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Atypical presentation and management of Persistent Neonatal Hypoglycemia

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ABSTRACT

Background: Neonatal hypoglycemia is a common metabolic disorder that manifests with non-specific clinical symptoms like poor feeding, irritability, apnoea, and seizures or may present asymptomatically. Screening of at-risk neonates; small for gestational age (SGA), preterm and infants of diabetic mothers (IDM)—is crucial for early diagnosis and prevention of long term sequalae. The Pediatric Endocrine Society defines neonatal hypoglycemia as blood glucose levels less than 50 mg/dL within the first 48 hours postnatally. Persistent hypoglycemia, characterized by the necessity for intravenous dextrose beyond this timeframe, mandates comprehensive critical sample analysis to elucidate its aetiology.

Clinical Description: A late preterm, SGA male infant had persistent hypoglycaemia despite normal insulin levels and the absence of identifiable sepsis, metabolic or endocrine disorders. Initial management entailed intravenous dextrose along with hydrocortisone; however, due to the persistence of hypoglycaemia and normal critical sample results neonate was managed effectively with an alternative drug.

Management & Outcome: Oral diazoxide was initiated at a dosage of 5 mg/kg/day, leading to the attainment of euglycemia within five days. The infant was subsequently discharged with instructions for continued medication and monitoring, ultimately tapering off diazoxide after four weeks while maintaining normal growth and developmental parameters.

Conclusion: Persistent hypoglycemia in preterm SGA infants was effectively managed with diazoxide, although the precise mechanisms underlying this phenomenon remains to be elucidated. Continued research is needed to clarify the pathophysiology and therapeutic implications of this treatment modality.

Keywords: *Diazoxide, Hypoglycemia, Neonate Manuscript text*

1. INTRODUCTION

Neonatal hypoglycemia is a common metabolic disorder, often presenting with non-specific symptoms such as poor feeding, irritability, apnea, and seizures; in many cases, may be asymptomatic. It is imperative to screen at-risk neonates like small for gestational age (SGA), preterm, infants of diabetic mothers (IDM), and other critically ill neonates—for hypoglycaemia through random blood sugar (RBS) monitoring. This approach is essential to prevent long term sequalae (1-2).

The Pediatric Endocrine Society categorizes neonatal hypoglycemia as a blood glucose level of less than 50 mg/dL within the first 48 hours after birth, followed by a level of less than 60 mg/dL thereafter (3). Transitional neonatal hypoglycemia usually gets resolved by first 48 hours of life (4).

Persistent neonatal hypoglycemia refers to low blood glucose in newborns requiring treatment beyond the first 48 hours to achieve normal levels. It signifies an underlying metabolic or endocrine issue affecting glucose regulation (3). In such cases, critical sample analysis becomes crucial for identifying the underlying aetiology of the persistent condition.

The initial treatment for hypoglycemia typically involves glucose infusion; however, in instances where blood glucose levels cannot be maintained, pharmacological interventions may be warranted. Treatments such as hydrocortisone, diazoxide, glucagon, and octreotide can be employed to manage the condition effectively (5).

Researchers have reported a case of a preterm SGA infant presenting with persistent hypoglycemia beyond two weeks of age, characterized by low serum insulin levels and no clear signs of hyperinsulinism, was successfully managed with diazoxide after failing to stabilize glucose levels with high intravenous glucose and continuous glucagon infusion. Diazoxide was later discontinued upon reaching a weight of 5 kg due to side effects (6).

A case of a preterm SGA neonate with persistent hypoglycemia with normal insulin levels and the absence of any other identifiable metabolic or endocrine disorders is reported here. The neonate was successfully treated with oral diazoxide, illustrating an effective therapeutic approach for managing this challenging condition.

2. CLINICAL DESCRIPTION

A preterm male neonate born to a 26-year-old primigravida booked mother at 36 weeks of gestation with uneventful antenatal period. Baby was delivered by emergency caesarean section; indicated for breech presentation with non-reassuring fetal monitoring. Baby was resuscitated with a bag-and-mask ventilation for 60 secs and shifted to the NICU for post-resuscitation care. The baby weighed 1710 grams (1st percentile), with the head circumference of 31.6 cm (24th centile), and the ponderal index of 1.55 (asymmetric intrauterine growth restriction- IUGR). No other significant anatomical and clinical abnormality noted.

The baby was started on intravenous fluids, and feeds were gradually established to full requirement in next 48 hrs. No episodes of hypoglycaemia were observed during routine RBS screening in the first 72 hours of life.

On day 4 of life, the baby had subtle seizures, and the RBS was 34 mg/dL. This was managed with a bolus of 10% dextrose fluid, and feeds were continued. As blood sugars were not maintained, dextrose infusion was started at 6 mg/kg/min and later increased to 12 mg/kg/min due to low blood glucose levels (range 30-60mg/dl). There was inconsistent response to hydrocortisone therapy. Baby received antibiotics for probable sepsis (only CRP-Positive with normal other sepsis screen parameters). Blood cultures showed no growth, and antibiotics were stopped thereafter. Neurosonogram revealed no abnormality.

In view of persistent hypoglycaemia despite glucose infusion and oral feeds on day 26 of life, critical sample analysis done. Results shown in Table 1. Serum beta-hydroxybutyrate was 2.3 mmol/L, (normal value < 2 mmol/L) slightly elevated. Serum Insulin level was 0.6mU/L - within normal range.

Table I. Critical Sample Results

Investigation	Result	Normal Value
S. Insulin	0.6 mU/L	< 2 mU/L
S. Cortisol	6.4 mcg/dL @ 9 am	5–25 mcg/dL (a.m.), 2–14 mcg/dL (p.m.)
Growth Hormone	10 ng/mL	5–23 ng/mL
Free Fatty Acid Levels	0.3 mmol/L	0.1–0.45 mmol/L
Urine for Reducing Sugars	Negative	Negative

S. Ketones (beta-hydroxybutyrate)	2.3 mmol/L	< 2 mmol/L
Blood Lactate	1.9 mmol/L	< 2 mmol/L

Abbreviations: S = serum, mmol/L = millimoles per litre, mU/L = milliunits per litre, mcg/dL = micrograms per decilitre, ng/mL = nanograms per millilitre.

There was no evidence of a hyperinsulinemic state or abnormalities in growth hormone and cortisol.

Metabolic screening profiles (TMS and GCMS) as shown in Figure.1 were also normal

INBORN ERRORS OF METABOLISM (IEM) SUMMARY REPORT

Sr. No.	Test Methodology	Result	Test Type	Page
1	TANDEM MASS SPECTROMETRY SCREENING REPORT	Negative	Screening	2
2	FLUOROMETRIC ENZYME IMMUNOASSAY SCREENING REPORT	Negative	Screening	5

Disorder	Parameter	Result* (1 – 10 – 100 – 1000)	Result Value	Reference	Remarks
Glucose 6 Phosphate Dehydrogenase deficiency	G6PD		20.1	NLT 3 U/dL	Normal
Classical Galactosemia	T GAL		6.0	NMT 25 mg/dL	Normal
Congenital Hypothyroidism	TSH**		0.3306	NMT 15 µIU/mL	Normal
Congenital Adrenal Hyperplasia	17-OHP		2.689	NMT 50 ng/mL	Normal
Profound Biotinidase deficiency	BTD		187.5	NLT 40 U	Normal
Cystic Fibrosis	IRT		36.619	NMT 110 µg/L	Normal

Figure 1: Inborn Error of Metabolism (IEM) Summary Report

3. MANAGEMENT AND OUTCOME

Oral diazoxide was initiated at 5 mg/kg/day based on institutional guidance and parental consent, supported by literature review. The infant achieved euglycemia, allowing for the gradual tapering of glucose infusion while optimizing enteral feeds. After five days of diazoxide therapy, the baby was euglycemic on breastfeeds.

Screening for retinopathy of prematurity and hearing was normal. The baby was discharged on day 35 of life with advice to continue medication along with a thiazide and home monitoring of blood sugar. Parents were counselled regarding complications of diazoxide like fluid retention and respiratory distress and were advised for regular follow-up. Echocardiography during follow-up was normal, ruling out pulmonary hypertension which may be related to Diazoxide.

The baby remained euglycemic, and diazoxide was tapered after four weeks. MRI Brain conducted at the three-month follow-up postnatally showed no abnormality. The baby is currently euglycemic without medication and shows normal growth and developmental parameters.

4. DISCUSSION

Persistent hypoglycemia in SGA and low birth weight infants beyond one month of age is an uncommon clinical scenario. A recent study examining the phenotype and genotype of neonates born SGA who developed hyperinsulinemic hypoglycemia found that plasma insulin levels can be undetectable during hypoglycemic episodes in this group. However, all the infants in the study exhibited other biochemical markers of hyperinsulinism, including low levels of β-hydroxybutyrate and non-esterified fatty acids, during hypoglycemia (7). In this case, low levels of insulin and elevated beta-hydroxybutyrate levels did not support the diagnosis of hyperinsulinism.

Another possible explanation for persistent hypoglycemia with low insulin levels could be deficiencies in cortisol or growth hormone, which are associated with increased insulin sensitivity and reduced fasting glucose (2). However, in this case, growth hormone levels were elevated, and cortisol levels were normal during hypoglycemia.

A plausible explanation for the need for intravenous glucose infusion to sustain euglycemia despite low insulin levels, elevated beta-hydroxybutyrate, and normalized serum fatty acid levels is that some SGA infants exhibit low insulin levels alongside heightened insulin sensitivity, leading to glucose elimination without suppression of lipolysis (2).

Arnon S et al in the year 2014 reported successful outcomes with diazoxide therapy and hypothesized that it reduces insulin sensitivity (6). However, the duration of diazoxide therapy and potential side effects need to be assessed in future evaluations.

Arya VB et al in the year 2013 reported that Diazoxide, an ATP-sensitive potassium channel agonist that prevents membrane depolarization, suppresses insulin secretion, and aids in maintaining normoglycemia in hyperinsulinism-like conditions (7).

Demirel F et al reported that diazoxide may induce reopening of the ductus arteriosus, pulmonary arterial hypertension, and cardiac arrest, with hypertrophic cardiomyopathy reported following prolonged treatment. Rare side effects such as feed intolerance and abdominal distension have also been documented, necessitating cautious use (8).

The precise pathogenesis of persistent hypoglycemia and the role of diazoxide in its management remain to be elucidated. Therefore, this case warrants reporting, and further studies are essential to evaluate the therapeutic benefits and long-term effects of diazoxide in similar clinical contexts.

5. CONCLUSION

Preterm SGA babies can exhibit prolonged hypoglycemia that extends past the neonatal stage, even with normal insulin levels and no other known cause, which may result from a delayed transition.

Persistent hypoglycemia requiring high glucose infusion rates and normal insulin levels may be managed with diazoxide, although its exact mechanism of action remains unclear and possibly reduces the sensitivity of insulin action. However, serious side effects have been associated with diazoxide use; therefore, it should be administered with caution.

This case report highlights that persistent neonatal hypoglycemia with normal insulin levels, in the absence of other metabolic disorders, can be effectively managed with diazoxide.

Lessons learnt

- Neonatal hypoglycemia can persist for prolonged durations in preterm, SGA, and low birth weight neonates.
- Possibility of atypical causes should be kept in mind.
- Studies are needed to elucidate the role and action of diazoxide in neonatal hypoglycemia.

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