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Non-specificity of symptoms in infantile-onset Pompe disease may delay the diagnosis and institution of treatment

Udara Dilrukshi Senarathne ,[1,2] Eresha Jasinge,[2] Sarojini Viknarajah Mohan,[3] Samantha Waidyanatha[3]

[1]Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka
[2]Department of Chemical Pathology, Lady Ridgeway Hospital for Children, Borella, Sri Lanka
[3]Paediatric Unit, Lady Ridgeway Hospital for Children, Borella, Western, Sri Lanka

Correspondence to
Dr Udara Dilrukshi Senarathne; udara.senarathne@sjp.ac.lk

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SUMMARY

Pompe disease is an autosomal-recessive inherited disorder of glycogen metabolism due to lysosomal acid alpha-glucosidase deficiency. The infantile-onset form is rapidly fatal if left untreated and presents with respiratory symptoms, a typical encounter during infancy. We discuss two infants presenting with respiratory symptoms since early infancy and found to have cardiomegaly, hypotonia, elevated muscle enzymes, leading to the diagnosis of Pompe disease with genetic confirmation. However, both infants expired before the enzyme replacement therapy due to complications of irreversible muscle damage despite supportive medical care. Presentation with respiratory symptoms common during childhood, absence of alarming symptoms such as hypoglycaemia, ketoacidosis or encephalopathy, and relative rarity of Pompe disease can contribute to lapses in the early diagnosis as observed in the index patients. Thus, these cases emphasise the importance of vigilant assessment of common paediatric presentations, which may be presenting symptoms of underlying sinister pathologies.

BACKGROUND

Pompe disease (PD; OMIM#232300), also known as glycogen storage disorder type-II, is a rare autosomal recessive genetic disorder of glycogen metabolism due to pathogenic variants of *GAA* gene coding for acid alpha-1,4-glucosidase (GAA; EC 3.2.1.20) enzyme. The overall incidence has been estimated at around 1 in 40 000; however, it is much higher in Taiwan and Missouri, perhaps due to founder effects.[1–6] The clinical picture of PD has a broad spectrum of phenotypes from infantile-onset PD (IoPD) to the late-onset adult form. IoPD, the most severe form in the spectrum, is characterised by cardiomegaly, hypotonia, respiratory distress, and feeding difficulties, all of which can be attributed to the underlying lysosomal glycogen accumulation causing lysosomal functional deficit leading to irreversible cellular damage. Despite its relative rarity, the presentation of IoPD can mimic common ailments such as respiratory infection or present with relatively nonspecific symptoms such as poor feeding, posing a diagnostic dilemma and subsequent delay in the early diagnosis.

Untreated IoPD is well known to be rapidly fatal, with death due to cardiorespiratory failure within the first year of life.[4 7] Therefore, prompt diagnosis and initiation of enzyme replacement therapy (ERT) are critical to reducing subsequent disability. Although the fatal outcome may not be prevented, the best possible clinical outcomes are attained by commencing ERT before significant muscle damage.[8 9] Therefore, it is imperative to have a high index of suspicion and rule out rare pathologies in common clinical presentations, as observed in these two infants presenting with respiratory symptoms since their early infancy.

CASE PRESENTATION

The first patient (infant A) was a 4-month-old female infant brought to medical attention with faltering growth and persistent cough since early infancy. The acute presentation was due to the worsening respiratory distress and apathy for 3 days without fever. She had a persistent nonproductive cough since the late neonatal period, which was not further investigated for it was attributed to episodes of uncomplicated respiratory infections. During the physical examination, she was not febrile, pale, or icteric, nor did she have any dysmorphic features. However, her mouth was visibly open at rest, possibly due to mild macroglossia. She was tachypneic (respiratory rate: 60/min, the normal range for 3–6 months: 30–55) and had subcostal and intercostal recessions with nasal flaring. Her heart rate was 136 bpm (the normal range for 3–6 months: 120–160) with an oxygen saturation >92% on nasal prong oxygen. There was a soft systolic murmur with reduced breath sounds on the left lower zone of the lungs on auscultation. Her abdomen was not tender, but she had mild hepatomegaly and reduced muscle tone in all four limbs. Her birth history was uncomplicated, for she was born at term by an elective caesarean section (indication: breech presentation) with a good Apgar score, average body weight (−1 SD), and length (+2 SD) at birth. There were no perinatal complications. However, her weight and length were observed to fall away from the mean, with both dropping to −2 SD of the respective growth charts by the age of 4 months. Her development assessment revealed difficulty in meeting gross motor milestones as she could not hold her head up while prone at the age of 4 months. Though she was a product of a second-degree consanguineous marriage (figure 1), a detailed inquiry into the family history of inherited or metabolic disorders did not reveal any affected relatives, and her elder sibling was apparently healthy.

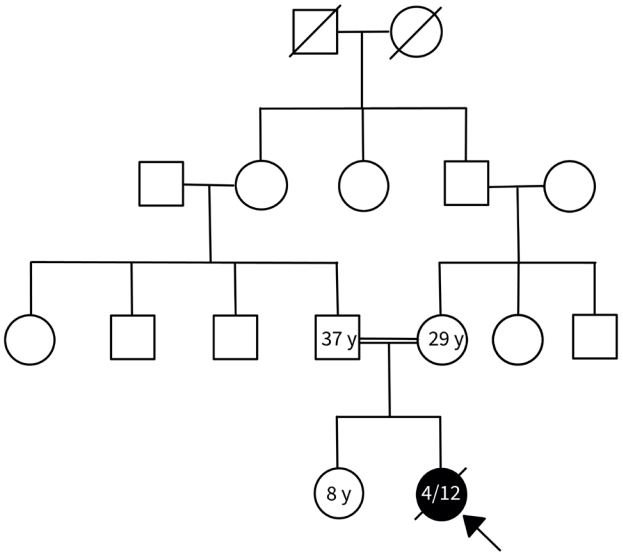

Figure 1 Genogram of infant A, demonstrating second-degree consanguinity (illustration by UDS).

The second patient (infant B) was a 7-month-old male infant brought to medical attention with a history of recurrent respiratory infections since early infancy and gross-motor delay. The infant initially presented with difficulty in breathing and poor feeding as early as 17-days-old, however, he was not further investigated as he recovered with supportive care. At the age of 1 month, he was referred to a cardiologist due to a systolic murmur and found to have mild biventricular hypertrophy (BVH), which was attributed to maternal gestational diabetes mellitus (GDM) at the time. However, the significant worsening of BVH during subsequent reviews led to a family screening but did not identify any cardiac abnormalities among immediate family members. His prenatal history revealed that his mother had GDM with reasonable glycaemic control on oral hypoglycaemics. He was born at term by an emergency caesarean section (indication: lack of progression of labour) with a good Apgar score, average body weight (+1 SD), and length (+2 SD) at birth. During the first 4 months, he required three hospital admissions due to episodes of breathing difficulty, all of which settled with supportive medical care and/or antibiotic therapy. Subsequently, at the age of 5 months, he was found to have moderate hepatomegaly; thus, directing the investigations towards inborn errors of metabolism leading to storage disorders. When he again presented at the age of 7 months, his growth had defaulted with weight and length at −1 SD of the respective growth charts. On physical examination, he had mild coarse facial features, and there were extra-axial Mongolian blue spots on his left forearm and both ankles. He was tachypneic (>40/min, the normal range for 6–9 months: 25–40), and his heart rate was >100 bpm (the normal range for 6–9 months: 100–150) on nasal prong oxygen. He had non-tender hepatomegaly of 4 cm and reduced muscle tone and power (grade 3/5–4/5; complete movement of limb against gravity but no resistance) in all four limbs. His developmental assessment revealed gross motor delay with head control and sitting achieved 1 month later than usual. He had a healthy sibling, and his family history did not reveal any consanguinity or familial disorders.

INVESTIGATIONS

The basic investigations of both infants were revealed to be within normal limits except for the elevated muscle enzymes. The metabolic screening, including plasma ammonia, lactate, arterial blood gas analysis, and urine ketones, failed to reveal any significant abnormality in both infants. However, at their acute presentations with respiratory distress, both infants demonstrated type II respiratory failure (infant A: respiratory acidosis with hypoxaemia, infant B: mixed respiratory and metabolic acidosis with hypoxaemia), indicating failure of the respiratory mechanism. A summary of the investigation findings is given in table 1.

Both infants had massive cardiomegaly on chest X-rays (figures 2 and 3). The echocardiography revealed left ventricular hypertrophy with a mild pericardial effusion in infant A (figure 2), while infant B had severe BVH (figure 3). In addition, infant B had tall QRS complexes on the ECG and non-specific hepatomegaly on the abdominal ultrasound scan. The histology of his liver biopsy was suggestive of metabolic hepatopathy with possible storage disorder (figure 4), and his skeletal survey to exclude dysostosis multiplex was normal.

Considering the key clinical features (respiratory distress, hypotonia, cardiomyopathy) and locally available laboratory investigations confirming muscle damage, PD was the most likely of the diagnostic possibilities (see differential diagnosis). As specialist confirmatory tests were not available in Sri Lanka, GAA level assessment was done at the Center of Medical Genetics at Sir Ganga Ram Hospital, India, and the genetic studies were done at Archimed Life Science, Austria (for infant A) and Supratech Micropath Laboratory and Research Institute, India (for infant B) using leukocytes of dried blood spots (DBS). Both infants had significantly low total and lysosomal GAA levels, confirming the diagnosis of PD (table 2). Given the clear-cut results, further confirmation by urinary glucose tetrasaccharide (UGlc4) analysis was unnecessary.[10] The molecular genetic studies based on next-generation sequencing revealed their genotypes as compound heterozygous variants of *GAA*, leading to a severe form of classic IoPD (table 3).

DIFFERENTIAL DIAGNOSIS

Based on the clinical presentation of index patients, the diagnostic workup considered two broad clinical entities: myopathy (due to presence of hypotonia and type II respiratory failure) and organomegaly (due to presence of cardiomegaly and hepatomegaly). For myopathy, glycogenoses (PD, Cori disease), fatty acid oxidation defects (FAOD), carnitine defects, and mitochondrial/oxidative phosphorylation (OXPHOS) defects were considered, whereas lysosomal storage disorders such as PD, mucopolysaccharidoses, and Niemann-Pick disease were considered for organomegaly. Each of the above differentials was tentatively excluded based on their key biochemical features. For example, Cori disease (glycogen storage disease, GSD-III) was excluded due to the absence of ketotic-hypoglycaemia, although the history and examination findings with increased markers of muscle damage were compatible. Similarly, OXPHOS defects were less likely due to the absence of prominent lactic acidosis despite the presence of clinical features. FAOD and carnitine disorders were also considered less likely due to the absence of hypoglycaemia but could not be confidently excluded without urine organic acid analysis and plasma carnitine profiling. Although the clinical presentation and cardiomegaly with pericardial effusion were compatible with infective myocarditis in infant A, the absence of fever and normal inflammatory markers

Table 1 Summary of the biochemical and haematological investigation findings

Parameter	Infant A (4 months)	Infant B (7 months)	Reference limits
Indicators of muscle damage			
Creatine kinase (U/L)	942	616	20–180
Lactate dehydrogenase (U/L)	780	540	180–430
Aspartate transaminase (U/L)	331	240	<35
Liver parameters			
Alanine transaminase (U/L)	112	107	<35
Alkaline phosphatase (U/L)	181	437	60–425
Gamma-glutamyltransferase (U/L)	13	125	5–32
Total bilirubin (µmol/L)	9	9	3–20
Total protein (g/L)	51	50	60–80
Albumin (g/L)	36	37	34–50
Renal parameters and electrolytes			
Creatinine (µmol/L)	50	31	35–40
Urea (mmol/L)	1.5	1.7	1.5–3.0
Sodium (mmol/L)	140	134	135–145
Potassium (mmol/L)	3.9	4.5	3.5–5.3
Total calcium (mmol/L)	2.46	–	2.2–2.7
Phosphate (mmol/L)	1.28	–	1.45–2.16
Haematological parameters			
Haemoglobin (g/L)	121	107	140–240
White cell count ($\times 10^9$/L)	5.8	8.4	3.1–21.6
Platelets ($\times 10^9$/L)	571	342	152–472
Metabolic parameters			
Total cholesterol (mmol/L)	5.76	5.25	1.71–5.91
Triglyceride (mmol/L)	1.6	1.5	0.62–3.12
Random glucose (mmol/L)	5.4	6.3	3.3–11.1
Ketone bodies*	Negative	Negative	Negative
Uric acid (µmol/L)	303	233	119–327
Ammonia (µmol/L)	67	74	40–80
Acid-base parameters (with respiratory support)			
pH	7.382	7.405	7.35–7.45
PaO_2 (mm Hg)	103	95	75–100
$PaCO_2$ (mm Hg)	30.2	36.1	35–45
Bicarbonate (mmol/L)	18.1	22.8	22–26
Base excess (mmol/L)	−5.4	−3.2	(−2) – (+2)
Lactate (mmol/L)	1.50	1.30	0.5–2.22
Acid-base parameters (at the acute presentation with respiratory distress)			
pH	7.325	7.039	7.35–7.45
PaO_2 (mm Hg)	80.5	22.6	75–100
$PaCO_2$ (mm Hg)	55.9	80.7	35–45
Bicarbonate (mmol/L)	17.4	22.0	22–26
Base excess (mmol/L)	−2.8	−8.9	(−2) – (+2)
Lactate (mmol/L)	1.80	7.30	0.5–2.22
Indicators of infection			
ESR (mm/first hour)	2	-	<10
C reactive protein (mg/L)	1.5	17.4	<5

All investigations were conducted on blood specimens (serum/plasma/whole blood).
*Investigations conducted on urine specimens
ESR, erythrocyte sedimentation rate; $PaCO_2$, Arterial partial pressure of carbon dioxide; PaO_2, Arterial partial pressure of oxygen.

made it less likely. Tables 4 and 5 summarise the essential clinical and biochemical findings of diseases with similar presentation to IoPD. Recently, a new search tool was launched by the Society for the Study of Inborn Errors of Metabolism to simplify the differential diagnosis in inborn errors of metabolism. This Inborn Errors of Metabolism Knowledgebase (IEMbase) is designed to match combinations of clinical symptoms and biochemical markers to produce a prioritised differential diagnosis with access to further information on disorders, which is freely available at IEMbase version 2.0.0.[11]

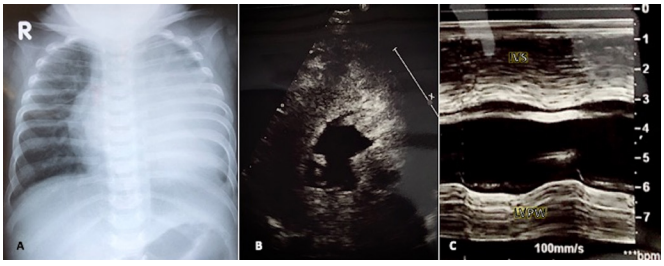

Figure 2 Radiological findings of infant A at the age of 4 months. (A) Massive cardiomegaly with obliteration of the left costophrenic angle due to pleural effusion on chest X-ray, (B)short axis view of the left ventricle demonstrating severe concentric left ventricular hypertrophy on echocardiogram, (C)M-mode echocardiogram showing gross left ventricular hypertrophy interventricular septum,left ventricular posterior wall).

OUTCOME AND FOLLOW-UP

Irreversible muscle damage had taken place in both infants by the time of confirming the diagnosis of IoPD with enzyme assays at 5 months in infant A and 8 months in infant B, by which time ERT was likely to be less effective.[9] Supportive medical care, including supplemental oxygen with positive airway pressure ventilation, clearing respiratory tract secretions, treating pulmonary infections, gavage feeding for adequate caloric intake, and fluid status management, were provided for both infants. However, both infants died due to cardiorespiratory failure before specific treatment could be started, as ERT was not available in Sri Lanka. Genetic screening of the siblings of index patients for the carrier state did not reveal any pathogenic *GAA* variants. The parents were given genetic counselling, and they were educated about the 25% possibility of conceiving another child with PD and the 50% possibility of the child being a carrier. Although prenatal diagnosis based on chorionic villus sampling could be undertaken in future pregnancies, it is not freely available in Sri Lanka and was not an affordable option for the families of index patients. Therefore, they were strongly advised to present for genetic testing in the newborn within the first 2 weeks, as a prompt diagnosis before irreversible muscle damage can significantly improve the clinical outcome of an affected infant, though the complete cure is not possible.

DISCUSSION

Glycogen is the principal storage form of carbohydrate in humans, found mainly in the liver and skeletal muscles. It is a large homopolymer of D-glucose linked by 1,4 glycosidic bonds, with 1,6 branch points at every 4–10 residues. The sequential action of cytoplasmic enzymes on the hepatic

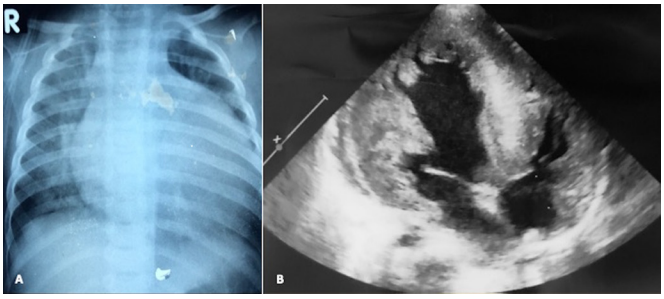

Figure 3 Radiological findings of infant B at the age of 7 months. (A) Massive cardiomegaly on chest X-ray, (B)short axis view of the heart demonstrating severe biventricular hypertrophy on echocardiogram.

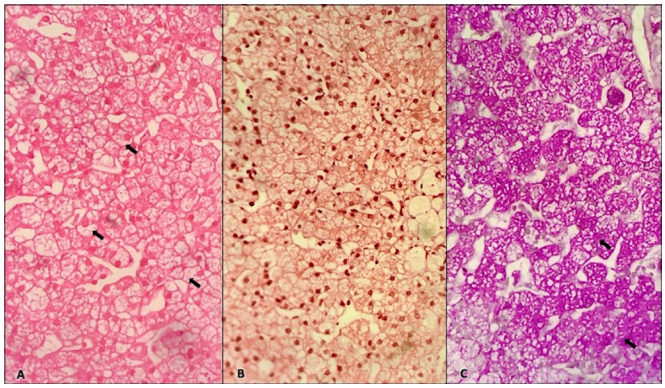

Figure 4 Histological findings of infant B at the age of 6 months. (A) H&E stain of the liver biopsy showing clusters of swollen hepatocytes with clear cytoplasm (arrow heads) and cytoplasmic granularity. There is mild chronic inflammation without bile stasis or steatosis. No typical Gaucher cells seen, (B)Masson trichrome staining of the liver biopsy showing a preserved liver architecture with no fibrosis, (C)Periodic Acid-Schiff (PAS) stain of the liver biopsy showing uniformly distended hepatocytes with the intracytoplasmic accumulation of glycogen (arrow heads) giving a positive PAS reaction (×200 magnification).

glycogen releases glucose into the circulation during fasting, whereas in the muscles, the same process would supply glucose for muscle contraction. Inherited deficiencies of enzymes involved in the glycogenolysis can lead to excessive glycogen accumulation, associated with episodic hypoglycaemia, muscle dysfunction or both.[12] Figure 5 summarises disorders of glycogen degradation alongside the respective enzyme defects. GAA, deficient in PD, releases glucose from glycogen by hydrolysing the 1,4-glycosidic bonds and, to a lesser extent, 1,6 bond. However, this is not to supply glucose but to degrade glycogen taken up by the lysosomes from the cytosol, presumably following the autophagy of damaged structural elements or organelles. Thus, deficiency of GAA causes glycogen accumulation, but not hypoglycaemia and the metabolic sequelae. Therefore, the lack of warning metabolic signs in PD may significantly contribute to the delay in diagnosis as observed in the index patients.

Lysosomes are membrane-bound organelles containing acid hydrolases, playing a central role in the catabolism of macromolecules such as glycogen, glycosaminoglycans, sphingolipids and proteins. Thus, functional deficits of these hydrolases lead to the accumulation of undigested substrates, a common hallmark of lysosomal storage disorders. The absence of GAA in PD leads to lysosomal accumulation of its substrate, glycogen, causing swelling and rupture of lysosomes with lysosomal dysfunction and subsequent cellular

Table 2 Acid alpha-1,4-glucosidase (GAA) activity in leukocytes of the dried blood spots

			Reference limits	
Parameter	Infant A	Infant B	Normal controls	Pompe disease
Total GAA (nmol/mL/hour)	4.24	4.46	10–60	<26
Lysosomal GAA (nmol/mL/hour)	<0.062	0.17	4.51–15	<3.7
Lysosomal: total GAA ratio	0.0	0.04	0.3–0.8	<0.22

Table 3 Summary of *GAA* variant analysis

		GAA variant details							
Patient		**Location**	**DNA nomenclature**	**Protein nomenclature**	**Type of variant**	**Predicted severity**	**CRIM status**	**Pathological impact**	**Zygosity**
Infant A	Allele 1	Exon 14	c.1935C>A*	p.Asp645Glu	Missense	Potentially less severe	+	Pathogenic	Compound heterozygous
	Allele 2	Exon 15	c.2104C>T*	p.Arg702Cys	Missense	Potentially less severe	+	Pathogenic	
Infant B	Allele 1	Exon 11	c.1560C>A†	p.Asn520Lys	Missense	Potentially less severe	+	Uncertain	Compound heterozygous
	Allele 2	Exon 18	c.2608C>T†	p.Arg870Ter	Nonsense	Very severe	–	Pathogenic	

Reference genome sequence: hg38 chr17.
Predicted severity is given according to the online Pompe disease GAA variant database.[29]
CRIM status: cross-reactive immunological material status is based on in silico predictions.[29]
*Reference sequences for GAA mRNA: *NM_000152.3
†NM_000152.4.
GAA, acid alpha-1,4-glucosidase.

injury, leading to multiorgan involvement.[13 14] Figure 6 illustrates the pathogenesis of PD at the cellular level. As the autophagy-lysosomal pathway plays a crucial role in the degradation of macromolecules, recycling the worn-out organelles, removing toxic substances and cellular adaptation to various stresses, dysfunctional autophagy leads to a cascade of events far beyond the progressive glycogen accumulation.[15] The organ systems involved include; heart (hypertrophic cardiomyopathy), skeletal muscle (hypotonia, reduced muscle power, motor delay, macroglossia and type II respiratory failure), smooth muscle (feeding difficulties), liver (hepatomegaly and hepatocellular damage), and central nervous system (physiological fatigue).[13 16] These symptoms classically manifest during infancy, presenting as IoPD, the most severe form in the PD spectrum. Generally, the disease severity is inversely correlated to the residual GAA activity, with the median age of clinical onset being 1.6 months for IoPD.[4] Muscles being the most prominently involved organ leading to hypotonia and weakness, PD is also classified as a metabolic myopathy.[17] Due to the general hypotonia and respiratory muscle weakness, infants with PD are more prone to pulmonary infections, a prominent clinical presentation observed in index patients.

The first description of a PD patient by PJ Pompe in 1932 states that it is a rapidly progressive disease with cardiomegaly, hepatomegaly, hypotonia and death due to cardiorespiratory failure within the first year of life, which describes the classical presentation of IoPD.[14 17] However, due to the nonspecific nature of the clinical symptoms that do not directly point towards PD unless considered together, the index of suspicion of PD during initial presentations could be low, especially in geographical areas with a lower incidence of PD. Cardiomegaly being the first alarming sign observed in both infants, it posed a significant diagnostic challenge due to heterogeneous aetiologies associated with hypertrophic cardiomyopathy, including; inborn errors of metabolism, malformation syndromes, neuromuscular disorders, and non-genetic conditions such as maternal GDM accounting for <10% of cases each, while sarcomeric-protein disease accounts for a majority (50%).[18] Due to the rarity of PD and a variety of disorders with a similar presentation, the initial diagnostic workup may overlook PD, as observed in the index patients. This may lead to a symptomatic-management approach during initial presentations, which is detrimental in PD as irreversible muscle damage occurs with time. In fact, the hypertrophic cardiomyopathy of infant B

Table 4 Comparison of clinical findings of diseases with similar presentation to IoPD

	Clinical presentations								
Disorder	**Cardiomegaly**	**Respiratory distress**	**Hypotonia**	**Myopathy and weakness**	**Macroglossia**	**Hepatomegaly**	**Feeding difficulties**	**Gross motor delay**	**Faltering growth**
Pompe disease (GSD-II)	++	++	++	++	+	+	+	++	+
Cori-Forbes disease (GSD-III)	++	–	+/-	+/-	–	++	+/-	–	+
Anderson disease (GSD-IV)	+	+	+	+	–	++	+	–	+
OXPHOS disorders	+	+/-	+/-	+	–	+	+	+/-	+
Fatty acid oxidation disorders	++	+/-	++	+	–	++	+	+	+
Carnitine disorders	+/-	+/-	+/-	+/-	–	+	+/-	+	+
Endocardial fibroelastosis	++	++	–	–	–	–	+	–	+
Myocarditis	+	+	+/-	–	–	–	++	–	–
Hypothyroidism	–	–	+	+	+	–	–	+	+
Congenital muscular dystrophy	–	+	++	++	–	–	+	++	+
Spinal muscular atrophy type I	–	++	++	++	–	–	++	++	+

General findings in each disorder during infancy are mentioned above. However, the above features may differ depending on the clinical scenario and the subcategory of diseases.[17 30–37]
GSD, glycogen storage disease; IoPD, infantile-onset Pompe disease; OXPHOS, oxidative phosphorylation.

Table 5 Key biochemical findings of pathologies with similar clinical presentations to IoPD

	Key biochemical findings								
Disorder	Elevated CK	Elevated LDH	Elevated transaminases	Hypoglycaemia	Lactic acidosis	Ketosis	Hyperuricaemia	Hypertriglyceridaemia	Abnormal carnitine panel
Pompe disease (GSD-II)	++	++	+	–	–	–	–	–	–
Cori-Forbes disease (GSD-III)	+/-	+	++	++	++	++	+/-	++	–
Anderson disease (GSD-IV)	+	+	++	+/-	+/-	+/-	–	–	–
OXPHOS disorders	+/-	+/-	+/-	+/-	++	+/-	+/-	–	–
Fatty acid oxidation disorders	++	++	++	++	+	–	+/-	–	++
Carnitine disorders	–	–	+	++	+	–	+/-	–	++
Endocardial fibroelastosis	++	–	–	–	+/-	+/-	–	–	–
Myocarditis	++	++	+/-	+/-	+/-	+/-	–	–	–
Hypothyroidism	+	+	+/-	–	–	–	–	–	–
Congenital muscular dystrophy	++	+	–	–	–	–	–	–	–
Spinal muscular atrophy type I	–	–	–	–	–	–	–	–	–

General findings in each disorder during infancy are mentioned above. However, the above findings may differ depending on the clinical scenario and the subcategory of diseases.[17 30–37]
CK, creatine kinase; GSD, glycogen storage disease; IoPD, infantile-onset Pompe disease; LDH, lactate dehydrogenase; OXPHOS, oxidative phosphorylation.

was initially attributed to the maternal GDM and expectantly managed until it was observed to increase significantly during serial echocardiography.

Due to the progressive nature of the disease, IoPD patients die within the first year of life without ERT.[4] ERT with recombinant human GAA (rhGAA) is the only treatment shown to increase the survival rate of patients, with cross-reactive immunologic material (CRIM) positive patients demonstrating a better immune tolerance.[19] CRIM status, determined based on the presence or absence of endogenous GAA, is a critical determinant of the successful response to ERT. The capacity to produce even a small amount of endogenous GAA (termed CRIM-positive) induces tolerance to the exogenous rhGAA protein in the patient, thus reducing the likelihood of an immunological reaction against GAA administered as ERT. Conversely, patients who do not produce any endogenous GAA (CRIM-negative) demonstrate poor immunological tolerance to the exogenous rhGAA due to antibody production against the protein, eventually reducing the efficacy of ERT.[8 20] Since the presence of at least one CRIM-positive variant results in CRIM-positivity, both index patients can be labelled as CRIM-positive, indicating that they were possible candidates for ERT.

Early initiation of treatment significantly improves the quality of life as the best motor outcome is achieved by introducing ERT before irreversible muscle damage caused by the buildup of lysosomal glycogen.[8 21 22] Thus, this necessitates early identification of the disease for the best possible clinical outcome of the patient. Initial steps in the diagnostic algorithm for IoPD include clinical vigilance in the early identification of probable PD by adding all the pieces in the puzzle together, including cardiac, respiratory, neuromuscular symptoms and investigation finding of elevated markers of muscle damage, especially CK, a sensitive though nonspecific indicator for PD.[17] The diagnosis is confirmed by measuring GAA activity, which is <1% of normal subjects in IoPD. The genetic analysis is complementary to the diagnosis and particularly useful for identifying the carriers during the family screening. The index patients were found to have compound heterozygous variants leading to IoPD, and the missense variant, c.1560C>A observed in infant B, has only been reported once in the literature as a novel mutation identified in late-onset PD.[23] This finding may add information to the current knowledge base on genotype–phenotype correlation.

The most effective way for early detection of PD would be to assess GAA level in DBS incorporated in the newborn screening, introduced in Taiwan and some states in the USA with a higher incidence of PD. However, this is a controversial area, with disadvantages such as the high cost of treatment and dilemma of whether and when to treat individuals with mild variants of uncertain pathogenicity.[24] To date, Sri Lankan newborn screening programme only tests for congenital hypothyroidism universally, while glucose-6-phosphate dehydrogenase deficiency is tested on-demand, and inclusion of PD in Sri Lankan newborn screening is controversial for the same reasons discussed above by van El *et al*.[24] In a large-scale pilot study on newborn screening for PD in Taiwan, Chien *et al* diagnosed IoPD in four newborns before the age of 1 month, compared with 3–6 months taken for the diagnosis in the control group.[25] At the time of diagnosis, none of the babies had any clinical symptoms but were found to have increased CK levels (mean=687 U/L) and vacuoles in the muscle biopsy, despite having normal muscle strength.[25] This finding highlights the possibility of using CK as a cost-effective surrogate marker for muscle damage in PD, especially in resource-poor settings. Thus, CK could be used for early selective screening of infants presenting with persistent respiratory symptoms and hypotonia for PD, which may provide a solution to the delayed diagnosis.

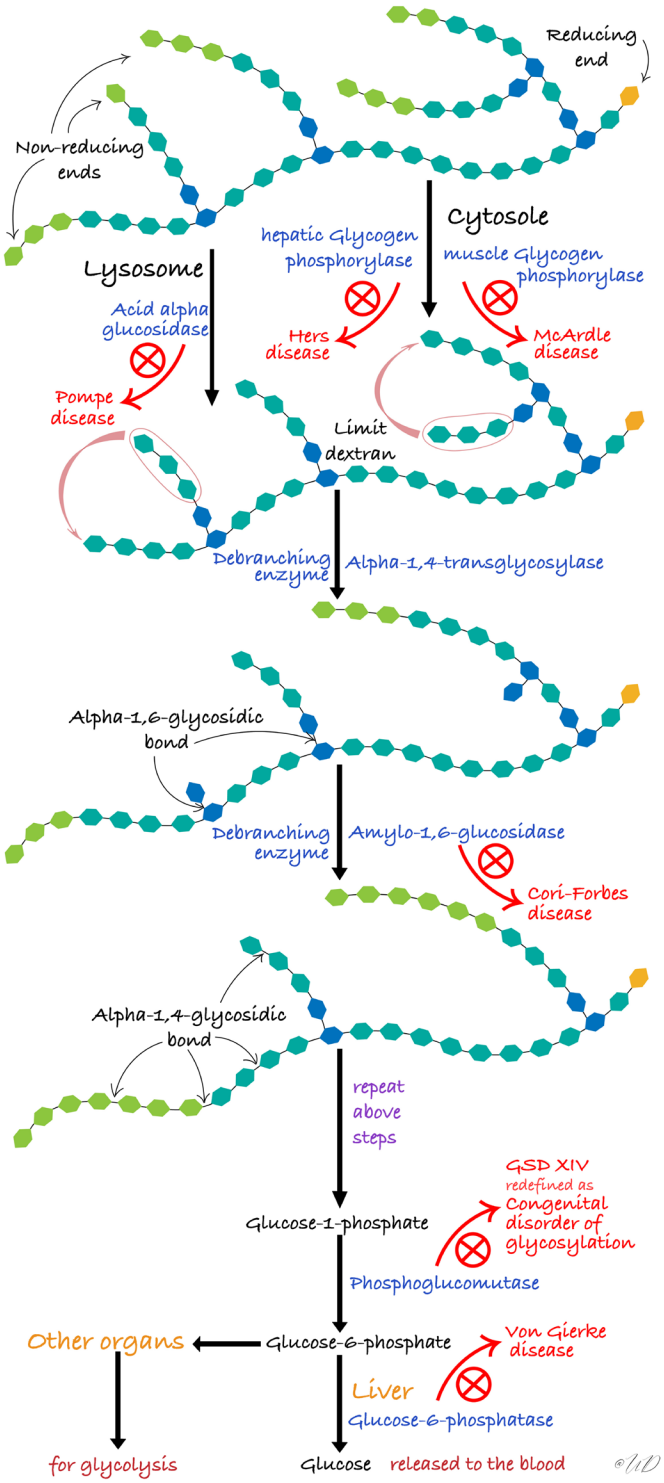

Figure 5 Glycogenolysis pathway with the respective disorders of enzyme deficiency (illustration by UDS). GSD, glycogen storage disease.

PD being a multisystem metabolic disorder, its clinical management requires a multidisciplinary team including a cardiologist, respiratory physician, neurologist, intensivist, metabolic specialist, physiotherapist, occupational and speech therapists, dietician, genetic and psychological counsellors led by an experienced paediatrician.[17] The care should be tailored according to the stage and extent of the disease, with the mainstay of treatment being ERT, which was approved by the FDA in 2006 and includes biweekly administration of rhGAA. However, as

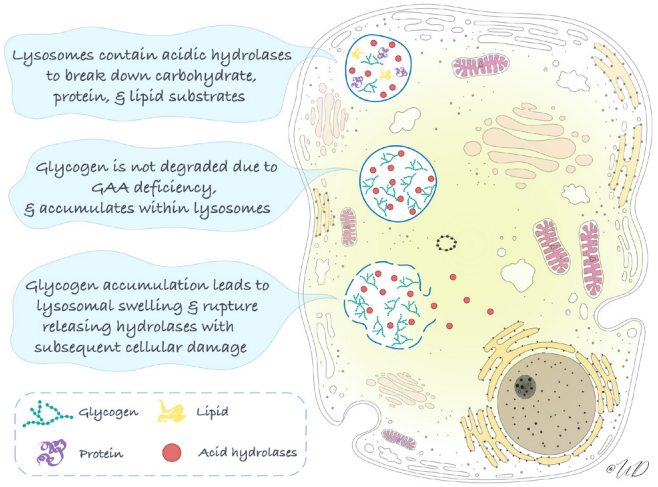

Figure 6 Pathogenesis of Pompe disease due to lysosomal glycogen accumulation (illustration by UDS). GAA, acid alpha-1,4-glucosidase.

rhGAA does not cross the blood–brain barrier, ERT cannot alleviate any neuropathology, thus warranting new treatment approaches capable of simultaneously treating muscular and neuropathology, such as gene therapy, which is still in the experimental state.[26] ERT can significantly improve the overall quality of patients' and indirectly their family members' lives, as evident by the conclusion of Chien *et al* in their study on the long-term prognosis of IoPD treated with rhGAA, which showed that patients achieved near-normal development with residual myopathy.[21] However, the high cost of ERT can be prohibitive to an

Patient's perspective

Given below is the English translation of the narrations in Sinhala by the parents of infant B.

'We understand that this is a genetic disease, so there is no complete cure for it. But it was heart-wrenching to see our beloved child suffer. We wonder if this disease was diagnosed earlier, before it became worse, would he have had less pain and suffering. We understand that there is a chance of our next child also being affected by this disease. Although a complete cure is not possible, it is a relief to know that a treatment is available to reduce the disability. We have only one child and wish to have a few more children. Therefore, we shall bring our next baby during the first week itself for the genetic testing.'

Learning points

- Common paediatric presentations should undergo vigilant assessment not to miss any underlying pathologies, especially when recurrent.
- Delayed diagnosis is a major determinant of the overall outcome in infantile-onset Pompe disease.
- Creatine kinase can be used as a cost-effective screening tool for Pompe disease in infants presenting with persistent respiratory symptoms associated with hypotonia.
- Pompe disease should be primarily considered in infants presenting with respiratory symptoms, hypotonia, cardiomyopathy and elevated creatine kinase in the absence of hypoglycaemia.

ordinary family, especially in a developing country, and its feasibility would depend on the proactive involvement of the government. Considering the progressive and lethal nature of IoPD, a significant responsibility falls on the clinical team in providing holistic care for the patient and the family, which essentially includes palliative care as IoPD patients can only coexist with treatment that prolongs life.[27] Furthermore, to empower the family in making suitable medical decisions, the genetic counselling of the family should focus on improving their genetic health literacy, understanding of the future risk and available therapy.[28]

Presentation with respiratory symptoms common during infancy, absence of alarming symptoms such as hypoglycaemia, ketoacidosis or encephalopathy, and relative rarity of PD can contribute to lapses in the early diagnosis of IoPD as observed in the index patients. Thus, these cases emphasise the importance of vigilant assessment of common paediatric presentations, which may be masking serious underlying pathologies.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD

Udara Dilrukshi Senarathne http://orcid.org/0000-0003-2329-6871

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