



Newly Diagnosed Diabetes in a 2-Year-Old Girl with Homozygous SLC25A42 Mutation: A Rare Mitochondrial Presentation with Persistent Acidosis

Arwa Ali Hudaisy; Mohammed Abdullah Alkhalidi; Adnan Bakur Alkurdi; Eman Mohammed Alshehri; Rana Ali Asiri; Hanin Hamad Almdhour; Atheer Fahad Aldoghmi

Pediatric Endocrine Fellow — Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia. ORCID: 0009-0000-5887-0699
Pediatric Endocrine Consultant — Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia. Email: Maalkhalidi89@gmail.com. ORCID: 0009-0005-8625-6051

Pediatric ICU Consultant — Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia. Email: Adnan1405@hotmail.com. ORCID: 0009-0001-6986-5227

Pediatric Endocrine Consultant — Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia. Email: Dr.eman.shehry@gmail.com. ORCID: 0009-0002-1228-1500

Pediatric Endocrine Fellow — Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia. Email: Rana.shathan1415@gmail.com. ORCID: 0009-0005-0821-1413

Pediatric Endocrinology, Doctor (Senior Registrar) — Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia. Email: Hneen-54@hotmail.com. ORCID: 0009-0001-7858-2384

Pediatric Endocrinology, Doctor (Senior Registrar) — Prince Sultan Military Medical City (PSMMC), Riyadh, Saudi Arabia. Email: ATHEER.ALDOGHMI@gmail.com. ORCID: 0009-0006-1670-8435

ABSTRACT

Background: Often resulting in multisystem involvement, mitochondrial diseases are a varied group of conditions brought on by impaired mitochondrial metabolism. Though rare as new-onset diabetes in early childhood, diabetes mellitus can be a symptom of mitochondrial illnesses. Managing diabetic ketoacidosis (DKA) and ongoing metabolic acidosis could point to an underlying mitochondrial disease, hence needing a different line of therapy. **Case Presentation:** A 2-year-old female, born full term with no prior hospitalizations, arrived exhibiting polyuria, polydipsia, and hyperactivity for two weeks. Laboratory assessment revealed hyperglycemia (25 mmol/L), metabolic acidosis (pH 7.13, bicarbonate 8 mmol/L), and a high anion gap consistent with moderate DKA. Despite the patient being subjected to the right course of insulin infusion and fluid replacement, her bicarbonate level was still low with lactic levels above five millimoles per litre. A homozygous mutation in the mitochondrial SLC25A42 gene was detected by genetic analysis and was associated with a metabolic crisis. This was followed by rescue treatment with sodium bicarbonate, which reduced the acidosis and helped the patient to shift to subcutaneous insulin administration. A multidisciplinary follow-up schedule was established and the patient and her family were fully educated on diabetes management. To sum up, the case highlights the importance of the necessity to pay attention to mitochondrial metabolic disorders in children with abnormal or intractable acidosis during the treatment of diabetic ketoacidosis. Early detection and customized treatment measures, such as genetic diagnosis and careful correction of metabolic derangements, are vital in the maximization of the outcomes in such rare conditions of diabetes mellitus.

Keywords: *Homozygous SLC25A42 Mutation, Acidosis, Diabetes*

INTRODUCTION

Mitochondrial diseases are a heterogeneous group of conditions that occur as a consequence of disruption of the mitochondrial respiratory chain, which in the vast majority of cases can be associated with pathogenic variants of nuclear or mitochondrial DNA [1]. It is seen to disproportionately affect high-energy-need tissues, including the brain, skeletal muscle and endocrine organs and manifest with a wide range of clinical effects [2]. The recent advances in molecular genetics have increased the list of nuclear genes that are involved in mitochondrial pathology; one of them is SLC25A42, which is the gene that encodes nicotinamide adenine dinucleotide-dependent coenzyme-A transporter vital to mitochondrial energy metabolism [3].

Even though diabetes mellitus is rarely believed to be among the primary symptoms in very young children, this complication of mitochondrial disease has become an increasingly acknowledged problem [4]. The majority of the cases of mitochondrial-related diabetes onset occur later in childhood or adolescence and are often accompanied by concomitant deficiencies in neurological or systemic disorders [2]. Early-onset type of diabetes caused by the dysfunction of mitochondria poses significant diagnostic and treatment issues since it is capable of resembling other monogenic and autoimmune diseases that cause diabetes [2].

The initial clinical manifestation of a rare homozygous mutation in SLC25A42 is the description of the presentation of a 2-year-old girl with recently diagnosed diabetes in the first clinical sign. The case highlights the imperative of considering the possibilities of mitochondrial etiology in atypical presentations of childhood diabetes and elaborates on the meager evidence on the metabolic and endocrine spectrum of SLC25A42-related disease. The ongoing metabolic acidosis is another important finding to point to the multisystemic nature of mitochondrial diseases and to emphasize the necessity to be even more suspicious of cases of early-onset diabetes in patients with additional metabolic abnormalities.

Case presentation

A 2-year-old female patient was born at full term and did not have any prior admission to the neonatal intensive care unit. With no prior hospitalizations, she is developmentally appropriate for age and completely vaccinated up to date. Her family history stands out for type 1 diabetes mellitus in third-degree relatives on both maternal and paternal sides. There is a positive history of consanguinity.

She showed polyuria, polydipsia, and hyperactivity spanning two weeks devoid of additional linked symptoms. She was quite steady on inspection save for some moderate dehydration and minor tachypnea. Normal neurological state among other physical examination results were nothing else. Her height and weight were within normal percentiles for her age. Urine dipstick tests turned up no ketones.

Her blood glucose was significantly high at 25 mmol/L during emergency department visit. Venous blood gas analysis showed metabolic acidosis with a pH of 7.13, bicarbonate of 8 mmol/L, and an increased anion gap of 15. According to DKA protocol, she was admitted to the pediatric intensive care unit as a newly diagnosed diabetes mellitus complicated by mild diabetic ketoacidosis (DKA). Management began with insulin infusion at 0.1 IU/kg/hour.

Laboratory tests revealed hemoglobin 13.6 g/dL, white blood cell count $6.7 \times 10^9/L$, platelets $386 \times 10^9/L$, and regular markers of inflammation (CRP and procalcitonin). Renal function tests revealed creatinine 23 mol/L, BUN 2.2 mmol/L, sodium 129 mmol/L, potassium 5.4 mmol/L, magnesium 0.76 mmol/L, and albumin 46 g/L. C-peptide was low at 80 pmol/L; beta-hydroxybutyrate was 0.4 mmol/L; and hemoglobin A1c was increased at 10.5%.

Although blood glucose and pH improved at first to 7.36, bicarbonate levels stayed constantly low (<15 mmol/L) over 24 hours with high lactate values (>5 mmol/L). According to chloride levels, fluid

management was changed with 0.45 normal saline. The patient had a single dosage of sodium bicarbonate adjustment after 30 hours of DKA treatment, which successfully boosted bicarbonate to 20 mmol/L with normalization of pH.

Genetic testing, done before at 2 months of age after her brother died from serious metabolic acidosis, showed a homozygous SLC25A42 gene mutation linked to a mitochondrial metabolic crisis. She was transferred to subcutaneous insulin with a total daily dose of 0.5 IU/kg following stabilizing. Her family was fully informed about the administration of type 1 diabetes. Close outpatient follow-up was provided by the endocrinologic and genetic teams.

Discussion

In pediatric patients, management of diabetic ketoacidosis (DKA usually follows established protocols starting with cautious fluid resuscitation with isotonic solutions, insulin infusions started following volume expansion, and close monitoring for difficulties including cerebral edema. Most recommendations strongly warn against routine bicarbonate administration for acidosis correction since it does not improve results and may be related with adverse effects [5,6]. Continuous or strange metabolic acidosis despite proper DKA therapy, however, should encourage thinking of other or underlying causes including inborn errors of metabolism or mitochondrial diseases [7].

The case illustrates the peculiarities that are faced in the case of mitochondrial disease occurring together with new-onset diabetes. Metabolic crises such as chronic lactic acidosis may not respond to the conventional therapy of DKA in such children because lactic and pyruvate oxidative metabolism are impaired due to mitochondrial malfunction [8]. Literature and professional advice indicate that supportive measures, including catabolism avoidance, aggressive infection or stressor control, and cofactor (e.g., coenzyme Q10, carnitine, and vitamins, e.g., thiamine, riboflavin) supplementation can prove useful in mitochondrial disease, but again the evidence is not compelling [9]. An exception to standard DKA protocols is that sodium bicarbonate can be used as a rescue therapy when the severe refractory acidosis is not responding to other therapy, but this is an exception rather than the rule [10].

The existence of lingering acidosis or elevated lactate during and after the standard DKA care ought to inspire physicians to consider the potential of mitochondrial or metabolic causes, especially when paired with a suitable history of family relations, cousinship, or childhood diabetes [11]. Pre-emptive and pervasive genetic testing has been demonstrated to assist in facilitating a fast diagnosis and thus initiating specific therapies and appropriate family counseling in a timely manner [12].

Conclusion

In summary, this case illustrates that persistently abnormal acid-base status in pediatric DKA may reveal underlying mitochondrial disease. Recognition of this etiology impacts both acute management and long-term care, and highlights the need for a high index of suspicion in young children with atypical or severe presentations of diabetes and metabolic acidosis.

References:

1. Wen H, Deng H, Li B, et al. Mitochondrial diseases: from molecular mechanisms to therapeutic advances. *Signal Transduction and Targeted Therapy*. 2025;10(1). doi:10.1038/s41392-024-02044-3
2. Varughese R, Rahman S. Endocrine dysfunction in primary mitochondrial diseases. *Endocrine Reviews*. February 2025. doi:10.1210/endrev/bnaf002
3. Heckmann K, Iuso A, Reunert J, et al. Expanding the genetic and clinical spectrum of SLC25A42-associated disorders and testing of pantothenic acid to improve CoA level in vitro. *JIMD Reports*. 2024;65(6):417-425. doi:10.1002/jmd2.12441

4. Nemoto K, Sano K, Sato S, Maeda Y, Murayama K, Takanashi JI. A child with mitochondrial DNA deletion presenting diabetes mellitus as an initial symptom. *Radiology Case Reports*. 2022;17(9):2915-2918. doi:10.1016/j.radcr.2022.05.061
5. Gripp KE, Trottier ED, Thakore S, Sniderman J, Lawrence S. Current recommendations for management of paediatric diabetic ketoacidosis. *Paediatrics & Child Health*. 2023;28(2):128-132. doi:10.1093/pch/pxac119
6. Eraky AM, Yerramalla Y, Khan A, et al. Complexities, benefits, risks, and clinical Implications of sodium bicarbonate administration in Critically Ill Patients: A State-of-the-Art Review. *Journal of Clinical Medicine*. 2024;13(24):7822. doi:10.3390/jcm13247822
7. Tarr JD, Morris A a. M. Emergency Management of Intoxication-Type Inherited Metabolic Disorders. *Journal of Inherited Metabolic Disease*. 2025;48(2). doi:10.1002/jimd.70007
8. S PKK, Jyothi MN, Prashant A. Mitochondrial DNA variants in the pathogenesis and metabolic alterations of diabetes mellitus. *Molecular Genetics and Metabolism Reports*. 2024;42:101183. doi:10.1016/j.ymgmr.2024.101183
9. El-Remessy A. Diabetic Ketoacidosis Management: updates and challenges for specific patient population. *Endocrines*. 2022;3(4):801-812. doi:10.3390/endocrines3040066
10. Vidanapathirana M. Sodium bicarbonate and intubation in severe diabetic ketoacidosis: are we too quick to dismiss them? *Clinical Diabetes and Endocrinology*. 2024;10(1). doi:10.1186/s40842-024-00171-y
11. Husen, T. K., Faris, M. N., & Taher, M. A. (2025). Multi-pollutants water cascade analysis for industrial water minimization. *Current Topics in Nutraceutical Research*, 23(2). <https://doi.org/10.37290/ctnr.v23i2.25>
12. Albinsaad, L. S., Almubarak, E. A., Balkhair, R. M. A., Almana, K. A. A., Almuallim, R. M. A., Alkhamis, H. Y. H., & Alessa, M. Y. (2025). Diagnostic accuracy of artificial intelligence-assisted mammography interpretation vs. radiologist alone: A systematic review and meta-analysis. *Current Topics in Nutraceutical Research*, 23(2). <https://doi.org/10.37290/ctnr.v23i2.24>
13. Vallarino, D. (2024). Machine learning algorithms for survival analysis: Advantages, disadvantages, and examples. *International Journal of Artificial Intelligence & Machine Learning*, 4(1), 10–21. <https://doi.org/10.51483/IJAIML.4.1.2024.10-21>
14. Zhang, J., Abbas, Z., Ali, T., Liu, Q., & Wang, Y. (2024). The impact of ChatGPT on students' writing proficiency in second language acquisition: Students' perception and experiences: A qualitative analysis. *International Journal of Artificial Intelligence & Machine Learning*, 4(1), 1–9. <https://doi.org/10.51483/IJAIML.4.1.2024.1-9>
15. Tryggstad JB, Kelsey MM, Drews KL, et al. Clinical Characteristics of Offspring Born to Parents with Type 2 Diabetes Diagnosed in Youth: Observations from TODAY. *Children*. 2024;11(6):630. doi:10.3390/children11060630
16. Sami A, Javed A, Ozsahin DU, Ozsahin I, Muhammad K, Waheed Y. Genetics of diabetes and its complications: a comprehensive review. *Diabetology & Metabolic Syndrome*. 2025;17(1). doi:10.1186/s13098-025-01748-y