

## Permanent neonatal diabetes mellitus presenting with mixed diabetic ketoacidosis and hyperglycemic hyperosmolar state, a diagnostic and therapeutic challenge

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### ABSTRACT

Neonatal diabetes mellitus (NDM) is a rare metabolic disorder affecting 1 in 90,000–1,60,000 live births. Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are the most serious and potentially fatal complications in patients with diabetes. Although considered two separate entities along the spectrum of hyperglycemic emergencies, they can coexist as a clinical presentation. Neonatal presentations of both these entities are extremely rare, and a mixed presentation is sparsely reported. We describe a rare case of a 42-day-old male infant, initially presenting with severe shock and sepsis, later diagnosed as a mixed presentation of DKA and HHS, in permanent NDM. Genetic analysis denoted autosomal dominant KCNJ-11 mutation encoding Kir6.2 subunit of K-ATP channel as the sole etiological factor. Very few case reports of mixed presentation of DKA and HHS in NDM are available. Early recognition of this rare presentation and prompt management reduce mortality. Genetic diagnosis is important as children with mutated K-ATP channels respond well to oral sulfonylurea therapy.

**Key words:** Mixed diabetic ketoacidosis and hyperglycemic hyperosmolar state, Monogenic diabetes, Neonatal diabetic ketoacidosis and neonatal hyperglycemic hyperosmolar state

**D**iabetes mellitus (DM) is a common, chronic, metabolic disease characterized by hyperglycemia as a cardinal biochemical feature. Neonatal DM (NDM) is the term used to describe diabetes occurring in the first 6 months of life, the incidence being 1 in 90,000–1,60,000 live births [1,2]. Approximately 50% of infants with NDM have Transient NDM (TNDM), which appears at an earlier age (median 6 days, range 1–81 days) and remits within a few weeks or months of diagnosis. Permanent NDM (PNDM) (median 27 days, range 1–127 days) requires life-long treatment. PNDM is more likely to present with diabetic ketoacidosis (DKA) than TNDM [1]. Hyperglycemic hyperosmolar state (HHS) is another complication of PNDM but it is rare. Rarer is the mixed presentation of DKA and HHS.

The unique aspect of our case is that it presented with mixed DKA and HHS. Mixed form is frequently unrecognized and, if managed inappropriately, may increase the risk of complications, including mortality. With this case report, we intend to highlight the importance of early recognition of this rare mixed entity and also the therapeutic challenge we faced.

### CASE REPORT

A 42-day-old male baby, weighing 3.56 kg, presented to the emergency department of a tertiary care hospital in eastern India with a history of fever for 3 days, difficulty in breathing, and an inability to take oral feed for 1 day. The child was born out of a non-consanguineous marriage by normal vaginal delivery with a normal 1-min and 5-min APGAR score and a normal birth weight of 2.8 kg. There was an uneventful antenatal, perinatal, and neonatal period, exclusively breastfed and immunized as per the National Immunization Schedule.

On presentation, the baby was drowsy, only responsive to pain, febrile (103.5°F), pulse rate 172/min, respiratory rate (RR) 68/min, appeared dehydrated, pale, and mottled with cold extremities, capillary refill time more than 5 s. He had severely increased work of breathing and intercostal and subcostal retractions. Capillary blood glucose (CBG) value was “high” on admission and remained high on repeat check after 30 min. There was no family history of diabetes. Arterial blood gas (ABG) analysis on admission showed severe metabolic acidosis, hypocarbia, high lactate, and hyperkalemia (Table 1). Urine dipstick analysis showed glucose 3+, ketones 2+, and protein negative. The rapid

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antigen test for malaria was negative. The initial diagnosis made was DKA in a case of NDM with underlying sepsis presenting with cardiorespiratory failure.

The patient was resuscitated with normal saline (NS) bolus 20 mL/kg and was put on non-invasive ventilation, but in view of worsening hemodynamic status and poor Glasgow Coma scale, the baby was put on mechanical ventilation. Infusion Adrenaline was started at 0.1 mcg/kg/min. Fluid resuscitation and inotropic support were titrated according to point-of-care ultrasound (POCUS) findings. Functional echocardiography showed poor myocardial function (EF-30%), and infusion dobutamine was also started.

Severe DKA was managed as per ISPAD clinical practice consensus guidelines 2022 [3]. A fluid deficit of 10% was corrected over the next 48 h with 0.9% NS, along with maintenance fluid ½ NS + KCl. KCl was added only after the potassium level came below 5.5 on repeat VBG. Intravenous (IV) insulin infusion started at 0.1 unit/kg/h, 1 h after beginning IV fluids. Monitoring sheets recording pH, CBG, blood pressure, heart rate, RR, urine output, fluid, and insulin infusion rate were meticulously monitored.

Despite protocol-wise appropriate management in the intensive care unit for 12 h, the baby was still not improving, and ABG did not show predictable improvement (Table 1). Fluid calculations were rechecked, inferior vena cava remained collapsed, required additional NS boluses, excess urine volume was replaced, and fluid deficit recalculated to 15%. Persistently low bicarbonate levels with poor myocardial function with hyperkalemia compelled us to start a sodium bicarbonate infusion in the correction dose. To check the persistently high glucose level, the insulin infusion rate was gradually increased up to 0.2 U/kg/h. Over the next 24 h, the biochemical derangements and clinical conditions showed improvements, and the baby was stabilized thereafter. The need for large-volume fluid administration and persistently high glucose level (the “high” value in the glucometer corresponds with >600 mg/dL) raised the suspicion that this was not a simple case of DKA. We reviewed the possibility of a HHS mixed with DKA, and our case fulfilled the criteria of mixed DKA and HHS (Table 2).

The baby was extubated in the next 2 days. During the weaning period, we encountered hyperchloremic metabolic acidosis, which was duly managed with a low-chloride-balanced salt solution (Plasma Lyte). Once feeding was established, subcutaneous regular insulin and Injection Glargine was started, and the insulin infusion was gradually tapered off. The routine investigation (Table 3) revealed raised C-reactive protein and procalcitonin but blood culture and urine culture were sterile. Cerebrospinal fluid study, liver function test was also within the normal limit. Renal function tests initially suggested of pre-renal acute kidney injury, which resolved later on. C-peptide level of 0.1 ng/mL and hemoglobin A1c (HbA1c) of 9.9% further confirmed a prolonged insulinopenic hyperglycemic state. Pancreatic agenesis or dysgenesis was excluded provisionally by contrast-enhanced computed tomography abdomen. Genomic sequencing revealed KCNJ-11 mutation (Fig. 1). Parental diabetic screening tests were

**Table 1: Serial ABG analysis**

ABG parameters	On admission	12 h	24 h	36 h	48 h	60 h
pH	6.808	6.920	7.122	7.29	7.448	7.39
pCO <sub>2</sub>	14.7	13.4	24.4	24.5	29.2	25.6
pO <sub>2</sub>	70.2	109.5	84.5	88.8	97.3	77.8
HCO <sub>3</sub>	2.9	2.7	9.1	12.7	17.1	21.8
BE	-28.3	-28.2	-16.8	-13.8	-9.1	-3.5
Lactate	3.07	2.51	1.90	1.81	1.10	1.09
Na <sup>+</sup>	148	147.7	142.5	148.7	152.7	150.5
K <sup>+</sup>	6.14	5.88	4.9	3.77	2.98	3.80
iCa <sup>+</sup>	1.19	1.10	1.05	1.10	0.85	0.98
Cl <sup>-</sup>	104	110	112	122	131	117

ABG: Arterial blood gas

**Table 2: Criteria for diagnosis of DKA, HHS, Mixed DKA, and HHS [3].**

DKA criteria	HHS criteria	Mixed DKA and HHS
1. pH <7.3, Serum bicarbonate <18 mmol/L.	1. Blood glucose >33.3 mmol/L (600 mg/dL)	Criteria for DKA Plus
2. Hyperglycemia: Blood glucose >11 mmol/L (200 mg/dL)	2. Effective osmolality >320 mOsm/kg	1. Blood glucose >33.3 mmol/L (600 mg/dL)
3. Ketonemia/mod. to severe Ketonuria	3. Arterial pH >7.3; Venous pH >7.25	2. Effective osmolality >320 mOsm/kg
	4. S. bicarbonate >15 mmol/L	
	5. Small ketonuria, absent to small ketonemia	
	6. Obtundation, combativeness, or seizures (in approximately 50%) (Effective osmolality (mOsm/kg)=2 (plasma Na)+plasma glucose mmol/L)	

DKA: Diabetic ketoacidosis, HHS: Hyperglycemic hyperosmolar state

**Table 3: Investigations of the patient**

Hb%	10.0 g%
TLC	17200/cmm
DLC	N-48, L-44, M-5, E-3
Platelet	4.4L/cmm
CRP	48 mg/L
Procalcitonin	2.2 µg/L
LFT	TS Bil-0.8 mg/dL, SGPT-22 U/L, SGOT-88 U/L, Alk-Phos-428 U/L, Albumin-3.3 g/L
RFT	Urea-110 mg/dL, Cr-1.1 mg/dL
Blood C/S	No growth
Urine analysis	Ketone body-2+, others normal
Urine C/S	No growth
CSF study	Cells-2 cells/HPF, Protein-65 mg/dL, Glucose-55 mg/dL, CSF C/S-no growth
Chest X-ray	Non-specific patchy opacities
CECT abdomen	Normal, no pancreatic agenesis/dysgenesis

TLC: Total leucocyte count, DLC: Differential leukocyte count, CRP: C-reactive protein, LFT: Liver function test, RFT: Renal function tests, CECT: Contrast-enhanced computed tomography, CSF: Cerebrospinal fluid

FINDINGS RELATED TO PHENOTYPE							
Gene&Transcript	Variant	Location	Zyosity	In silico Parameters**	Disorder(OMIM)	Inheritance	Variant Classification
KCNJ11 NM_000525.4	c.602G>A p.Arg201His	Exon 1	Heterozygous	CADD: 28.5 SIFT: Deleterious MT: Damaging	DIABETES MELLITUS, PERMANENT NEONATAL, 2; PNDM2:618856 DIABETES MELLITUS, TRANSIENT NEONATAL, 3:610582	Autosomal Dominant	<b>Pathogenic</b>

\* Genomic Position based on Assembly GRCh37, \*\*Number of applied in silico programs predicting the effect of the variant on the protein outcome (CADD: Combined Annotation Dependent Depletion (v1.6), SIFT, PolyPhen 2, MT: Mutation Taster), N/A: Not Applicable, \*\*\*Minor Allele Frequency as described in GnomAD (Controls), \*\*\*\*based on ACMG Guidelines. het-heterozygous, hom-homozygous, hemi-hemizygous.

**Figure 1: Report of whole exome sequencing**

negative, and due to financial constraints, parental genetic studies could not be carried out.

We gradually shifted the baby to oral sulfonylureas, Tab Glibenclamide @ 0.2 mg/kg/day in two divided doses while still giving once a day nighttime Injection Glargine. We faced great difficulty in achieving the proper euglycemic state, and the Tab Glibenclamide dose had to be increased to 0.8 mg/kg/day. Finally, after about 4 weeks, we were able to stop Injection Glargine and put the patient on oral sulfonylureas alone. At the time of discharge, the baby was 3 months old, having achieved a social smile, proper eye contact with cooing and babbling, and hand regard, and an HbA1c of 5.5%. The hearing and visual screening tests were also normal. Ethics approval was not required for this case report, as this was deemed not to constitute research at our institution, but the consent of the parent was obtained.

## DISCUSSION

Monogenic diabetes has been established as the most common cause of NDM. In a large international cohort study from 79 countries on 1020 children with NDM diagnosed before 6 months of age, a genetic diagnosis of monogenic diabetes could be ascertained in >80% [4]. Monogenic diabetes includes Maturity-onset diabetes of the young, NDM, and syndrome-associated DM that may present in neonates or infants [5].

Mutations in K-ATP channel genes, named KCNJ-11, coding for the pore-forming protein potassium channel, inwardly rectifying Kir 6.2, and ABCC8 coding for sulfonylurea receptor 1, SUR1, constitute 2/3<sup>rd</sup> of the cases of PNDM. Activating mutations in K-ATP channel genes lead to NDM: TNDM, or PNDM, reducing the ability of ATP to close the channel, so insulin exocytosis is hampered. Apart from KCNJ-11 and ABCC8 mutations, the other notable mutations are FOXP3, INS, PDX1, 6q24 abnormalities, etc. In nearly 40% of cases of NDM, the genetic etiology remains unknown [6]. Like polygenic diabetes, monogenic diabetes usually is not associated with autoantibodies and human leukocyte antigen predisposition as in Type 1 DM or environmental influences as in Type 2 DM, but the presence of autoantibodies does not rule out monogenic diabetes [7]. In our

case, although we could lead to a genetic diagnosis, screening of autoantibodies could not be done.

Sulfonylurea drugs can close the mutant channels; hence, they are often the treatment of choice in monogenic diabetes due to KCNJ-11 and ABCC8 gene mutations [8]. They are safe and highly effective in glycemic control for long-term use of at least 10 years [9]. In PNDM, Glibenclamide is started at 0.2 mg/kg/day in two divided doses; the dose can be gradually increased weekly till a 0.8–1 mg/kg/day value is reached, at which point insulin may be discontinued in the majority cases [9,10]. In our patient, Glibenclamide was started at 0.2 mg/kg/day in two divided doses and has been gradually increased to 0.8 mg/kg/day over 4 weeks. Alongside Glargine, 2U is being given at night with strict monitoring of blood glucose. Rafiq *et al.* observed NDM with the SUR1 mutation (ABCC8) would require lower doses of sulfonylureas than Kir 6.2 mutation (KCNJ-11) [11].

Another unique aspect of our case is that it presented with mixed DKA and HHS. Mixed form is frequently unrecognized and, if managed inappropriately, may increase the risk of complications. Children with mixed presentation meet the criteria for diagnosis of DKA partially and have hyperosmolality (Table 2). In a study, pure HHS presentation in the pediatric population was rare (0.8%); mixed DKA-HHS was a commoner presentation (13.8%), the most common being DKA [12]. Our patient responded to large-volume fluid administration and a higher insulin infusion rate. In a similar study reported from China, a case of mixed presentation of DKA and HHS was not responsive to fluid-insulin therapy with progressive worsening and required continuous renal replacement therapy [13,14]. Since a POCUS-guided approach to fluid therapy was undertaken, we could prevent the occurrence of cerebral and pulmonary edema despite large-volume fluid administration. The management of mixed DKA-HHS is being increasingly given importance in the most recent ISPAD clinical practice consensus guidelines 2022 [3].

## CONCLUSION

Mixed DKA-HHS presentation in the pediatric age group is rare, and very few case reports and case series are present in

the literature. Mixed presentation in neonatal DM is extremely rare. It poses a great challenge to identify and manage this entity, but if recognized early and managed properly, it can give a better outcome. Managing PNDM needs genetic analysis, a proper understanding of pathophysiology, and appropriate use of sulfonylureas after stabilizing the patient with insulin and fluid therapy.

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