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Lactic acidosis, rhabdomyolysis, and hyperammonemia: Atypical presentation in a new patient with PDE-ALDH7A1 defect

Marina Bottino [a], Monica Boyer [b], Maija R. Steenari [c,d], Rebekah Barrick [b], Jose E. Abdenur [b,d,*]

[a] Fundación Para la Lucha Contra las Enfermedades Neurológicas de la Infancia (FLENI), Servicio de Neuropediatría, Buenos Aires, Argentina
[b] Division of Metabolic Disorders, Children's Hospital of Orange County (CHOC), Orange, CA, United States of America
[c] Division of Pediatric Neurology, Children's Hospital of Orange County (CHOC), Orange, CA, United States of America
[d] University of California, Irvine, Department of Pediatrics, United States of America

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ABSTRACT

Pyridoxine-Dependent Epilepsy (PDE) is an autosomal recessive disorder caused by biallelic variants in ALDH7A1. The most common presentation is intractable seizures in the neonatal/early infantile period, which respond to pyridoxine. Other manifestations include perinatal asphyxia, hypoglycemia, and neuroimaging abnormalities. Despite early treatment, patients often have neurodevelopmental abnormalities. Treatment guidelines recommend triple therapy with pyridoxine, dietary lysine restriction, and arginine supplementation.

We report an individual presenting with laboratory abnormalities suggestive of mitochondrial disease. Born full-term, via NSVD, with normal Apgar scores and cord gases. At 30 min, grunting developed, and at 4 h of life, jerky movements with eye deviation were noted. Laboratory results revealed acidosis (pH 7.15) and increased lactate (11.4 mMol/L, rr <2.1). The patient was started on IV fluids, given 1 mEq/kg of sodium bicarbonate, and transferred for higher-level care. Upon arrival, the evaluation was notable for hypotonia, non-rhythmic jerking movements, rapid eye blinking, and a critically low pH (6.92), high lactate (15.3 mMol/L), hyperammonemia (153 μMol/L, rr < 75), and a creatine kinase level of 15,742 U/L (rr 35–230). A single dose of phenobarbital was given, and the baby was intubated and ventilated. Video electroencephalogram (vEEG) showed a discontinuous background with abnormal, sharply contoured bursts alternating with suppression, with no clinical correlation. The patient was treated with continuous sodium bicarbonate drip and IV fluids, restricting glucose. Abnormal movements, lactic acidosis, and hyperammonemia resolved within 24 h. An electroencephalogram (EEG) at 5 days of life (DOL) showed a mildly discontinuous background with no epileptic activity, and MRI showed a thin corpus callosum, cysts, and cerebellar hypoplasia. Creatine kinase peaked at 30,995 U/L and normalized on DOL 8. Organic acids revealed significant increases in lactate, 2-OH-butyrate, pyruvate, 3-OH-butyrate, 2-OH-isovalerate, and a mild increase in Krebs-cycle intermediates.

Rapid whole genome sequence (rWGS) was available on DOL 9, disclosing two variants in *ALDH7A1*: c.1559C > T p.Ser520Phe, previously reported, and c.1540 A > G p.Lys514Glu, considered a VUS. Treatment with pyridoxine started at 30 mg/kg/day. Pre-treatment biomarkers were consistent with the diagnosis of PDE-ALDH7A1: urine Pipecolate 117.8 mMol/mol, RR ≤10, 6-oxo-Pipecolate 8.4 mMol/mol, RR ≤2.0 and plasma alpha-aminoadipic semialdehyde (AASA) 5.2 uMol/L, RR <0.4. Treatment with arginine was added on DOL 10 (200 mg/kg/day) and a lysine-restricted diet on DOL 12, after TPN was discontinued. Clinical exam improved, no seizures were observed, and EEG normalized. PDE biomarkers decreased, and the patient was discharged home on DOL 25.

Elevated lactic acid has been reported in up to 70.3 % of PDE-ALDH7A1 patients with neonatal-onset; however, there is limited information about its severity, etiology, or pathophysiologic mechanism. We, therefore, conducted a review of published cases of neonatal-onset PDE-ALDH7A1 whose actual lactic acid values were reported. A total of 12 patients were analyzed and compared to this case. In most instances, a trigger (such as pulmonary hemorrhage, postnatal hypoxia, or status epilepticus) could be identified as the cause of elevated lactic acid; nevertheless, in many individuals, lactic acidosis remained unexplained.

* Corresponding author at: Division of Metabolic Disorders, Children's Hospital of Orange County (CHOC), Orange, CA, United States of America.
E-mail address: jabdenur@choc.org (J.E. Abdenur).

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This case expands on the biochemical presentation of PDE-ALDH7A1 and highlights the importance of identifying increased lactic acid as another of its manifestations. We also provide evidence to support the reclassification of the c.1540 A > G (p.Lys514Glu) variant as pathogenic.

1. Introduction

Pyridoxine-dependent epilepsy (*PDE-ALDH7A1; OMIM 266100*) is an autosomal recessive disorder due to biallelic pathogenic variants in *ALDH7A1* that cause deficiency of alpha-aminoadipic semialdehyde (α-AASA) dehydrogenase, an enzyme involved in lysine catabolism. The estimated incidence varies between 1:65,000 to 250,000 live births, but the disease is likely underdiagnosed [1,2]. The most typical presentation includes intractable seizures in the neonatal or early infantile period, with a therapeutic response to pharmacological doses of pyridoxine and resistance to conventional antiepileptic drugs (AEDs). Other neurological and systemic manifestations include perinatal asphyxia, hypoglycemia, and neuroimaging abnormalities [3]. Atypical PDE-ALDH7A1 presents with later-onset seizures beginning after infancy or even during adolescence [4]. While receiving daily pyridoxine treatment, most children with PDE remain seizure-free, but they often have neurodevelopmental, cognitive, and behavioral manifestations, even with early treatment. Improved neurodevelopmental outcomes have been reported in patients with PDE-ALDH7A1 treated with a combined triple therapy of pyridoxine, lysine-restricted diet, and arginine supplementation, leading to new guidelines published in 2021 [5].

Seizures dominate the initial clinical presentation of PDE-ALDH7A1, and while there are usually no electrolyte imbalances, hypoglycemia has been reported in 37.5 % and increased lactic acid in 70.3 % of patients at presentation [6]. However, in most reported cases, there is no detailed information on the lactic acid level, trigger of the lactic acidosis, or potential mechanisms.

We report a new patient with PDE-ALDH7A1 without a history of perinatal complications, who presented in the newborn period with severe lactic acidosis, rhabdomyolysis, and hyperammonemia, leading to a presumptive diagnosis of a mitochondrial disease. PDE-ALDH7A1 was diagnosed at 9 DOL through rWGS, and the patient was treated with pyridoxine, arginine supplementation, and a lysine-restricted diet, with good clinical and biochemical response. To better understand the mechanism of the severe biochemical abnormalities in our patient, we conducted a thorough review of the literature, focusing on patients with PDE-ALDH7A1 who had a neonatal onset and similarly abnormal documented values. Their genotype, phenotype, and laboratory values were compared. We also explore the potential metabolic mechanisms implicated in these laboratory abnormalities.

2. Materials and methods

We reviewed the medical records of a new patient with PDE-ALDH7A1 from birth until discharge from the NICU at DOL 30. Metabolic laboratory tests were performed at the Metabolic Laboratory at CHOC Children's. Plasma amino acids were measured with a Biochrom aminoacid analyzer, and urine organic acids with Agilent 6890 GC coupled with 5973 MS system, following standard laboratory procedures. Pipecolic acid (PIP) and 6-oxo-pipecolate (6-OXO-PIP) in urine were measured with a Xevo TQD LC/MS-MS system (Waters ®) using a previously published method, with minor modifications [7]. Alpha-aminoadipic semialdehyde (AASA) and piperideine 6-carboxylate (P6C) in blood were measured at the Biochemical Genetics Laboratory at Seattle Children's Hospital. rWGS was performed at the Clinical Genome Center, Rady Children's Institute, San Diego, CA. **Analysis of the mitochondrial genome was included in the rWGS.**

3. Data sources and search strategy

To evaluate the frequency and magnitude of the biochemical findings, we initially analyzed the information published by Fang et al. in their systematic review [6]. The authors identified 56 eligible articles involving 169 genetically confirmed patients with neonatal-onset PDE, reported from January 2006 to August 2023. The main search terms were "pyridoxine-dependent epilepsy" AND "neonatal." From the review of these 56 articles, we identified 31 patients with elevated lactic acid, 26 of whom were also detected by Fang et al., as shown in their Suppl. Table S1. To account for any new publications, we conducted a PubMed search with the same terms for the period January 2023 to April 30, 2025, and identified 38 new publications. In addition, we performed a PubMed search without time limit restrictions, combining the terms "pyridoxine-dependent epilepsy" with the following: "lactic acidosis," "elevated lactate," "elevated ammonia," "ammonium," "hyperammonemia," "elevated CK," "hyperCKemia," "hyper-CK," "elevated serum CK," and "high CK levels," identifying 7 publications. After eliminating duplicate records, we identified 40 patients in whom the report mentioned "elevated lactic acid." Only 12 out of the 40 patients had their actual lactic acid value reported. To compare with our patient, we conducted an in-depth analysis of these 12 patients. A complete description of the Search strategy is shown in **Supplemental Fig. 1.** Data analyzed included genotype, clinical presentation, biochemical abnormalities, including lactic acid, creatine kinase, ammonia, plasma amino acids, urine organic acids, and PDE biomarkers, when available.

4. Results

4.1. Case report

A full-term female infant was born by spontaneous vaginal delivery to parents of Mexican descent. **Maternal health was monitored during the pregnancy, and there were no reported complication**s. The patient was appropriate for gestational age, with birth weight 2.570 kg [17.9 percentile], length 48.3 cm [51.9 percentile], and head circumference 32 cm [19.5 percentile]. Apgar scores at 5 and 10 min were 8 and 9, there were no complications, and cord blood gases were normal (Table 1). At 30 min, she appeared agitated, with grunting respiration while maintaining normal O2 saturation. She was admitted to the Neonatal Intensive Care Unit (NICU) and did not meet criteria for therapeutic hypothermia. **The patient had a sepsis work-up with negative results. Specifically, blood, urine and CSF cultures were negative.**

At 4 h of life (HOL), a physical exam performed by the neonatologist, described frequent jerky movements, restlessness, and short episodes of eye deviation and rigidity lasting 3–10 s, without changes in vital signs. Laboratory results revealed acidosis, with a pH of 7.15 (7.32–7.45); HCO3 13.5 mMol/L (22.0–26.0), lactate of 11.4 mMol/L (<2.1), and normal blood glucose. D10% IV fluids with sodium-acetate 77 mEq/L were started, she received a dose of sodium bicarbonate (1 mEq/kg), and at 12 h of life, she was transferred to CHOC Children's NICU for higher level of care. On arrival, the baby was noted to be irritable and agitated, with non-rhythmic jerking movements of the four extremities, and rapid eye blinking. The baby was also noted to have axial hypotonia, prominent distal flexion in hands and feet, cortical thumbing and absent gag reflex. She had adequate oxygen saturation, blood pressure, pulses, perfusion, and a normal cardiovascular examination, including an echocardiogram. Due to clinical concern for ongoing

seizure activity, the patient was given a phenobarbital load of 20 mg/kg without clinical response and was intubated and ventilated. Subsequent vEEG showed a discontinuous background with abnormal, sharply contoured bursts alternating with suppressed interburst intervals, without clinical correlation (Fig. 1a**). Laboratory studies unexpectedly revealed a critically low pH of 6.92, very high lactate at 15.3, hyperammonemia of 153 uMol/L (< 75), and significantly elevated CK of 15,742 IU/L (⟨230) which peaked at 30,995 IU/L, concerning for an underlying inborn error of metabolism**. The patient was treated with sodium bicarbonate drip and intravenous fluids were adjusted to restrict glucose (dextrose D5%). Lactic acidosis and hyperammonemia were corrected within 24 h, with full resolution of the abnormal movements. Total parenteral nutrition (TPN) started on DOL 2. No further antiepileptic treatment was given and an EEG at DOL 5 showed a mildly discontinuous background with no epileptic activity (Fig. 1b). Brain magnetic resonance (MRI) revealed a diffusely thin corpus callosum, multiple subependymal cysts along the lateral ventricles anteriorly and at the left caudothalamic groove, mild inferior cerebellar hypoplasia, and asymmetric mild enlargement of the posterior body and temporal horn of the left lateral ventricle with white matter volume loss. No lipid or lactate peak was seen on MR-spectroscopy. (Fig. 2). Ventilatory support was discontinued on DOL 7 and TPN on DOL 11.

Due to clinical and laboratory abnormalities, a mitochondrial disease was suspected; specific biochemical testing was initiated, and a sample for rapid WGS was obtained on DOL 3. Urine organic acids showed a massive increase in lactate, a large increase in 2-OH-butyrate, pyruvate, 3-OH butyrate, and 2-OH isovalerate, consistent with a defect in energy metabolism. A mild increase in succinate, fumarate, malate, 2-ketoglutarate, aconitate, and citrate, in a higher amount than usually seen in normal newborns, was noted, suggesting some degree of Krebs cycle dysfunction. Moderate increases in 4-OH phenylacetate, 4-OH phenylpyruvate, with a significant increase in 4-OH phenyllactate, were consistent with liver disease as well as lactic acidosis (Fig. 3). Plasma aminoacids showed a mild increase in glutamine of 922 uMol/L (376–709), tyrosine 168 uMol/L (55–147), and histidine 151 uMol/L (30–138) with normal levels of alanine, threonine, glycine, phenylalanine, and arginine and a borderline low serine 69 uMol/L (99–395). Carnitine levels and acylcarnitine profile were normal, AST and ALT were borderline elevated, and total bilirubin increased to a maximum level of 13.5, without requiring phototherapy.

At DOL 9, the results of rWGS revealed two heterozygous missense variants in the ALDH7A1 gene. The maternally inherited, c.1559C > T (p.Ser520Phe), has been previously reported as a pathogenic homozygous change in a patient with PDE-ALDH7A1 [8]. The paternally inherited, c.1540 A > G (p.Lys514Glu), has not been previously reported or functionally characterized in the literature to our knowledge, and was classified by the laboratory as a variant of uncertain significance. Both variants affect highly conserved amino acids and are predicted by multiple in-silico tools to have a deleterious effect on protein function. Neither variant is present in gnomAD. **No variants in other nuclear- or mitochondrial-encoded genes were reported by the genetic testing laboratory.**

After obtaining samples for biochemical confirmatory testing, treatment with pyridoxine (30 mg/kg/day) was initiated. Pre-treatment biomarkers were consistent with PDE-ALDH7A1, with elevated urine PIP of 117.8 mMol/mol (<10), 6-OXO-PIP of 8 mMol/mol (<2.0), and plasma AASA of 5.2 uMol/L (<0.4). Treatment with arginine was added on DOL 10 (200 mg/kg/day) and a lysine-restricted diet on DOL 12, after TPN was discontinued. On triple therapy, all biomarkers progressively decreased, with PIP reaching 60.4 mMol/mol, 6-OXO-PIP 2.1 mMol/mol, and AASA 0.8 uMol/L at DOL 23. (Table 2), **no clinical seizures or abnormal EEG were appreciated after initiation of treatment.**

Dietary recommendations were made based on the updated nutrition guidelines, which advocate for lysine-reduction therapies to improve long-term neurologic outcomes, with caution against over-restriction, which can result in malnutrition and poor growth [9]. Expressed human breast milk was initially utilized as an intact protein source and later transitioned to Similac® Advance® infant formula (Abbott Nutrition) to meet an initial target lysine intake of 100 mg/kg/day. Additional lysine-free, low tryptophan powdered infant formula (GA-1 Anamix® Early Years, Nutricia, USA) and a protein-free powder (Duocal®, Nutricia, USA) were incorporated to meet total protein and energy requirements. Plasma amino acids were monitored frequently with special attention to lysine, tryptophan, and arginine levels. Her growth parameters were closely monitored, and serial adjustments in energy and lysine intake were made as needed, targeting lysine values within the lower quartile of the normal reference range for her age and age-expected/catch-up growth.

On DOL 25, she was discharged home with a weight of 2.780 kg (5.8 percentile), a length of 49.00 cm (17.4 percentile), and a head circumference of 33.00 cm (9.5 percentile). Her metabolic recipe at discharge was updated to provide lysine of 116 mg/kg/day to address serially low lysine levels. At the time of writing this manuscript, the patient is 4 months old, and she remains stable, seizure-free, with good weight gain. Diet continues to be adjusted frequently.

Table 1
Significant laboratory abnormalities during initial presentation.

DOL	0					1		2	3	4	5	8	
Lab	Cord blood Arterial	Cord blood Venous	VBG	ABG									ABG normal range
PH	7.30 (7.12–7.35)	7.34 (7.23–7.45)	**7.15 (7.32–7.45)**	**7.18**	**6.92**	**7.31**	**7.37**	**7.49**	7.42	**7.54**	7.4	7.4	7.35–7.45
PCO2	52 (40–74)	42 (28–58)	39 (35–50)	34	**52**	**21**	**61**	**46**	**52**	37	39	38	35–45
HCO3	25 (12–26)	23 (12–26)	13 (22–26)	**13**	**10**	**10**	**35**	**34**	**33**	**31**	25	23	20–28
Lactic acid	–	–	**11.4 (<2)**	**10.6**	**15.27**	**9.12**	2.1	1.64	1.75	1.65	1.2	1	0.7–2.1
Lab	**Blood**												
NH3 (uMol/L)	–	–	**91**	–	**153**	46	48	29	33	–	–	–	20–75
AST (U/L)	–	–	–	–	**204**	–	–	–	–	**107**	**129**	–	24–72
ALT (U/L)	–	–	–	–	32	–	–	–	–	**69**	**68**	–	8–32
CK (U/L)	–	–	–	–	**15,742**	**30,995**	–	**21,644**	**4807**	**1285**	**949**	**121**	35–230

Normal range is denoted in parentheses unless specified.
Bold denotes abnormal result.

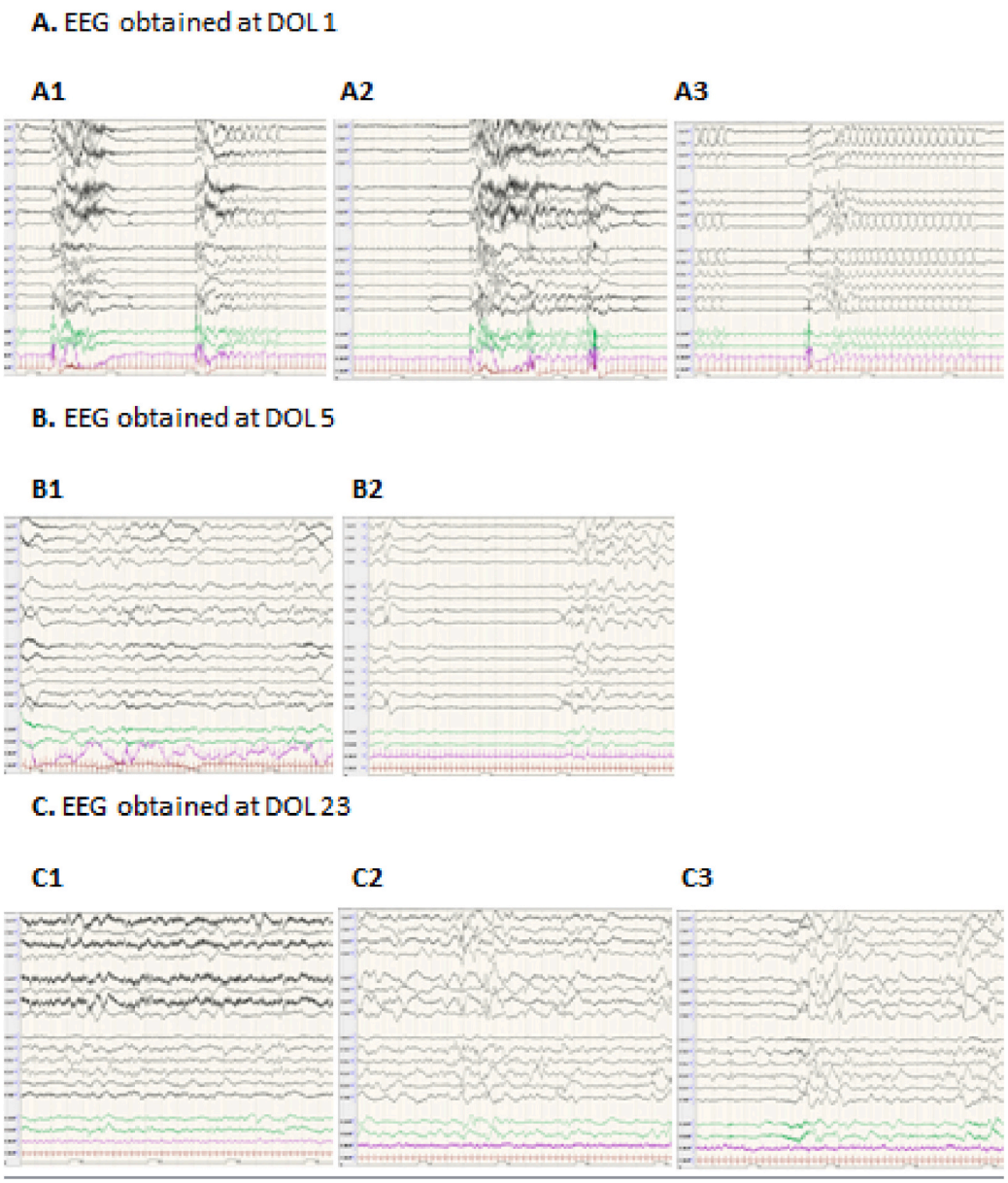

Fig. 1. EEG recordings and response to treatment. All recordings were performed using a neonatal double-distance montage, displayed at 7 μV sensitivity with 16 s per page.
A. EEG on DOL 1:
A1. Discontinuous background activity during wakefulness.
A2–A3. Discontinuous EEG pattern during sedation, with features resembling burst suppression. In between suppression, rhythmic sharp wave discharges consistent with brief, potentially ictal rhythmic discharges were seen.
B. EEG on DOL 5:
B1. Continuous background activity during wakefulness.
B2. Discontinuous pattern during quiet sleep, with interburst intervals ranging from 2 to 8 s.
C. EEG on DOL 23 (15 days after initiation of pyridoxine therapy):
C1–C3. Normal background activity observed across all vigilance states, indicating a favorable response to treatment.

4.2. Comparative review

The clinical, biochemical, molecular, and neuroimaging findings of our patient were compared with those of 12 other cases of PDE-ALDH7A1 presenting in the neonatal period, for whom elevated lactic acid values were reported (Table 3) [3,8,10–17].

The age of onset ranged from birth (<24 HOL) to 6 weeks. In all cases, the clinical presentation was severe and included respiratory distress, seizures, hypotonia, and irritability, with 1 case with a fatal outcome at 15 HOL [10]. **Our patient also had a neonatal presentation with irritability and jerking movements concerning for seizures; however, the movement abnormalities corrected with electrolyte management, without pyridoxin.** Of note, Apgar scores and blood gases were normal, with no evidence of perinatal insult that could justify the severe biochemical abnormalities. The above appears to correlate with most of the other patients, as only two out of seven had a low Apgar score at 1 min with good recovery at 5 min. Lactic acidosis was an early neonatal manifestation in 10 out of 12 cases. In the patient reported by Jaber et al. (2024), lactic acidosis was first documented at one month; however, seizures were present at DOL 2, and respiratory

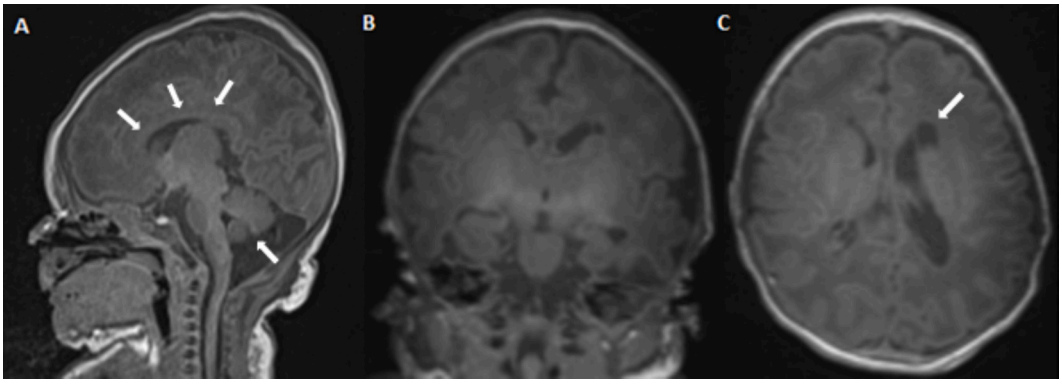

Fig. 2. Brain MRI (3 T) Findings at 6 DOL. Sagittal T1-weighted image (A) shows a diffusely thin corpus callosum and inferior vermian hypoplasia (arrows). Coronal (B) and axial (C) T1-weighted images demonstrate multiple subependymal cysts adjacent to the left frontal horn (arrows). Enlargement of the left lateral ventricle is also evident.

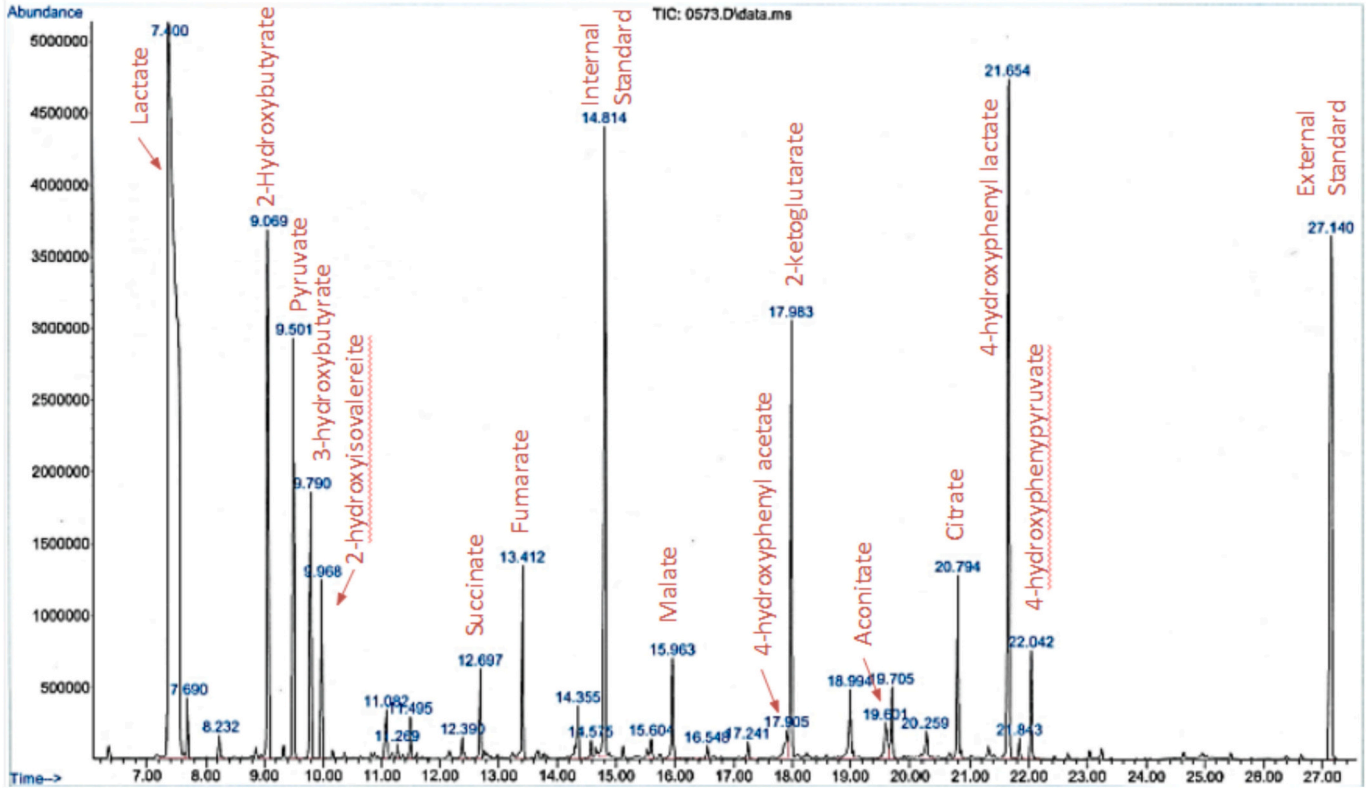

Fig. 3. Urine organic acid profile obtained 1 DOL: Urinary organic acid analysis revealed increased excretion of lactate, pyruvate, 2-hydroxybutyrate, 3-hydroxybutyrate, 2-hydroxyisovalerate, succinate, fumarate, malate, α-ketoglutarate, and citrate. Elevated levels of 4-hydroxyphenyllactate and 4-hydroxyphenylpyruvate, considered markers of liver immaturity or dysfunction, were also observed. This pattern is suggestive of mitochondrial dysfunction and impaired energy metabolism, findings frequently associated with neonatal metabolic crises such as those seen in PDE-ALDH7A1.

distress and hypotonia at DOL 12 [17]. In the remaining patient, lactic acid was documented at DOL 60 when he presented with vomiting, hypoglycemia, and hyperammonemia, although he had seizures and respiratory failure at DOL 5 [14]. Plasma lactate levels ranged from 3.9 to 18 mmol/L, with a median of 9.9. In our patient, lactic acid levels reached 15.27 mmol/L, higher than the median and comparable to the most severe cases. Ammonia levels were mildly elevated reaching 153 μmol/L, lower than the value of 315 μmol/L reported by Chauhan et al. (2024), however, CK was markedly increased, with a maximum value of 30,995 U/L. Only one other patient was reported with high CK, at 2845 U/L [13]. Amino acid profiles, reported in 3 patients, showed minimal deviations from the normal range with no clear pattern. Similar to our patient, Kim et al. reported a mild elevation in glutamine; however, their patient had normal ammonia levels [15].

Urinary organic acids were consistent with a defect in energy production (Fig. 3), with a profile that appears to be more severe than that reported in the other two patients (Table 3). Notably, vanillactic acid—a known marker of aromatic L-amino acid decarboxylase (AADC) deficiency, a PLP-dependent enzyme, was not detected in any of the 3 patients. Disease-specific biomarkers in our patient were significantly elevated, consistent with the diagnosis of PDE-ALDH7A1, and were abnormal in all 8/12 patients where it was reported. However, a direct comparison of the values is not possible due to the differences in matrices (blood, urine) and biomarkers reported. Brain MRI findings

Table 2
Longitudinal treatment and biochemical monitoring of PDE biomarkers.

Age (Days)	9	10	11	12	16	17	18	19	23
Treatment									
Pyridoxine (mg/kg/day)	30	30	30	30	30	30	30	30	30
Arginine supplementation (mg/kg/day)	–	200	200	200	200	200	200	200	200
Lysine restricted diet (Lys intake mg/kg/day)	–	–	–	100	100	100	100	100	100
Lab Results (reference range)									
Pipecolic acid in urine (≤10 mMol/mol)	**117.8**	**–**	**100.4**	**53.7**	**64.3**	**–**	**81.2**	**60.6**	**60.4**
6-oxo-pipecolate in urine (≤2 mMol/mol)	**8**	**–**	**8.4**	**7.3**	**2.9**	**–**	**4.3**	1.9	**2.1**
AASA plasma (≤0.4 mcmol/L)	**5.2**	**–**	**–**	**–**	**–**	**–**	**–**	**1.2**	**0.8**
P6C plasma (≤0.8 mcmol/L)	**29.8**	**–**	**–**	**–**	**–**	**–**	**–**	**6.6**	**4.6**
Pyridoxal phosphate (B6) (5–50 mCg/L)	–	–	34	–	–	–	–	47	–
Plasma Amino Acids (reference range)									
Arginine (6–140 umol/L)	**190**	**–**	**–**	**214**	97	**–**	**–**	101	79
Lysine (92–325 umol/L)	277	**–**	**–**	185	**87**	**–**	**–**	**51**	**31**
Tryptophan (0–60 umol/L)	48	–	–	36	44	–	–	42	39

Bold denotes abnormal result.

were generally consistent with the spectrum described in the literature, ranging from normal to extensive brain abnormalities, with no apparent correlation with the degree of lactic acidosis reported.

In this series, PDE-ALDH7A1 variants most frequently affected the catalytic domain, and included missense, frameshift, splice, and nonsense variants, which is also consistent with the literature [2]. Notably, the c.1559C > T (p.Ser520Phe) variant, identified in our case, has only been reported as homozygous in one other patient, who also exhibited markedly elevated lactate levels [8]. It is possible that this variant could be associated with a particularly severe neonatal presentation (**Supplemental Fig. 2**).

5. Discussion

The clinical spectrum of PDE associated with ALDH7A1 mutations (PDE-ALDH7A1) encompasses a wide range of neurological and systemic manifestations, which can be classified as typical or atypical. Classical features include prenatal movement abnormalities, perinatal asphyxia, neonatal respiratory distress, meconium-stained amniotic fluid, low Apgar scores, abnormal muscle tone, eye movement abnormalities, irritability, gastrointestinal symptoms (e.g., distention, nausea, vomiting), and seizures, starting in the neonatal period or early infancy with poor response to conventional antiseizure medications. Atypical cases may exhibit a later onset, an initial response to antiseizure medications followed by intractable seizures, or a delayed response to pyridoxine therapy [3,18,19]. EEG may reveal various abnormalities, including burst suppression and hypsarrhythmia, while brain MRI findings range from normal to structural anomalies such as corpus callosum hypoplasia, abnormal white matter signal, ventriculomegaly, cysts, delayed myelination, cerebellar hypoplasia, and cortical migration defects [6,20]. No consistent genotype–phenotype correlation has been established to date [21].

Laboratory abnormalities are not usually considered the hallmark of the PDE-ALDH7A1 presentation; however, they are recorded in a significant number of patients. Fang et al found that hypoglycemia occurred in 3/8 (37.5 %) and elevated lactic acid (LA) in 26/37 (70.3 %) of patients at presentation [3,6] . Therefore, elevated lactic acid should be highlighted as one of the most frequent manifestations of PDE. Lactic acidosis in neonates can be due to several factors, including hypoxia, sepsis, cardiac disease, prolonged seizures, and others. However, the etiology of increased LA in PDE is not clear. As seen in this series of patients with documented increase in LA, potential triggers were status epilepticus, emesis, and respiratory distress, while perinatal asphyxia was not common. Additional contributory factors reported were pulmonary hemorrhage, diminished left ventricular function, and pulmonary hypertension (Table 3).

Our patient did not have perinatal complications, cardiac or respiratory disease, or evidence of infection. Initial abnormal movements prompted administration of phenobarbital, indicating clinical suspicion for seizures, however there was no apnea, desaturation. Additionally, the abnormal movements did not correlate with ictal activity in the vEEG, and they did not improve with phenobarbital, but resolved with fluid and electrolyte treatment. While it is not possible to completely rule-out that ongoing seizure activity before 12 HOL could have contributed to the biochemical abnormalities, the severity of the lactic acidosis, hyperCKemia and the elevated ammonia were strongly suggestive of an underlying mitochondrial disease.

The cause of the apparent mitochondrial dysfunction in PDE is not clear. Biallelic pathogenic variants in ALDH7A1 result in the absence or dysfunction of α-AASA dehydrogenase (antiquitin, ATQ) [22], the enzyme that oxidizes α-AASA to α-aminoadipic acid, leading to the accumulation of α-AASA [23], P6C [24], pipecolic acid [25] and the recently discovered biomarkers 2S,6R-oxopropylpiperidine-2-carboxylic acid (2-OPP) [26] and 6-oxo-PIP [7]. Accumulated P6C binds and inactivates pyridoxal 5-phosphate (PLP), which is the active form of pyridoxine and plays a crucial role as a cofactor in several biological processes, including neurotransmitter and amino acid metabolism, folate and carbohydrate metabolism, lipid metabolism, mitochondrial function, heme, polyamines, molybdenum cofactor, and protein synthesis [27,28]. PLP is a cofactor for enzymes such as cysteine desulfurase and aminolevulinic acid synthase (ALAS), which are required for iron-sulfur (Fe-S) clusters and heme biosynthesis required by various enzymes in the mitochondria, including those involved in the respiratory chain (complexes I, II, and III) and the citric acid cycle. It has been hypothesized that PLP depletion could lead to partial deficiencies of those enzymes and subsequent mitochondrial dysfunction [29]. While defects in ALAS have not been reported to be associated with neonatal lactic acidosis, cysteine desulfurase deficiency, due to defects in Nitrogen Fixation 1 Homolog gene (NFS1), has been reported to cause an infantile mitochondrial disease with complex II and III deficiencies [30–33]. The disease typically presents with early-onset fatigue, hypotonia, respiratory failure, and feeding difficulties, followed by rapid deterioration with lactic acidosis, elevated liver enzymes, hyperCKemia, and multiorgan failure. Yang et al. (2022) described a particularly severe case with lactate levels of 12.5 mmol/L and CK of 41,475 U/L, accompanied by cardiomyopathy, which partially overlaps with some of the patients in our review [34]. It is possible that a partial decrease in the activity of cysteine desulfurase plays a role in PDE. Minenkova et al. also speculate that defects in PDE-ALDH7A1 may result in a reduced

Table 3
Clinical, biochemical, and molecular characteristics of 13 cases of PDE-ALDH7A1 presenting with neonatal-onset lactic acidosis. This case report is highlighted. α-AASA: alpha-aminoadipic semialdehyde; 6-oxo-PIP: 6-oxo-pipecolate; P6C: piperideine-6-carboxylate; PIP: pipecolic acid; CSF: cerebrospinal fluid; U: urine. P: plasma; CK: creatine kinase. Reference ranges are denoted in parentheses. NR: not reported; WNL: within normal limits.

	Patient	Sex	Plasma lactic acid (mmol/L) (<2.1)	CK (UI/L)	NH3 (μmol/L)	Plasma amino acids (μMol/L)	Urine organic acids	PDE biomarkers	ALDH7A1 Variants	Age of Onset	Initial Presentation	CT or MRI
This report	P1	F	15.27	30,995 (<230)	153	↑ Glutamine ↑ Tyrosine ↑ Histidine ↓ Serine	Suggestive of mitochondrial disease. See Fig. 1 for chromatogram	PIP-U 182.9 mmol/mol (≤10) 6-oxo-PIP-U 9.1 mmol/mol (≤2) α-AASA-P 5.2 μmol/L (≤0.4) P6C-P 29.8 μmol/L (≤0.8)	c.1559C > T (p. Ser520Phe)/ c.1540 A > G (p.Lys514Glu)	< 24 h	Apgar 8/9, grunting, abnormal movements	Thin corpus callosum, cysts, cerebellar hypoplasia. See Fig. 2 for imaging.
Aquilano et al., 2022	P1	M	18	NR	NR	Unremarkable	NR	PIP-P 10.6 μmol/L (<2.4)	c.1279G > C (p. Glu427Gln)/ c.1279G > C (p. Glu427Gln)	< 24 h	Apgar 9/10, normal cord blood, meconium-stained amniotic fluid, postnatal asphyxia, respiratory distress, pulmonary hypertension, myoclonic movements, d.15 h	NR
Mercimek-Mahmutoglu et al., 2012	P1	F	11	NR	NR	NR	NR	α-AASA-U 21.3 mmol/mol creatinine (<1)	c.1192G > C (p. Gly398Arg)/ c.834G > A (p. Val278Val)	3 d	Apgar 4/9, emesis, hypoglycemia (10.8 mg/dL), refractory seizures	Bilateral symetrical inferior temporal lobe hemorrhages, petechial hemorrhages in cerebellum and supratentorial brain, small amounts of intraventricular blood and restricted diffusion in bilateral ventrolateral thalami, and, to a lesser extent, in the dorsal pons
Marguet et al., 2016	P2	F	11	NR	NR	NR	NR	NR	c.1279G > C (p. Glu427Gln) / c.1279G > C (p.Glu427Gln)	< 24 h	Prematurity (36 weeks), hypoglycemia (10.8 mg/dL), irritability, abdominal distension, myoclonic jerks, respiratory distress	Diffuse white matter hypersignal on T2 sequences in both cerebral hemispheres, cortical edema
Dowa et al., 2020	P1	M	10.2	2845	WNL	NR	NR	PIP-CFS 5.6 μmol/L (<0.12) PIP-P 23.7 μmol/L (<3.2) α-AASA CFS 8.1 μmol/L (<0.1) α-AASA-P 7.5 μmol/L (<0.2)	c.1196G > T (p. Glu399Val)/ c.1200 + 1G > A	< 24 h	Apgar 7/9, respiratory distress, pulmonary hemorrhage, status epilepticus	Thin corpus callosum, diffuse cerebral white-matter signal abnormalities, delayed myelination, thin hematoma in posterior fossa
Fortin et al., 2023	P1	M	10	NR	NR	Unremarkable	NR	NR	c.1559C > T (p. Ser520Phe)/ c.1559C > T (p.Ser520Phe)	< 24 h	Apgar 8/9, respiratory distress, status epilepticus, severe encephalopathy	Multiple small areas of periventricular white matter injury, a small cerebellum, thin corpus callosum, mild pontine atrophy, mega cisterna magna.

(*continued on next page*)

Table 3 (*continued*)

	Patient	Sex	Plasma lactic acid (mmol/L) (<2.1)	CK (UI/L)	NH3 (μmol/L)	Plasma amino acids (μMol/L)	Urine organic acids	PDE biomarkers	ALDH7A1 Variants	Age of Onset	Initial Presentation	CT or MRI
												Normal spectroscopy in basal ganglia
van Karnebeek et al, 2016	P.2	F	9.8	NR	NR	NR	NR	PIP-CFS 11.6 μmol/L (PIP-P 32.7 μmol/L (<7.0)	c.1286G > T (p. Ser429Leu)/ c.1286G > T (p.Ser429Leu)	< 24 h	Prematury (34 weeks), generalized myoclonus	Small subependymal hemorrhage in right hemisphere, diffuse punctate bleeding in periventricular white matter
	P.4	M	10.8	NR	NR	NR	NR	PIP-P 52.3 μmol/L (< 2.5)	c.1195G > C (p. Glu399Gln)/ c.1195G > C (p. Glu399Gln)	< 24 h	Apgar 6/8, cord blood pH = 7.09, tachypnea, movement disorder, status epilepticus (withdrawal syndrome)	NR
Chauhan et al, 2024	P1	M	8.9	NR	315	NR	NR	NR	c.187G > T (p. Gly63Ter)/ c.1456_1457insG (p. Leu486ArgfsTer4)	5 d	At 5 days: Seizures, respiratory failure At 60 d: Emesis, hypoglycemia (<45 mg/dL), hyperuricemia (17.5 mg/dL)	Normal MRI
Kim et al., 2022	P1	M	6.3	NR	WNL	↓ Citrulline ↑ Glutamine ↑ Alanine/ Lysine	Increased: Lactate, 2-OH-isovalerate, 4-OH-phenyllactate, 4-OH-phenylpyruvate	PIP-U 1687 μmol/g creatinine (⟨200)	c.1279G > C (p. Glu427Gln)/ c.1279G > C (p.Glu427Gln)	3 d	Fever, seizures, respiratory distress, decreased cardiac function (EF 45.2 %)	Mild diffuse thinning of the corpus callosum
Alfadhel et al., 2012	P1	F	5.2	NR	NR	NR	NR	α-AASA-U 7.1 mmol/mol creatinine (<0.5)	c. 1195G > C (p. Glu399Gln)/ c.1429G > C (p.Gly477Arg)	2 d	Apgar 9/9, fetal deceleration (c-section required), status epilepticus	Normal CT
	P2	F	5.4	NR	NR	NR	NR	α-AASA-U 1.4 mmol/mol creatinine (<0.5)		6 w	Apgar 9/9, status epilepticus	Normal CT
Jaber et al, 2024	P1	F	3.9	NR	79.7	NR	Increased: β-OH-butyric acid, acetoacetic acid, β-ketovaleric acid	NR	c.1597del (p. Ala533Profs*109)/ c.1597del (p. Ala533Profs*109)	2 d	At 2 days: Seizures At 12 d: Respiratory distress, hypotonia	7 d CT: Bilateral calcifications surrounding the caudate nucleus 1 month MRI: Absence of calcifications

availability of acetyl-coenzyme A, the end product of lysine catabolism, as well as a diminished supply of succinate due to decreased activity of the B6-dependent enzyme GABA transaminase. The above scenario would lead to an overall reduction of Krebs cycle intermediates and decreased energy production [29].

HyperCKemia was highly unusual and it has only been reported in one additional patient in this series, in the context of status epilepticus. It is possible that rhabdomyolysis could be another manifestation of partial Cysteine desulfurase deficiency [34]. Another potential contributory factor could be a partial decrease in the activity of muscle glycogen phosphorylase, another PLP-dependent enzyme. Muscle glycogen phosphorylase deficiency causes McArdle's disease, which usually presents with exercise intolerance and rhabdomyolysis later in life. However, neonatal severe presentations with moderate elevation of CK have been published [35–37].

Hyperammonemia has also been reported in two other patients in association with increased LA. This abnormality could also be linked to secondary dysfunction of PLP-dependent enzymes, such as ornithine aminotransferase (OAT). Although OAT deficiency typically presents at a later age, a distinct phenotype manifests in the neonatal period, with hyperammonemia and normal or reduced plasma ornithine levels. Our patient's peak ammonia level was comparable with levels reported in neonates with symptomatic OAT deficiency (110–812 μmol/L) [38–42].

Plasma amino acids showed a mild increase in histidine, glutamine and tyrosine, which use PLP as a coenzyme for their metabolism. However, the elevated glutamine could be secondary to hyperammonemia, and the patient's mild liver disease could explain elevation in tyrosine. On the other hand, we did not observe elevated levels of threonine, glycine, or serine, which have been reported as the amino acids most sensitive to B6 depletion [27,28]. These results suggest that amino acid pathways that require PLP as a cofactor were not significantly affected,

A rapid WGS performed on DOL 9 revealed two heterozygous variants in ALDH7A1. The known pathogenic variant c.1559C > T (p.Ser520Phe) [8] and the c.1540 A > G (p.Lys514Glu) initially reported as VUS. The clinical presentation and biomarker profile in our patient support the pathogenicity of this variant, which aligns with the predictions of bioinformatic tools that indicate a deleterious effect.

PDE consortium guidelines support the use of lysine restriction therapy (LRT) to improve neurodevelopmental outcomes [5] and initiation of this therapy, particularly within the first six months of life, has been reported to lead to better cognitive outcomes [21,43–45]. Biomarker levels decreased by ~70 % within the treatment period (Table 2), suggesting that the treatment had a beneficial effect; **however, a clear correlation between biomarker levels and disease severity, or outcome, has not been established (9, 44, 45).** Therefore, it is difficult to predict if the early initiation of therapy in this subject will completely prevent neurocognitive impairment.

6. Summary and conclusions

This case expands on the biochemical presentation of PDE-ALDH7A1 and highlights the importance of identifying mitochondrial-like metabolic profiles as a relatively common manifestation of the disease. It underscores the importance of biomarker-guided diagnosis in rare metabolic diseases and the utility of rapid rWGS in critically ill neonates. Our findings also support the reclassification of the c.1540 A > G (p.Lys514Glu) variant as pathogenic.

In light of the growing evidence supporting the efficacy of triple therapy, the availability of PDE-specific biomarkers, and preliminary data supporting the feasibility of detection via newborn screening, PDE should be strongly considered as a new disease to be added to the Recommended Universal Screening Panel [7,46–48].

Future studies in larger cohorts are warranted to understand the role of mitochondrial dysfunction in the phenotypic spectrum of PDE-ALDH7A1 defects. In-Vitro, studies could be helpful in this endeavor.

CRediT authorship contribution statement

Marina Bottino: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Monica Boyer:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Maija R. Steenari:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Rebekah Barrick:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Jose E. Abdenur:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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