Original Article

Late-Onset Pompe Disease Presenting as Acute Hypercapnic Respiratory Failure in an Adolescent Male: A Diagnostic Challenge

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Abstract

Background: Late-onset Pompe disease (LOP) is a rare inherited disorder also known as acid alpha-glucosidase deficiency (GAA deficiency) in which the acid alpha-glucosidase enzyme is either not made or does not work properly, causing a gradual build-up of glycogen in the muscles of the body, including those in the skeletal and respiratory systems. Proximal muscle weakness and respiratory insufficiency are common symptoms that are often misdiagnosed because the disease slowly progresses over several months. **Case Presentation:** We here describe the case of a juvenile patient (age 15) with progressive proximal muscle weakness, frequent upper and lower respiratory tract infections, orthopnoea and hypercapnic respiratory failure. Over the past 5 years the patient experienced gradually progressive weakness in the upper and lower limbs at the proximal articular surface and was experiencing difficulty climbing stairs and exercise intolerance. At the time of admission he complained of severe type 2 respiratory failure and the arterial blood gas showed severe respiratory acidosis (pH 6.885, pCO2 245 mmHg). The results of detailed investigations such as muscle biopsy, electrophysiological and autoimmune markers were not conclusive. Subsequently, diagnostic confirmation for the diagnosis of late-onset Pompe disease was made by an enzymatic assay that shows a decrease in alpha-1,4-glucosidase activity. Intensive supportive care, physiotherapy, and ventilator weaning led to a gradual improvement in the patient. **Conclusion:** Progressive proximal myopathy, scapular winging, orthopnoea, recurrent respiratory infections and unexplained hypercapnic respiratory failure are suggestive of late-onset Pompe disease in adolescents. Prompt diagnosis and disease-specific therapy begins with the ability to recognize and be able to test for the correct enzyme.

Keywords: Acid alpha-glucosidase deficiency (also known as Pompe disease), Late onset pompe disease, Hypercapnic respiratory failure, Proximal myopathy, Glycogen storage disease type II.

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Introduction

Pompe disease (glycogen storage disease type II, acid maltase deficiency) is a rare disease that affects a person's ability to metabolize glycogen in their muscle and tissues, causing glycogen to build up in the person's tissues (lysosomal storage disease). (Source: Genetics Home Reference) The disease is transmitted as an autosomal recessive disorder and is caused by a lack of the lysosomal enzyme, acid alpha-glucosidase (GAA), which breaks down glycogen. The GAA gene is located on chromosome 17q25.2-q25.3, and more than 350 pathogenic mutations have been described. The clinical spectrum ranges from severe infantile-onset disease with cardiomyopathy to late-onset Pompe disease presenting during childhood, adolescence, or adulthood with progressive skeletal muscle and respiratory involvement.

Late-onset Pompe disease commonly manifests with proximal muscle weakness, exercise intolerance, respiratory muscle involvement, orthopnoea, and recurrent respiratory infections. Respiratory insufficiency may occasionally precede limb weakness, making diagnosis challenging. Early diagnosis is critical because enzyme replacement therapy (ERT) can significantly improve survival and quality of life.

We present a case of late-onset Pompe disease in a 15-year-old male who presented with progressive proximal muscle weakness and acute hypercapnic respiratory failure requiring prolonged ventilatory support.

Case Presentation

A 15-year-old male from Mumbai, Maharashtra, India, with previously normal developmental milestones and age-appropriate psychomotor development, presented with gradually progressive proximal muscle weakness involving both

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upper and lower limbs over a period of five years. The weakness initially affected the upper limbs more prominently and was first noticed during physical training activities at school.

The patient experienced progressive difficulty with overhead abduction of the arms, climbing stairs, turning sides in bed, and performing activities requiring proximal muscle strength. He also reported exercise intolerance, recurrent respiratory tract infections, orthopnoea requiring two pillows during sleep, and progressive exertional breathlessness.

On 24 November 2024, the patient developed fever associated with chills, productive cough, and progressive breathlessness over three days. He was admitted to the intensive care unit with severe orthopnoea and paroxysmal nocturnal dyspnoea.

Clinical Examination

At time of admission the pulse was 130 beats per minute (bpm), blood pressure 110/90 mmHg and oxygen saturation was kept at 98% on 4L /min oxygen through nasal cannula.

Respiratory system exam showed decreased air entry with bronchial breath sounds in the left hemithorax. This was confirmed by chest radiography, which showed patchy infiltrates in the left lower lobe suggestive of pneumonia.

Neurological examination did not show any defects of higher mental functions or any damage to the cranials. Tone was normal in all four limbs. Proximal muscle power was reduced to 3/5 in both upper and lower limbs, while distal muscle power was relatively preserved at 4/5. Scapular winging, lumbar lordosis, and positive Gowers' sign were noted. Sensory examination and cerebellar examination were normal.

The patient had weak cough reflex, orthopnoea, and restricted diaphragmatic movement suggestive of respiratory muscle involvement.

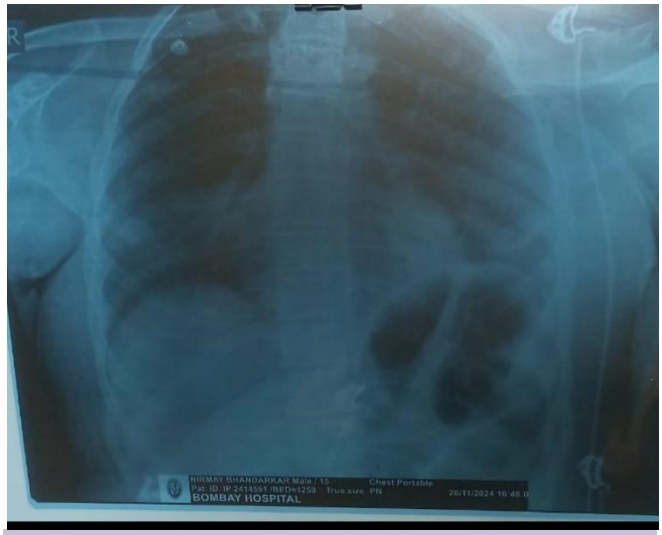


Figure 1- Initial chest xray.

Investigations and further work up:

Initial laboratory investigations showed leucocytosis, polycythaemia, elevated creatine phosphokinase levels, and electrolyte abnormalities.

Arterial blood gas analysis on admission revealed hypoxia with mild carbon dioxide retention.

Ultrasonography of the chest and abdomen demonstrated significantly restricted bilateral diaphragmatic movement, more pronounced on the left side, without paradoxical movement.

Electrocardiography and echocardiography were normal.

Initially, the patient was managed as a case of pneumonia with myositis and treated with non-invasive ventilation, intravenous piperacillin-tazobactam, hydration, and supportive care.

Subsequently, the patient developed severe hypercapnic respiratory failure with arterial blood gas showing:

- pH: 6.885
- pCO2: 245 mmHg
- HCO3: 43 mmol/L
- pO2: 100 mmHg
- Oxygen saturation: 93%

Despite improvement in infective parameters demonstrated clinical as patient became afebrile and via laboratory parameters –wbc count s, serial procalcitonin levels and resoluation of patch seen in chest xray [Figure 2] previously -the patient developed worsening muscle weakness and progressive respiratory failure requiring endotracheal intubation and invasive mechanical ventilation. (Hypercapnic respiratory failure)

Autoimmune workup including myositis panel and acetylcholine receptor antibodies was negative. The patient received pulse methylprednisolone therapy (1 g/day for 5 days) with mild transient improvement in muscle power.

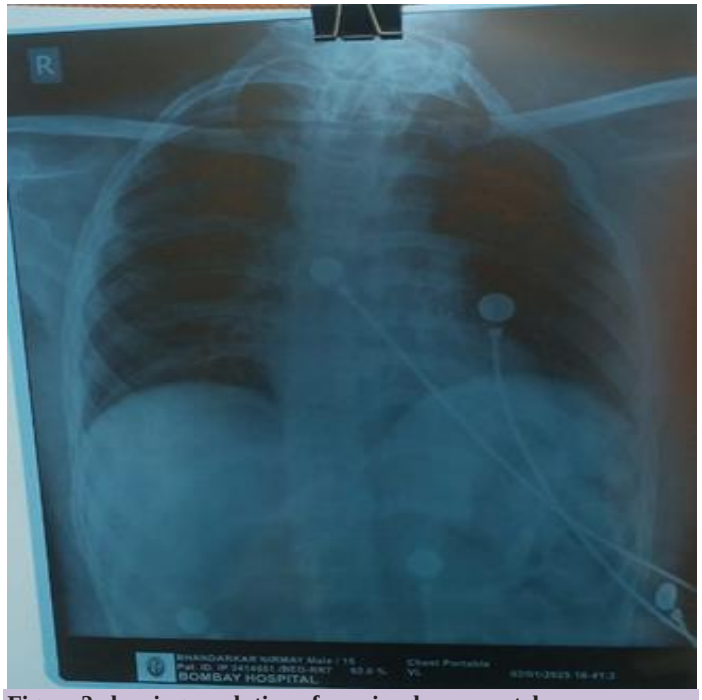


Figure 2-showing resolution of previously seen patch.

Due to prolonged ventilator dependence, tracheostomy was performed.

Given the progressive proximal myopathy, recurrent respiratory infections, orthopnoea, positive Gowers' sign, scapular

winging, and type 2 respiratory failure, late-onset Pompe disease was suspected.

Electromyography and nerve conduction studies demonstrated mild myopathic changes predominantly involving proximal muscles without evidence of motor neuron disease or neuromuscular junction disorder.

Genetic testing for facioscapulohumeral muscular dystrophy (FSHD) was negative.

Muscle biopsy from the left deltoid showed occasional small muscle fibres with clumped sarcolemmal nuclei but no evidence of active inflammation, dystrophy, neurogenic atrophy, vasculitis, or myositis.

Enzymatic assay demonstrated reduced alpha-1,4-glucosidase activity consistent with Pompe disease.

Table 1: Enzymatic Assay Findings

Parameter	Result	Reference Range
Total acid alpha-glucosidase	31.11 nmol/hr/mL	10–60
Lysosomal acid alpha-glucosidase	8.48 nmol/hr/mL	4.51–15.0
Ratio (B/A)	0.27	0.3–0.8
Alpha-1,4-glucosidase	0.23	>0.29 normal

Table 2: Sensory Nerve Conduction Study

Nerve / Site	Recording Site	Onset Latency (ms)	Amplitude (µV)	Distance (cm)	Velocity (m/s)	Remark
R Median – Index	Wrist	3.0	23.9	14	47.2	Normal
R Ulnar – Little Finger	Wrist	2.3	16.9	11	46.9	Normal
L Medial Plantar – Medial Sole	Ankle	2.5	20.0	12	48.0	Normal

Table 3: Motor Nerve Conduction Study

Nerve / Site	Muscle	Latency (ms)	Amplitude (mV)	Amp 2–4 (mV)	Distance (cm)	Velocity (m/s)	Area (mVms)	Remarks
R Median – APB (Wrist)	APB	6.04	0.8	1.1	7	–	1.6	Severely attenuated
R Median – APB (Elbow)	APB	11.20	0.6	0.8	29	56.2	1.2	Severely attenuated
R Ulnar – ADM (Wrist)	ADM	3.85	2.7	4.4	7	–	9.1	–
R Ulnar – ADM (At ME)	ADM	8.33	2.5	4.5	23	51.3	9.5	Low amplitude for age
R Peroneal – Tibialis Anterior	Tibialis Anterior	3.02	1.5	3.0	–	–	6.3	Low amplitude
R Peroneal – Fibular Head	Tibialis Anterior	2.40	1.3	2.6	–	–	6.2	Low amplitude
R Tibial – AH	AH	3.85	12.1	20.5	8	–	37.1	Normal
R Tibial – Popliteal Fossa	AH	12.66	10.3	17.7	36	40.9	35.8	Normal
L Tibial – AH	AH	5.26	11.0	20.3	8	–	44.3	Normal
R Tibial – Gastrocnemius	Gastrocnemius	3.75	15.3	22.9	–	–	31.1	Normal
R Tibial – Popliteal Fossa	Gastrocnemius	3.02	9.9	12.2	–	–	–	Normal
R Femoral – Vastus Medialis	Vastus Medialis	3.39	3.1	5.2	–	–	17.7	Low amplitude for age

Table 4: H-Reflex Study

Nerve	H Amplitude Left (mV)	H Amplitude Right (mV)	H Latency Left (ms)	H Latency Right (ms)	Remarks
Tibial – Soleus	10.0	8.3	25.31	26.41	Normal

Table 5: Repetitive Stimulation Study

Anatomy / Train	Baseline Amplitude (mV)	d. Amp 1 (%)	Remarks
R Peroneal – Tibialis Anterior	1.6	-3.2	Negative
R Ulnar – ADM	2.4	-2.1	Normal

Table 6: Electromyography (EMG)

Muscle	Nerve	Roots	Spontaneous Activity	MUAP Findings	Recruitment	Remarks
R Tibialis Anterior	Deep Peroneal (Fibular)	L4–L5	Nil	Small, short MUPs	Early and full	Mild muscle involvement
L Gastrocnemius (Medial Head)	Tibial	S1–S2	Nil	Normal	Full	Normal
R Vastus Medialis	Femoral	L2–L4	Nil	Small, short MUPs	Early and full	Mild muscle involvement
R Iliacus	Femoral	L1–L4	Nil	Small, short,	Early and full	Suggestive of muscle

				polyphasic MUPs		disease
R First Dorsal Interosseous	Ulnar	C8–T1	Nil	Normal	Full	Normal
R Biceps Brachii	Musculocutaneous	C5–C6	Nil	Small, short, polyphasic MUPs	Early and full	Suggestive of muscle disease

These findings supported the diagnosis of late-onset Pompe disease.

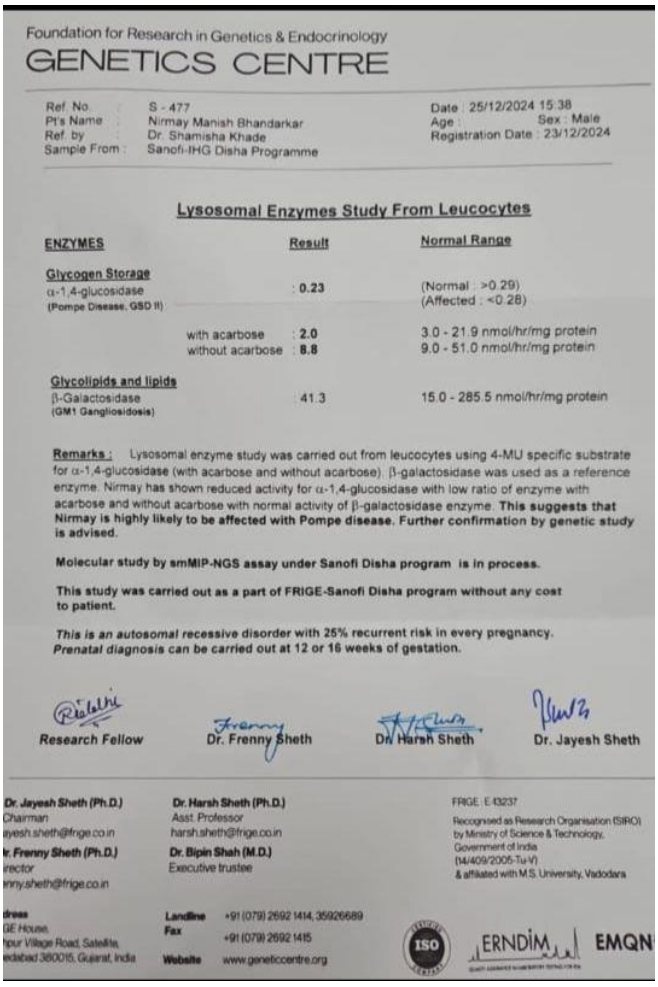
Outcome and Follow-Up

The patient gradually improved with intensive respiratory care, physiotherapy, and progressive ventilator weaning. T-piece trials were successfully tolerated, and diaphragmatic movement improved on follow-up ultrasonography.

An extubation attempt was initially unsuccessful, resulting in respiratory arrest and reinstitution of pressure support ventilation. However, gradual clinical improvement allowed eventual successful ventilator weaning.

The patient and family were counselled regarding the diagnosis, prognosis, and potential role of enzyme replacement therapy.

After a total intensive care unit stay of 46 days, the patient was discharged in stable condition with advice regarding home respiratory care, suctioning, oxygen monitoring, physiotherapy, and follow-up for tracheostomy management and genetic evaluation.



Foundation for Research in Genetics & Endocrinology

GENETICS CENTRE

Ref. No. : S - 477
Pt's Name : Nirmay Manish Bhandarkar
Ref. by : Dr. Shamisha Khade
Sample From : Sanofi-IHG Disha Programme

Date : 25/12/2024 15:38
Age : Sex : Male
Registration Date : 23/12/2024

Lysosomal Enzymes Study From Leucocytes

ENZYMES	Result	Normal Range
Glycogen Storage α-1,4-glucosidase (Pompe Disease, GSD II)	: 0.23	(Normal : >0.29) (Affected : <0.28)
with acarbose	: 2.0	3.0 - 21.9 nmol/hr/mg protein
without acarbose	: 8.8	9.0 - 51.0 nmol/hr/mg protein
Glycolipids and lipids β-Galactosidase (GM1 Gangliosidosis)	: 41.3	15.0 - 285.5 nmol/hr/mg protein

Remarks : Lysosomal enzyme study was carried out from leucocytes using 4-MU specific substrate for α-1,4-glucosidase (with acarbose and without acarbose). β-galactosidase was used as a reference enzyme. Nirmay has shown reduced activity for α-1,4-glucosidase with low ratio of enzyme with acarbose and without acarbose with normal activity of β-galactosidase enzyme. **This suggests that Nirmay is highly likely to be affected with Pompe disease. Further confirmation by genetic study is advised.**

Molecular study by smMIP-NGS assay under Sanofi Disha program is in process.

This study was carried out as a part of FRIGE-Sanofi Disha program without any cost to patient.

This is an autosomal recessive disorder with 25% recurrent risk in every pregnancy. Prenatal diagnosis can be carried out at 12 or 16 weeks of gestation.

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Discussion

In adolescents and adults, progressive proximal myopathy and respiratory insufficiency may also be caused by late onset Pompe disease and is not widely recognized as such. Late onset Pompe disease typically does not have cardiomyopathy and has a more insidious clinical course than the infantile-type.

In late-onset Pompe disease, weakness of respiratory muscles is a significant cause of morbidity and mortality, and can sometimes be the first sign of disease. Patients may have recurrent LRTIs, unexplained type 2 respiratory failure, orthopnoea or sleep disordered breathing.Our patient demonstrated several classical features of late-onset Pompe disease, including:

- Progressive proximal muscle weakness
- Positive Gowers' sign
- Scapular winging
- Lumbar lordosis
- Exercise intolerance
- Orthopnoea
- Recurrent respiratory infections
- Severe hypercapnic respiratory failure

The diagnosis was particularly challenging because electrophysiological findings and muscle biopsy findings were relatively nonspecific. These same problems have been experienced in the past as described in the literature: Electromyography may show that the muscle is slightly myopic and muscle biopsy is sometimes not definitive.

The differential diagnosis that were considered in this patient included inflammatory myopathy, limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy, myasthenia gravis and metabolic myopathies. Autoimmune markers, FSHD genetic testing were all negative.

Finally, the diagnosis was confirmed by decreased activity of alpha-glucosidase enzyme.

The severe respiratory acidosis seen in this patient illustrates the severity of diaphragmatic and respiratory muscle involvement that may occur in late onset Pompe disease. Early recognition of respiratory muscle weakness is essential because delayed diagnosis may lead to respiratory decompensation.

Conclusion

This case highlights late-onset Pompe disease as an important yet often overlooked cause of progressive myopathy with respiratory muscle involvement in adolescents. Severe hypercapnic respiratory failure may be the presenting manifestation and can delay recognition when conventional investigations are inconclusive. Maintaining a high index of suspicion and performing early enzyme assay testing are essential for establishing diagnosis and improving long-term clinical outcomes.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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