Respiratory Medicine Case Reports 17 (2016) 50–53

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Case report

A 62-year-old man with dyspnea

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ARTICLE INFO

Article history:
Received 28 September 2015
Received in revised form
8 January 2016
Accepted 9 January 2016

Keywords:
Acid α-glucosidase enzyme
Bilevel positive airway pressure
Enzyme replacement therapy
Forced vital capacity
Glycogen storage disease
Pompe disease

ABSTRACT

We describe the case of a 62-year-old man who presented with shortness of breath that had progressed over several years. He had a history of a paralyzed right hemidiaphragm for at least the previous 10 years. He also reported weakness in his proximal legs and daytime sleepiness. On examination, he was found to have thoracoabdominal paradox when in supine position. Pulmonary function testing revealed severe restriction; arterial blood gas showed chronic respiratory acidosis. Electromyography showed chronic phrenic neuropathy bilaterally, with mild proximal myopathy. Serum aldolase level was mildly elevated, but serologic tests for connective tissue disorders were within reference range. After extensive clinical investigations, the patient was found to have severely reduced acid α-glucosidase. Genetic analysis confirmed the diagnosis of adult-onset Pompe disease. The patient started treatment with bilevel positive airway pressure titrated during polysomnography, and acid α-glucosidase enzyme replacement was recommended.

1. Introduction

Pompe disease is a rare genetic, autosomal recessive glycogen storage disorder caused by an absence or a deficiency of the lysosomal enzyme acid α-glucosidase (GAA). Adult-onset Pompe disease is a rare cause of dyspnea, and its exact incidence in the United States is not known. Nevertheless, this condition is necessary for a clinician to keep in mind when considering the differential diagnosis of the causes of respiratory muscle weakness. Early recognition of Pompe disease can lead to the timely replacement of the deficient enzyme, which can be beneficial to some patients with this disease.

We report the case of an older man with severe restrictive lung disease, hypercapnic respiratory failure, chronic phrenic neuropathy bilaterally, and proximal muscle weakness who was found to have Pompe disease. Our case highlights the diagnostic challenges that clinicians may face while providing a work-up of this uncommon disease.

1.1. Patient information

A 62-year-old man with a long history of apparently idiopathic right hemidiaphragm paralysis presented with progressive shortness of breath, especially on exertion. He noted his symptoms to be more prominent over the past 6 months. He could walk only 1 city block at a slow pace before stopping because of breathlessness. Additional symptoms were hypersomnolence during the day and proximal muscle weakness with no sensory loss. His past medical history included chronic obstructive pulmonary disease, diabetes mellitus type 2, hypertension, hypercholesterolemia, and coronary artery disease.

About 12 years previously, the patient had elevated serum creatine kinase levels, after which statin therapy was discontinued. A rheumatologic consult was obtained at that time, and no evidence of connective tissue disease was found. At the same time, he also underwent muscle biopsy and electromyography, both of which showed nonspecific myopathic features associated with mild denervation. The patient was lost to follow-up after these investigations. He was an exsmoker with 40–80 pack-years of smoking. Medications at presentation to our facility included aspirin, clopidogrel, simvastatin, diltiazem, sitagliptin, metformin, budesonide and formoterol inhaler, tiotropium bromide inhaler, and albuterol inhaler.

Abbreviations: FRC, functional residual capacity; GAA, acid α-glucosidase.

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http://dx.doi.org/10.1016/j.rmcr.2016.01.003

1.2. Clinical findings

On presentation, the patient's vital signs were a temperature of 36.5 °C (97.7 °F); heart rate, 94 beats/minute; blood pressure, 104/70 mm Hg; respiratory rate, 22 breaths/minute; oxygen saturation, 90% when receiving 2 L of supplemental oxygen per minute; and body mass index, 29.9 kg/m^2. A general examination showed a man with greater-than-ideal body weight who appeared sleepy. Chest examination showed decreased air entry bilaterally. The rest of the systemic examination was normal except for paradoxical respirations on supine position: Respiratory distress immediately developed when he was lying flat.

1.3. Diagnostic assessment

The patient's laboratory values were the following: hemoglobin, 120 g/L; platelets, 279 × 10^9/L; white blood cells, 7.7 × 10^9/L; sodium, 140 mmol/L; potassium, 5.1 mmol/L; bicarbonate, 40 mmol/L; serum urea nitrogen, 3.6 mmol/L; creatinine, 70.7 μmol/L; and calcium, 2.48 mmol/L Fig. 1 shows posteroanterior and lateral plain radiographs. Compared with prior images, computed tomography of the patient's chest showed a stable, mild elevation of the right hemidiaphragm, with bibasilar compressive atelectasis. Centrilobular emphysema with upper lung predominance and with fatty atrophy of paraspinal muscles and rotator cuff musculature was also found (Fig. 2). Tests for resting room-air arterial blood gases showed a pH of 7.29; PCO_2, 89.4 mm Hg; PO_2, 67.6 mm Hg; and serum bicarbonate, 43 mmol/L. Pulmonary function test results are shown in the Table 1.

Fluoroscopy showed right diaphragm paralysis and weakness in left hemidiaphragm. These findings prompted a consultation with neurology services. Electromyography showed complete absence of phrenic compound muscle action potentials bilaterally. No activation of motor unit potentials was seen within the diaphragm, either with respiration or with volitional effort. Ultrasonography showed that the left hemidiaphragm was hyperechoic, 0.14 cm thick at functional residual capacity (FRC), with a thickening ratio of 1.1 (the thickening ratio is thickness at total lung capacity/thickness at FRC). The right hemidiaphragm was hyperechoic, 0.15 cm thick at FRC, with thickening ratio of 0.9. (Normal thickness is >0.15 cm, normal thickening ratio is >1.2.) The aldolase concentration was slightly increased at 9 U/L (reference level, <7.7 U/L). The following tests were within reference range: creatine kinase, thyroid function tests, erythrocyte sedimentation rate, serum and protein electrophoresis, antinuclear antibody profile, and anti-Jo antibodies. To complete the evaluation for rarer causes of diaphragmatic dysfunction, neurology services requested testing for inherited neuropathies. Three weeks later, the patient's serum GAA level was 1.0 nmol/mL/hour (reference level, >7.4 nmol/mL/hour). This test was followed by genetic testing, and the patient was found to have c.525delT and c.-32-13T > G alterations, consistent with a diagnosis of Pompe disease.

Therapeutic intervention replacement treatment with recombinant acid α-glucosidase (GAA) was started. Consultation with sleep medicine services, followed by polysomnography, was obtained, and the patient received a prescription for bilevel positive airway pressure in the spontaneous, timed mode for respiratory failure from restrictive lung disease. Results of follow-up blood gases testing were pH of 7.40; PCO_2, 46 mm Hg; PO_2, 64 mm Hg; and bicarbonate, 29 mmol/L.

2. Discussion

Pompe disease, also known as *glycogen storage disease type II*, was first discovered by the Dutch pathologist Johann C. Pompe in 1932 when he carried out a postmortem examination of a 9-month-old girl who died of pneumonia [1]. In the autopsy, Pompe described accumulation of glycogen in muscle tissue. This rare genetic (autosomal recessive) lysosomal storage disorder is caused by the absence or deficiency of the lysosomal enzyme GAA. Glycogen degradation requires this enzyme; when a person has GAA deficiency, glycogen accumulates in tissues, although it mainly affects cardiac, skeletal, and smooth muscles. In the United States, the disease incidence of Pompe disease is not known. Three common mutations in the Dutch population have carrier frequencies that implicate an estimated frequency of late-onset Pompe disease as 1 in 57,000 persons [2].

Pompe disease is mainly divided into 2 types: infantile and late-onset (presenting after 1 year of age). The infantile type presents with cardiomegaly, generalized muscle weakness, hypotension, enlarged tongue, and hepatomegaly [3,4]. This form results in severe Pompe disease and poor prognosis. In the late-onset or adult form, the heart and the liver are not involved. The late-onset form can present at any age, with the major characteristics of proximal muscle weakness and diaphragmatic involvement that leads to respiratory failure [5–7].

In contrast to the other myopathies, the respiratory neuromuscular unit is particularly susceptible to involvement by Pompe disease [8,9]. Nighttime respiratory difficulty usually precedes its daytime symptoms [10]. Impaired cough and retained respiratory secretions lead to frequent pneumonia bouts and finally to acute respiratory failure. Approximately 60% of patients with late-onset Pompe disease have mild reductions in vital capacity and, according to 1 study, their vital capacity shows a variable, but in most

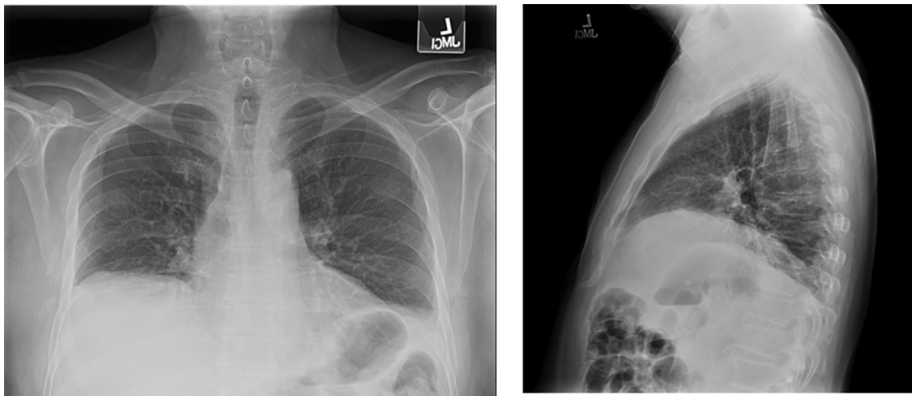

Fig. 1. Hemidiaphragm With Bibasilar Atelectasis. Posteroanterior and lateral chest radiographs show an elevated right hemidiaphragm and atelectasis.