

# Adult-onset Pompe's disease presenting with insidious hypercapnic respiratory failure

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## Keywords

Hypercapnia, myopathy, orthopnoea, Pompe's disease.

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## Abstract

Orthopnoea is commonly attributed to heart failure but can be caused by diaphragm weakness, which, when severe, is often associated with hypercapnic respiratory failure. Bilateral diaphragm weakness is generally due to systemic nerve or muscle disease and usually occurs in the setting of severe generalized muscle weakness, but the diaphragm can be the initial or only muscle involved. Here, we report the case of a 39-year-old female who presented with slowly progressive orthopnoea and daytime somnolence. Pulmonary function studies and polysomnogram confirmed bilateral diaphragm weakness complicated by nocturnal hypoventilation and she was subsequently diagnosed with adult-onset Pompe's disease, a rare metabolic myopathy.

## Introduction

Orthopnoea is a cardinal symptom of bilateral diaphragm weakness. When severe, bilateral diaphragm weakness can lead to nocturnal hypoventilation and respiratory failure, making early diagnosis important to reduce long-term morbidity and mortality. Neuromuscular diseases and generalized myopathies are the most common cause of gradual diaphragm paralysis and respiratory failure. Adult-onset Pompe's disease (PD), also known as acid-maltase deficiency, is a rare lysosomal storage disorder that is associated with a slowly progressive myopathy that frequently involves the diaphragm. Unlike many neuromuscular diseases where supportive therapy is the mainstay of treatment, enzyme-replacement therapy (ERT) is a disease modifying treatment option available for patients with PD.

## Case Report

A 39-year-old mother of six children presented with a 3-year history of progressive exertional dyspnoea with prominent orthopnoea. She was unable to tolerate lying supine due to severe orthopnoea which occurred within minutes of lying down. She had also noted excessive breathlessness when swimming and over the last 2 months had developed

significant daytime somnolence with associated pounding morning headaches. She was known to snore but there had been no witnessed apnoeas. Epworth score was 21/24. There was no history of antecedent illness or trauma. Past history was significant for unprovoked pulmonary emboli 6 years prior for which she was on persistent anticoagulation in the setting of pelvic venous congestion syndrome being diagnosed on follow-up imaging. Family history was non-contributory. On examination, oxygen saturations were 97% on room air, body mass index (BMI) 21 kg/m<sup>2</sup>, neck circumference <40 cm, and modified Mallampati score II. Craniofacial and upper-airway anatomy appeared normal. She was euvolaemic. Heart sounds were normal and the chest was clear to auscultation. Neurological examination was significant for a mildly waddling gait and limited weakness on hip flexion. Reflexes and sensation were normal. There were no signs of muscle wasting, fasciculation, or fatigability. Full blood count, C-reactive protein, thyroid function tests, vitamin B12, and biochemistry were normal apart from minimally increased transaminases. Creatine kinase was mildly elevated at 624 U/L. Serum angiotensin-converting enzyme level was normal. Antinuclear antibodies were weakly positive at 1:160 titre speckled, while antibodies to extractable nuclear antigens and a vasculitic screen were negative. Acetylcholine receptor and

**Table 1. Pulmonary function tests including positional spirometry.**

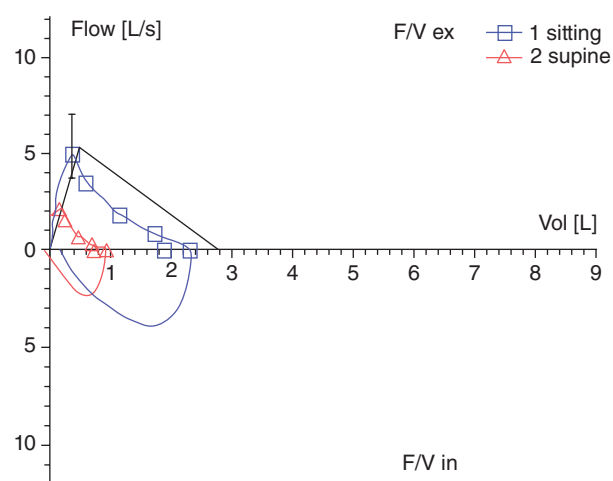
		Pred	Sitting	% Pred	Supine	% Pred	% Diff
FEV1	[L]	2.11	1.87	89	0.73	35	-60.98
FVC	[L]	2.79	2.29	82	0.92	33	-60.05
VC	[L]	2.79	2.29	82	1.12	40	-51.20
FEV1/VC%	[%]	76	82	108	65	86	-20
MMFR	[L/sec]	1.77	1.74	98	0.55	31	-68.39
PEF	[L/sec]	5.36	4.94	92	2.10	39	-57.48
RV	[L]	2.01	2.02	100			
FRC	[L]	2.63	2.81	107			
TLC	[L]	4.70	4.15	88			
RV%	[%]	43	49	113			
DLCO	[mL/min/mmHg]	19.76	21.72	110			
KCO	[mL/min/mmHg/L]	4.52	5.37	119			
VA	[L]	4.37	4.04	92			
VIN	[L]	2.79	2.08	74			

Diff, difference; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 sec; FRC, functional residual capacity; FVC, forced vital capacity; KCO, transfer coefficient for carbon monoxide; MMFR, maximal midexpiratory flow rate; PEF, peak expiratory flow; Pred, predicted; RV, residual volume; TLC, total lung capacity; VA, alveolar volume; VIN, inspired volume.

muscle-specific tyrosine kinase antibodies were likewise negative. Chest radiograph, electrocardiograph, and transthoracic echocardiogram findings were normal. Pulmonary function test findings (Table 1) were normal apart from positional spirometry which demonstrated a 60% decrease in sitting-supine forced vital capacity (FVC; Fig. 1). Random daytime arterial blood gas evaluation revealed a pH of 7.39, partial pressure of carbon dioxide (pCO<sub>2</sub>) 54 mmHg, partial pressure of oxygen (pO<sub>2</sub>) 85 mmHg, and bicarbonate (HCO<sub>3</sub>) 32 mmol/L. Diagnostic overnight polysomnogram demonstrated moderate obstructive sleep apnoea (OSA) with an apnoea hypopnea index (AHI) of 27.1/h, moderate sleep disruption (arousal index 32/h), and severe desaturation during rapid eye movement sleep (nadir 68% room air). Continuous positive airway pressure (CPAP) failed to control sleep-disordered breathing (SDB) with sustained desaturation and daytime hypercapnia, suggestive of nocturnal hypoventilation. She was commenced on bi-level ventilation on spontaneous timed mode with significant improvement. Alpha glycosidase enzyme measurement on blood spot testing was ordered and the alpha glycosidase enzyme level activity was <0.1 L (0.3–3.0). Repeat testing yielded the same result. Urine glucose tetrasaccharide analysis was ordered, and the level was 190 mmol/mol creatinine (<20), confirming PD. She is awaiting commencement of disease-specific ERT.

## Discussion

The prominent orthopnoea and presence of breathlessness on immersion in water, in combination with the greater



**Figure 1.** Positional spirometry: sitting flow volume loop shown in blue (1) and supine in red (2). FV: flow volume ex, expiratory portion of flow volume loop; FV: flow volume in, inspiratory portion of flow volume loop.

than 50% drop in FVC on lying down, were highly suggestive of bilateral diaphragmatic weakness. The major differential diagnosis for this patient's insidiously evolving diaphragmatic weakness included polymyositis, limb girdle muscular dystrophy, motor neurone disease, and PD. There was no strong evidence for other conditions that can cause gradually progressive bilateral diaphragmatic weakness including dermatomyositis, thyroid-related myopathy, myasthenia gravis, or amyloid myopathy.

PD is a rare metabolic myopathy that affects skeletal, cardiac, and smooth muscle. It is an autosomal recessive

disorder resulting from mutations in the acid alpha-glucosidase gene, which encodes a lysosomal enzyme that degrades glycogen into glucose. Clinical manifestations of PD are heterogeneous, reflecting the level of residual enzyme activity. Adult-onset disease results from partial enzyme deficiency (1–30% activity) and most commonly manifests in the third decade of life [1]. Although adults usually present with slowly progressive proximal weakness in a limb girdle distribution, especially of the hip flexors, respiratory symptoms are the primary presenting symptom in about one-third of adult patients with PD [2]. This is in contrast to other inherited neuromuscular diseases, where respiratory muscle weakness typically manifests late in the disease course when the patient is no longer ambulant.

Bilateral diaphragm weakness can be difficult to diagnose given that CXR, fluoroscopy, and even spirometry results may appear normal. Measurement of FVC in the supine position has greater sensitivity and specificity for detecting diaphragm weakness. A drop of  $\geq 15\%$  in FVC from the upright to lying position is diagnostic of diaphragm weakness, while a drop of  $\geq 50\%$  is indicative of bilateral weakness and predicts nocturnal hypoventilation [3]. In most inherited neurological disorders, nocturnal hypoventilation occurs when FVC falls below 50% of predicted; however, in PD it can occur when FVC is only moderately abnormal. This is due to disproportionate diaphragmatic weakness. Initially, hypoventilation only occurs during rapid eye movement (REM) sleep, due to suppressed intercostal and accessory muscle function in the setting of a weakened diaphragm which is exacerbated by supine positioning [2]. As PD progresses, hypoventilation also occurs during non-rapid eye movement (NREM) sleep, due to both reduced lung volumes when supine and a blunting of the ventilatory response to hypercarbia [2]. Less commonly, patients with PD develop OSA due to upper airway dilator muscle weakness and consequent increased airway resistance [3].

Recognition of nocturnal hypoventilation is particularly important as it can cause significant functional impairment, due to cognitive dysfunction and daytime

somnolence, and also contributes to the development of respiratory failure which is the most common cause of premature death [3]. Treatment with non-invasive ventilation (NIV) is generally well tolerated by patients and has been shown to decrease symptom burden, improve quality of life, reduce frequency of hospitalizations, and increase life expectancy in patients with neuromuscular disease [4]. Of even greater therapeutic benefit in PD is ERT which has been available since 2006. Treatment with ERT is associated with enhanced survival and improvement or stabilization of motor performance and respiratory function in at least two-thirds of patients with PD and in some cases has resulted in successful withdrawal of ventilatory support [5].

### Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

### References

1. Winked L, Hagemans M, van Doorn P, et al. 2005. The natural course of non-classic Pompe's disease: a review of 225 published cases. *J. Neurol.* 252:875–884.
2. Mollies U, and Lofaso F. 2009. Pompe disease: a neuromuscular disease with respiratory muscle involvement. *Respir. Med.* 103:477–484.
3. Aboussouan L. 2015. Sleep-disordered breathing in neuromuscular disease. *Am. J. Respir. Crit. Care Med.* 191:979–989.
4. Annan D, Orlikowski D, and Chevret S. 2014. Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. *Cochrane Database Syst. Rev.* doi:10.1002/14651858.CD001941.pub3.
5. Toscano A, and Schoser B. 2013. Enzyme replacement therapy in late-onset Pompe disease: a systematic literature review. *J. Neurol.* 260:951–959.