

Late-onset Pompe: Why lungs fail before limbs

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Late-onset Pompe disease (LOPD) presents a diagnostic challenge, often mimicking more common neuromuscular or respiratory conditions. Clinicians frequently encounter patients with unexplained respiratory insufficiency, only to discover later that limb girdle weakness is also present, or develops subsequently. This sequence of symptom presentation can obscure the underlying metabolic disorder, delaying the initiation of enzyme replacement therapy.

KEY TAKEAWAYS

- **The Pivot:** Respiratory dysfunction, particularly diaphragmatic weakness, is a common initial manifestation of LOPD, often appearing before overt skeletal muscle weakness.
- **The Data:** Early recognition of respiratory compromise, even in the absence of significant limb weakness, is critical for timely diagnosis.
- **The Action:** GPs and specialists should consider LOPD in adults presenting with unexplained progressive respiratory insufficiency, especially nocturnal hypoventilation, even if limb weakness is subtle or absent.

Late-onset Pompe disease, a rare autosomal recessive lysosomal storage disorder, results from a deficiency of acid alpha-glucosidase (GAA).¹ This enzyme is vital for breaking down glycogen in lysosomes. When GAA activity is insufficient, glycogen accumulates in various tissues, particularly skeletal, cardiac, and smooth muscles.¹ The clinical spectrum of LOPD is broad, ranging from slowly progressive muscle weakness to severe respiratory failure, with significant variability in age of onset and disease progression.^{1,2} The insidious nature of LOPD means that symptoms can be subtle for years, often leading to misdiagnosis or delayed diagnosis, which has profound implications for patient outcomes.²

The disease typically manifests in childhood or adulthood, distinguishing it from the infantile-onset form, which is rapidly progressive and often fatal in the first year of life without treatment.¹ In LOPD, the residual GAA activity, though low, is sufficient to prevent the rapid, severe progression seen in infantile Pompe disease. Patients with LOPD often present with proximal muscle weakness, affecting the hips and shoulders, leading to difficulties with ambulation, climbing stairs, and rising from a chair.¹ But the respiratory system is also a primary target, with diaphragmatic weakness being a hallmark feature.^{1,2,3} This can lead to significant respiratory compromise, often before limb weakness becomes debilitating.¹

The Respiratory Predominance

The diaphragm, being a skeletal muscle, is highly susceptible to glycogen accumulation in LOPD. Diaphragmatic weakness can manifest as exertional dyspnea, orthopnea, and recurrent respiratory infections.¹ A key indicator is nocturnal hypoventilation, which can lead to morning headaches, daytime somnolence, and fatigue.^{1,3} These symptoms

are often non-specific and can be attributed to other conditions like asthma, COPD, or sleep apnea, delaying the consideration of LOPD.² The cough assessment gap in respiratory disease is a persistent issue, and LOPD adds another layer of complexity.

Pulmonary function tests often reveal a restrictive ventilatory defect, with reduced forced vital capacity (FVC), particularly in the supine position. A significant drop in FVC when moving from an upright to a supine position (typically >20%) is a strong indicator of diaphragmatic weakness. This specific finding should prompt further investigation for neuromuscular disorders, including LOPD. Arterial blood gas analysis may show hypercapnia, especially during sleep, reflecting chronic hypoventilation.⁴ The OxiPro OX2 Pulse Oximeter can be a useful tool for monitoring oxygen saturation at home, though it will not directly detect hypercapnia.

The progression of respiratory symptoms can be insidious, with patients adapting to their declining lung function until a precipitating event, such as an infection, leads to acute respiratory failure.² This can be the first time LOPD is considered, often after significant and irreversible damage has occurred. Early recognition of these respiratory signs is paramount because enzyme replacement therapy (ERT) is most effective when initiated before extensive muscle damage.³ This is a common theme in rare diseases, where late-onset presentations in adult clinics often mask conditions with childhood origins.

Diagnostic Pathways and Challenges

Diagnosing LOPD requires a high index of suspicion. When a patient presents with unexplained progressive muscle weakness, particularly involving the proximal muscles and axial musculature, LOPD should be on the differential. But when respiratory symptoms dominate the clinical picture, the diagnostic pathway can be diverted.^{2,3} Electromyography (EMG) and nerve conduction studies can show myopathic changes, but these are not specific to Pompe disease. Muscle biopsy can reveal vacuolar myopathy with glycogen accumulation, but it is an invasive procedure and may not always be conclusive.

The definitive diagnosis relies on measuring GAA enzyme activity in dried blood spots or fibroblasts, or genetic testing for mutations in the GAA gene.¹ Dried blood spot testing is a non-invasive screening tool that can be performed in a primary care setting, making it accessible for initial evaluation. If GAA activity is found to be low, confirmatory genetic testing is then performed. This diagnostic approach helps to differentiate LOPD from other conditions that might present with similar symptoms, such as limb-girdle muscular dystrophies, polymyositis, or other forms of glycogen storage diseases. The challenge lies in knowing when to order these tests, especially when the clinical picture is dominated by respiratory complaints.²

But the diagnostic journey for LOPD is often protracted. Patients may see multiple specialists, including pulmonologists, neurologists, and rheumatologists, before the correct diagnosis is made.³ The average time to diagnosis can be several years, during which irreversible muscle damage can occur. This delay highlights the need for greater awareness among general practitioners and specialists about the early, often subtle, respiratory manifestations of LOPD.² For instance, lifespan phenotypes of acute respiratory failure can sometimes mask underlying genetic conditions.

Therapeutic Implications

Enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase is the established standard of care for LOPD.¹ ERT aims to replace the deficient enzyme, reducing glycogen accumulation and improving muscle function.

Clinical experience shows that ERT can stabilize or improve respiratory function, increase muscle strength, and enhance quality of life. The earlier ERT is initiated, the greater the potential for preserving muscle function and preventing irreversible damage. This is particularly true for respiratory muscles, where early intervention can prevent the need for ventilatory support.

But ERT is not a cure. It is a lifelong treatment that requires regular intravenous infusions. The efficacy of ERT can vary among patients, and some individuals may still experience progressive disease despite treatment. The open-label design of many early studies is an obvious caveat, but the consistent clinical improvements observed provide a strong rationale for early diagnosis and treatment. The long-term management of LOPD also involves supportive care, including respiratory support (e.g., non-invasive ventilation), physical therapy, and nutritional support.^{1,3} The comprehensive management of LOPD requires a multidisciplinary approach, involving neurologists, pulmonologists, geneticists, and rehabilitation specialists.³ The Oxford Handbook of Respiratory Medicine provides a concise reference for managing such complex respiratory conditions.

The challenge remains to identify patients before significant clinical deterioration.² The subtle onset of respiratory symptoms, often preceding overt limb weakness, means that LOPD should be considered in any adult with unexplained progressive respiratory insufficiency, especially if there is a family history of neuromuscular disorders or if other common causes have been excluded.³ A proactive approach to screening for LOPD in these patient populations could significantly reduce diagnostic delays and improve long-term outcomes.

CLINICAL IMPLICATIONS

The persistent underdiagnosis of late-onset Pompe disease, particularly when respiratory symptoms are the primary complaint, highlights a significant gap in clinical awareness. GPs and pulmonologists are often the first point of contact for these patients, but the non-specific nature of dyspnea and fatigue means LOPD is rarely on the initial differential. This leads to years of misattribution to more common conditions, costing patients valuable time during which irreversible muscle damage progresses.

Specialists need to be more vigilant. A patient presenting with unexplained restrictive lung disease, especially with supine FVC decline or nocturnal hypoventilation, warrants a broader diagnostic net that includes rare neuromuscular disorders. Simply ruling out COPD or asthma is not enough. The availability of dried blood spot testing means that a definitive diagnosis is not an arduous process once the suspicion is raised.

For the pharmaceutical industry, the focus must shift beyond simply developing therapies to ensuring early access to diagnosis. Educational initiatives targeting primary care and respiratory specialists are essential. Without earlier identification, even highly effective enzyme replacement therapies will struggle to achieve their full potential in preventing long-term disability and improving quality of life for these patients.

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