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WHEN THE DIAPHRAGM FAILS: VISUAL HALLUCINATIONS DUE TO ISOLATED RESPIRATORY MUSCLE WEAKNESS AS A FIRST MANIFESTATION OF LATE-ONSET POMPE DISEASE

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ABSTRACT

Background: Late-onset Pompe disease (LOPD) is a rare autosomal recessive disorder caused by a deficiency of acid alpha-glucosidase (GAA), leading to progressive skeletal and respiratory muscle weakness. In about 10% of cases, diaphragmatic weakness may be the sole presenting feature. Early diagnosis is crucial, as ventilatory support improves outcomes and enzyme replacement therapy can slow disease progression.

Case presentation: A 60-year-old male with a medical history of heart failure presented with dyspnoea, orthopnoea and fluctuating visual hallucinations. Initial metabolic alkalosis, presumed secondary to diuretics, masked chronic hypercapnic respiratory failure. Despite optimised heart failure treatment, symptoms persisted. Pulmonary function tests showed a restrictive pattern with preserved diffusion. Hypercapnic respiratory failure prompted admission to the intensive care unit and invasive ventilation. A significant drop in vital capacity between upright and semi-recumbent positions and absent phrenic nerve responses indicated diaphragmatic weakness. Low GAA activity and genetic testing confirmed the diagnosis of LOPD. Neurological and immunological work-up excluded alternative causes. Non-invasive ventilation improved symptoms, and enzyme replacement therapy with avalglucosidase alfa was initiated.

Conclusion: This case illustrates the diagnostic challenge of isolated respiratory failure due to LOPD when early signs are masked by comorbidities and metabolic disturbances. Nocturnal hypoventilation may cause atypical symptoms such as hallucinations. Systematic neuromuscular evaluation is essential to enable timely ventilatory support and disease-specific treatment.

KEYWORDS

Late-onset Pompe disease, diaphragmatic weakness, respiratory failure, visual hallucination

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LEARNING POINTS

- Isolated respiratory failure due to diaphragm weakness can be the first manifestation of late-onset Pompe disease.
- Diagnosing diaphragmatic weakness is challenging in cardiopulmonary disease, as symptoms may be misattributed.
- Visual hallucinations are a rare symptom of nocturnal hypoventilation.

INTRODUCTION

Pompe disease, a rare autosomal genetic disorder caused by acid alpha-glucosidase deficiency, is characterized by pathological glycogen accumulation in lysosomes. The disease has a broad clinical spectrum, ranging from the severe infantile-onset form, characterized by cardiomyopathy, profound hypotonia, and respiratory failure, to the more slowly progressive late-onset form (LOPD), with an onset beyond 12 months of age, often in adolescence or adulthood[1]. LOPD typically manifests with proximal limb girdle weakness and respiratory insufficiency. In some cases, respiratory muscle involvement may be the sole presenting symptom. However, symptoms of diaphragmatic dysfunction, such as dyspnoea and orthopnoea, are non-specific and initial nocturnal hypoventilation may develop insidiously and go unnoticed until it progresses to overt respiratory failure. Timely diagnosis is however crucial, as non-invasive respiratory support can alleviate symptoms and prevent respiratory complications, while enzyme replacement therapy may slow further deterioration[1,2].

Here we report a case of LOPD presenting as isolated respiratory failure with a 3-month diagnostic delay. This case highlights the challenges of recognizing respiratory muscle weakness in patients with cardiopulmonary comorbidities, emphasizing careful evaluation when symptoms persist despite treatment and consideration of visual hallucinations as a rare manifestation of hypoventilation.

CASE DESCRIPTION

A 60-year-old male active smoker, with a medical history of traumatic right leg amputation, subarachnoid haemorrhage with aneurysm clipping, atrial fibrillation, myocardial infarction and ischemic heart failure presented to the emergency department (ED) with fluctuating visual hallucinations, dyspnoea and orthopnoea. Prior to this moment, he had no known cognitive or neurodegenerative disorders. The patient had been hospitalized 3 months earlier with dyspnoea and orthopnoea, mild limb oedema and small left-sided pleural effusion. Despite treatment with loop diuretics, heart failure medication and bronchodilators, his dyspnoea and orthopnoea persisted, prompting his return to the ED. Other chronic therapy included a statin, an antiplatelet agent, and osteoporosis treatment with a bisphosphonate and calcium/vitamin D supplementation.

On physical examination, the patient was alert with normal cranial nerve, motor and sensory examination, except for the known right lower leg amputation. Cardiovascular examination showed no overt signs of heart failure. Respiratory examination revealed a respiratory rate of 10 breaths/min, normal breath sounds, with a peripheral oxygen saturation of 92% while breathing room air. Arterial blood gas analysis revealed metabolic alkalosis (pH 7.48, HCO_3 38 mmol/l) *(Table 1)*, initially attributed to diuretic therapy, with a compensatory increase in pCO_2 (52 mmHg). Computed tomography (CT) scan and lumbar puncture ruled out structural abnormalities, infectious and auto-immune encephalitis as potential causes of hallucinations. To counterbalance the alkalinizing effect of the loop diuretics, as a potential metabolic cause of the hallucinations, acetazolamide was associated, and the patient was discharged.

Two weeks after discharge, the patient was readmitted with persistent symptoms and elevated bicarbonate levels. Results from the cardiopulmonary and neurological work-up that had been initiated showed a left ventricular ejection fraction of 49% with normal end-diastolic pressure, ruling out heart failure as the cause of dyspnoea. Pulmonary function tests revealed a restrictive pattern with diffusion impairment but normal carbon monoxide transfer coefficient (forced vital capacity, FVC 38% of predicted [%pred] diffusion capacity, TLCO 39%pred, carbon monoxide transfer coefficient, KCO 90%pred) *(Table 2)*. Fluoroscopy showed limited but normal movement of the diaphragm. CT imaging revealed centrilobular and paraseptal emphysema without interstitial lung disease. Neurological assessment, including electroencephalogram, nerve conduction studies, 3 Hz repetitive nerve stimulation, and electromyography of the upper and lower limbs, showed no evidence of a neurogenic or myogenic disorder. On day 3, arterial blood gas analysis, performed because of desaturation and worsening dyspnoea, revealed hypercapnia (pCO_2 72 mmHg) and acidosis (pH 7.29) *(Table 1)*. Taken together, these findings indicated hypercapnic respiratory failure due to a neuromuscular disease, with fluctuations in CO_2 levels likely triggering the hallucinations. When specifically questioned, the patient reported sleep disturbances, headaches, and daytime sleepiness.

The patient was monitored in the intensive care unit (ICU) for 48 hours, stabilized without respiratory support, and was transferred to the ward. Follow-up spirometry revealed worsening pulmonary function compared to four weeks prior, with inspiratory and expiratory muscle weakness (maximal inspiratory pressure: 4.85 kPA, 56%pred; maximal expiratory pressure: 6.44 kPA, 48%pred). On day 7, the patient was readmitted to the ICU because of severe hypercapnic respiratory failure (pCO_2 130 mmHg, pH 7.18)

	Day 1	Day 3	Day 4	Day 7	Day 10	Day 19	Reference
pH	7.48	7.29	7.37	7.18	7.45	7.42	7.35-7.45
pCO_2 (mmHg)	52	72	58	130	45.1	39	33-48
pO_2 (mmHg)	59	49	62	65	83.4	81.6	80-104
HCO_3-(mmol/l)	38	34	32	47	31.1	25.2	21-28
O_2 saturation(%)	94	84	91	90	98.3	96	95-100

Day 1: presentation in the ER with visual hallucinations and dyspnoea; Day 3: first transfer to the intensive care unit (ICU); Day 3: normalisation of pH levels in the ICU; Day 7: second transfer to the ICU because of hypercapnic respiratory failure; Day 10: normalisation of pH and pCO_2 after 2 nights of invasive ventilation in a tertiary centre; Day 19: after extubation with nightly non-invasive ventilation.

Table 1. Evolution of arterial blood samples.

		Day 5	Day 31	Day 7	Day 10
	Ref	Pre-bronchodilator	Post-bronchodilator	Sitting up	Lying down (45°)
	Pred	Measured (%pred)	Measured (%pred)	Measured (%pred)	Measured (%pred)
FVC (l)	4.41	1.47 (38)	1.56 (40)	1.79 (41)	1.37 (31)
FEV1 (l)	3.42	1.25 (41)	1.34 (44)	1.39 (41)	1.08 (32)
FEV1/FVC (%)	77.67	85.44 (112)	85.99 (113)	77.80 (100)	78.60 (101)
VC (l)	4.04	1.71 (42)	NA	NA	NA
RV (l)	2.32	1.73 (75)	NA	NA	NA
TLC (l)	6.50	3.44 (53)	NA	NA	NA
TLco (mmol/min/Kpa)	8.90	3.50 (39)	NA	NA	NA
Kco (mmol/min/kPa/l)	1.37	1.23 (90)	NA	NA	NA

Day 5: first admission after presentation in the emergency department; Day 31: At a tertiary centre, supine (45°) and upright position.

Abbreviations: NA, not applicable; Ref, reference; Pred, predicted; FVC, forced vital capacity; FEV, forced expiratory volume after 1 second; VC, vital capacity; RV, rest volume; TLC, total lung capacity; TLco: diffusion capacity; Kco, carbon monoxide transfer coefficient.

Table 2. Pulmonary function tests.

(Table 1). Non-invasive ventilation was attempted but failed, necessitating intubation. Given the need for specialized neuromuscular work-up, the patient was transferred to a tertiary centre on day nine.

Severe diaphragmatic dysfunction was corroborated by a 24% FVC reduction in FVC in the semi-recumbent position, as full supine testing was not tolerated, and by bilaterally absent responses on phrenic nerve conduction study. Further investigations, including acetylcholine receptor, muscle-specific kinase, and low-density lipoprotein receptor-related protein (LRP4) antibodies, myositis and systemic disease screening, ganglioside antibodies, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) antibodies, angiotensin-converting enzyme (ACE), and serum protein electrophoresis, were all normal. Positron emission tomography scan, magnetic resonance imaging of the cervical spine, and brain imaging also revealed no abnormalities.

The patient's hospital course was complicated by *Klebsiella pneumonia*, delaying extubation until day 18. The patient was immediately transitioned to continuous non-invasive ventilation, which was gradually weaned to nighttime use only. Hallucinations had completely resolved, and the patient was discharged from the ICU on day 28 and from the hospital on day 32. Subsequently, earlier testing revealed low acid alpha-glucosidase (GAA) activity, leading to exome analysis that confirmed the diagnosis of LOPD, identifying heterozygosity for two pathogenic variants (c.-32-13T>G and c.525del (p.Glu176Argfs*45)). Treatment with intravenous avalglucosidase alfa, an enzyme replacement therapy, was initiated.

DISCUSSION

We describe a case of late-onset Pompe disease, presenting as isolated respiratory failure, with symptoms initially falsely attributed to cardiopulmonary comorbidities, and metabolic alkalosis attributed to diuretic use. The 3-month delay in diagnosis highlights the challenges in recognizing

neuromuscular causes of chronic respiratory failure, particularly in patients with cardiopulmonary comorbidities. LOPD, manifesting usually in late adolescence or adulthood, typically presents with proximal limb weakness and respiratory muscle involvement[3]. In about 10% of cases, initial presentation is limited to respiratory muscle weakness[4]. In our patient, limb weakness was absent, and symptoms of orthopnoea and dyspnoea were misinterpreted as cardiac decompensation, leading to treatment with diuretics. However, persistent symptoms despite optimized heart failure therapy prompted further investigation.

A key challenge in this case was the presence of metabolic alkalosis (pH 7.48, HCO_3^- 38 mmol/l), which masked chronic hypercapnic respiratory failure, as it was presumed secondary to diuretic use. In diaphragmatic weakness, nocturnal hypoventilation leads to CO_2 retention, prompting renal bicarbonate retention, typically keeping pH at the lower end of normal rather than causing overt alkalosis. Dyspnoea and orthopnoea were attributed to cardiac failure, while fluctuating visual hallucinations, likely due to CO_2 fluctuations, provided another clue. However, as a rare manifestation of nocturnal hypoventilation, they were not initially recognized as such. Diaphragmatic weakness was only suspected upon overt respiratory failure with hypercapnic acidosis[5]. At that point, the absence of cardiac failure on ultrasound, a restrictive lung pattern with normal diffusion per unit lung volume, and absence of interstitial lung disease on CT scan, pointed to a neuromuscular cause of restriction[5].

Diaphragmatic weakness was confirmed by a phrenic nerve conduction study, which showed no bilateral response. To exclude technical issues, both seated and semi-recumbent spirometry were performed. The latter was chosen because full-supine spirometry was not tolerated and revealed a significant reduction in vital capacity compared with the seated position. Chest X-ray and fluoroscopy, which often miss bilateral weakness, did not reveal abnormalities in this patient. Ultrasound, though useful for diagnosing diaphragmatic weakness, was inconclusive due to poor visualization.

Extensive biochemical, neurophysiological, and imaging evaluations ruled out potential causes, including structural spinal cord pathology, motor neuron diseases, neuromuscular junction disorders, inflammatory, autoimmune, and drug-induced myopathies, as well as malignancies and infectious causes. However, a few weeks after admission, alpha-glucosidase activity determined prior to transfer to the tertiary hospital was found to be deficient, and genetic testing subsequently confirmed Pompe disease[4].

Treatment consisted of chronic respiratory support with nocturnal non-invasive ventilation, which significantly improves quality of life and is critical in preventing respiratory complications. Additionally, enzyme replacement therapy (avalglucosidase), was initiated as the standard of care, expected to slow disease progression and improve survival, while gene therapy remains a promising future approach[2].

This case highlights the diagnostic challenge of LOPD, particularly when isolated respiratory failure is masked by cardiorespiratory comorbidities and the confounding effects of diuretic-induced acid-base disturbances, delaying recognition of respiratory muscle weakness. Visual hallucinations were an unusual manifestation of nocturnal hypoventilation but an early clue to its presence. This case underscores the need for awareness of atypical presentations of LOPD and adopting a systematic approach to diagnosing unexplained respiratory symptoms. An important clue in this case was the significant difference in lung function testing in upright and supine position, which indicated a diaphragmatic weakness. Early detection is crucial to prevent respiratory complications through timely ventilatory support, while enzyme replacement therapy can slow disease progression and improve long-term outcomes.

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