to monitor her general health and muscle strength. Over time, physical activities became increasingly difficult for the patient; she started to experience breathing difficulty in the supine position and gradually showed signs of respiratory insufficiency. Use of an oxygen concentrator was advised.

At age 78 years, the patient developed ptosis in her left eyelid, and was hospitalized 3 months later because of a respiratory tract infection. A neurological examination conducted at the hospital revealed scapular winging, waddling gait, and difficulty climbing stairs (Supportive Video 3), indicative of weakness in the shoulder and pelvic girdle musculature. Pulmonary function tests showed a reduced VC of 62% (1.51 L) of the predicted value (2.43 L) in the sitting position; the patient's VC decreased to 0.92 L in the supine position, representing 23% of the predicted value. Because of the pattern of muscle weakness, the disease progression, and the symptoms of respiratory insufficiency, Pompe disease was suspected and subsequently confirmed 30 years after symptom onset, by a blood-based assay demonstrating a reduced level of GAA enzyme activity in purified lymphocytes: fraction acid, 0.03 nmol/hour/mg protein (range, 0.49–1.27); fraction neutral, 0.76 nmol/hour/mg protein (range, 0.63–1.20); and neutral: acid ratio, 25 (range, 0.60–1.30).

The patient refused ERT and is currently receiving supportive care. This case illustrates that a diagnosis of Pompe disease may be made in elderly patients and that ptosis (often unilateral) can be a presenting symptom. Furthermore, it represents the long journey (30 years) of misdiagnoses and missed diagnosis when the clinical presentation of Pompe disease is unrecognized and excluded from the differential diagnosis.

DISCUSSION

The 3 patients described in this report presented initially with proximal weakness followed by progression to respiratory muscle weakness. Recognition of this common symptom pattern should raise suspicion of Pompe disease early in the disease course. Moreover, the cases emphasize that enzyme testing is essential for the definitive diagnosis of Pompe disease, as muscle biopsy analysis was normal in 1 patient and showed minimal, misleading abnormalities in the others.

Failure to recognize characteristic symptoms of Pompe disease led to delayed diagnosis in all 3 patients. In case 1, failure to consider Pompe disease in the differential diagnosis of NMDs led to deterioration of the patient's respiratory symptoms and disease progression. Case 2 demonstrated failure to consider that proximal muscle weakness and respiratory insufficiency were suggestive of Pompe disease, resulting in symptom progression. The pattern of muscle weakness with preservation of the quadriceps was unrecognized as a feature of Pompe disease in this patient.[9] In case 3, ptosis shifted the diagnosis to myasthenia gravis, although the pattern of muscle weakness was

highly compatible with Pompe disease. Preservation of the quadriceps allowed this patient to climb stairs 30 years after symptom onset. Enzyme replacement therapy was used in cases 1 and 2, and both patients reported improvement in their symptoms and general well-being.

To differentiate the musculoskeletal characteristics of Pompe disease from those of other NMDs, diagnosis should rely on the pattern of muscle weakness and its association with other features such as contractures, scoliosis, or respiratory insufficiency. Progressive proximal muscle weakness typically reflects a limb-girdle pattern, with the pelvic girdle affected more than the shoulder girdle and the pelvic muscles affected more than the quadriceps femoris, resulting in a compensatory waddling gait and lumbar hyperlordosis.[7,19] Limb-girdle muscle weakness is greater in the lower extremities than in the upper extremities and more pronounced in the posterior (hamstring, gluteus muscles) than in the anterior (quadriceps femoris) compartments. Upper limb involvement affects proximal more than distal muscles, with or without scapular winging; neck flexors and tongue muscles are also commonly affected.[19] Trunk extensors (paraspinal muscles) and abdominal muscles are frequently and markedly affected, causing difficulty in sitting upright from the supine position without assistance.[19] Patients often use a "Gower-like" maneuver, which involves rolling on to the side before standing, indicative of weak abdominal muscles. However, because patients with Pompe disease have good quadricep function, they do not use a self-climbing motion that is characteristic of a typical Gower maneuver. Excessive fatigue, weariness, and lower back pain are common early symptoms of Pompe disease[19] and may occur before muscle weakness (as in case 1). Difficulty sitting upright from a supine position because of weak abdominal muscles is a relatively consistent finding when patients are asked about their physical abilities in childhood or adolescence.

Symptoms suggestive of respiratory insufficiency attributed to diaphragm muscle weakness are less common than proximal muscle weakness in Pompe disease; they develop in 50% of patients, and may require NIV.[7,19] Approximately one-third of adult patients with late-onset Pompe disease present with respiratory failure.[20] The most common respiratory symptom reported in patients with Pompe disease is shortness of breath after exercise.[7] No correlation between respiratory insufficiency and skeletal muscle weakness was detected among our described cases, or in 2 earlier reports.[19,21] One study showed a moderate correlation between these parameters ($\rho = 0.55$, $P < 0.001$) in 88 of 92 patients with late-onset Pompe disease.[22] Mild or moderate reduction in VC is compatible with regular daily activities that exclude vigorous exercise, which may cause physicians to overlook this early disease feature. Likewise, symptoms of hypercapnia such as morning headaches or excessive daytime sleepiness can be overlooked or misinterpreted if Pompe disease is not considered in the differential diagnosis. Therefore, pulmonary tests such as VC measurement are important for assessment of respiratory muscle strength, particularly because signs and symptoms of respiratory insufficiency differentiate Pompe disease from many other NMDs.

Unilateral or bilateral eyelid ptosis[19,23] and tongue weakness leading to dysarthria or swallowing problems have been reported in Pompe disease.[24] Other findings that might raise suspicion of Pompe disease are elevated serum CK levels, which can vary from a normal range up to 2000 IU/L[25]; EMG analysis indicating myopathy with increased muscle membrane irritability[1]; and normal nerve conduction findings.[1] Blood-based testing for GAA enzyme activity should be considered early in patients presenting with these symptoms.[11] Additionally, physicians should retrospectively analyze the medical records of patients suspected to have an unspecified LGMD with elevated CK levels of unknown cause accompanied by proximal muscle weakness.[15,26]

Once Pompe disease is confirmed in a symptomatic patient, ERT should be initiated promptly. An optimal management plan should include a comprehensive, multidisciplinary approach for evaluation, intervention, monitoring, and support.[1] It is reasonable to assume that optimal benefit could be derived with treatment initiation early in the disease course, before irreversible muscle damage occurs.

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ULNAR NERVE LESION AT THE WRIST RELATED TO PISOTRIQUETRAL JOINT ARTHROPATHY

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ABSTRACT: *Introduction*: Ulnar nerve lesions at the wrist (UNLW) are always difficult to localize clinically and sometimes electrophysiologically. Finding conduction block when studying ulnar motor nerve conduction (CB) across the wrist is sometimes the only way to demonstrate that the ulnar deep motor branch (UDMB) is entrapped. *Methods*: An elderly woman who had bilateral carpal tunnel syndrome (CTS) and thumb osteoarthritis for many years experienced worsening of left hand impairment recently. *Results*: Electrodiagnostic and ultrasound examinations revealed an acute and severe UDMB lesion related to pisotriquetral joint effusion. The patient received a local injection of a corticosteroid that provided rapid recovery. *Conclusions*: The diagnosis of UDMB lesion is especially difficult when CTS coexists, but CTS may allow for early diagnosis, if CB at the wrist is not overlooked. Chondrocalcinosis was responsible for the systemic inflammation, the CTS, the pisotriquetral joint effusion, and the UDBM compression, which has not been reported previously.

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Ulnar nerve lesions (UNL) at the wrist (UNLW) are always difficult to localize clinically and sometimes electrophysiologically.[1–13] When motor and sensory symptoms and signs are present, diagnosis is difficult, but when sensory complaints are absent, atypical, or related to another nerve lesion, clinical diagnosis is especially difficult. Therefore, electro-diagnosis is essential to differentiate an UNL from a plexus lesion, root disease, or myelopathy and to localize the exact site of the UNL. To assist diagnosis, many authors have recommended studying motor nerve conduction to the first dorsal interosseous (FDI)[5,14–17]; only a few have recommended searching for conduction block (CB) across the wrist.[9–11,13,15,17,18]