

A preterm very low birth weight male neonate with refractory hypoglycemia and hyperinsulinemia and hyperammonemia: A rare case report

**Jillalla Narsing Rao, Swathi Chacham, Uppin Narayan Reddy,
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ABSTRACT

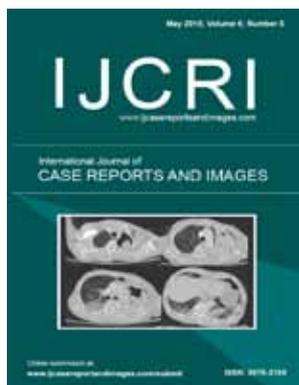
Introduction: Hypoglycemia is an important metabolic complication in neonates, more so in newborns with perinatal risk factors. Physiological immaturity of gluconeogenesis, lipolysis coupled with hyperinsulinemia contributes to hypoglycemia in small for gestational age (SGA) neonates. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), a hyperinsulinemic condition is an important differential diagnosis for intractable and refractory hypoglycemia. Hyperinsulinemic-hyperammonemia (HI/HA) syndrome, a rare autosomal dominantly inherited disorder, is the second most common cause for hyperinsulinemic-hypoglycemia in infancy. Both symptomatic as well as asymptomatic hypoglycemia involves the occipital cortex leading to cortical blindness, necessitating early etiological diagnosis and prompt intervention. We report a preterm male neonate with rare manifestations of refractory hypoglycemia, hyperinsulinemia and hyperammonemia.

Case Report: A 30 weeks, 1300 grams male neonate, born by C-section had respiratory distress, requiring mechanical ventilation (MV) for 10 days. On 11th day of life, neonate developed recurrent apneic episodes along with jitteriness and seizures. Initial evaluation revealed low blood sugar levels which persisted despite high glucose infusion rate (GIR 12 mg/kg/min). There was hyperammonemia (serum NH₃ levels 273 µg/dL) along with hyperinsulinemia. However, the serum cortisol, thyroid, growth hormone levels and blood lactate were normal. Similarly, metabolic screening for inborn errors of metabolism (IEM) was normal. Abdominal imaging with ultrasound and contrast-enhanced computed tomography (CT) scan did not reveal pancreatic hyperplasia. Persistent hypoglycemia, hyperinsulinemia along with hyperammonemia could suggest hyperammonemic hyperinsulinemic syndrome in this neonate. The infant responded to oral diazoxide.

Conclusion: We report a preterm, very low birth weight (VLBW) male neonate with refractory hypoglycemia and hyperinsulinemia and hyperammonemia, which responded to diazoxide.

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A preterm very low birth weight male neonate with refractory hypoglycemia and hyperinsulinemia and hyperammonemia: A rare case report

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autosomal dominantly inherited disorder, is the second most common cause for hyperinsulinemic-hypoglycemia in infancy. Both symptomatic as well as asymptomatic hypoglycemia involves the occipital cortex leading to cortical blindness, necessitating early etiological diagnosis and prompt intervention. We report a preterm male neonate with rare manifestations of refractory hypoglycemia, hyperinsulinemia and hyperammonemia. **Case Report:** A 30 weeks, 1300 grams male neonate, born by C-section had respiratory distress, requiring mechanical ventilation (MV) for 10 days. On 11th day of life, neonate developed recurrent apneic episodes along with jitteriness and seizures. Initial evaluation revealed low blood sugar levels which persisted despite high glucose infusion rate (GIR 12 mg/kg/min). There was hyperammonemia (serum NH₃ levels 273 µg/dL) along with hyperinsulinemia. However, the serum cortisol, thyroid, growth hormone levels and blood lactate were normal. Similarly, metabolic screening for inborn errors of metabolism (IEM) was normal. Abdominal imaging with ultrasound and contrast-enhanced computed tomography (CT) scan did not reveal pancreatic hyperplasia. Persistent hypoglycemia, hyperinsulinemia along with hyperammonemia could suggest hyperammonemic hyperinsulinemic syndrome in this neonate. The infant responded to oral diazoxide. **Conclusion:** We report a preterm, very low birth weight (VLBW) male neonate with refractory hypoglycemia and hyperinsulinemia and hyperammonemia, which responded to diazoxide.

Keywords: Hyperammonemia, Hyperinsulinemic, Hypoglycemia, Persistent hyperinsulinemic hypoglycemia of infancy, Prematurity

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INTRODUCTION

Hypoglycemia is one of the most common metabolic complication in neonates. Healthy as well as sick neonates are predisposed to hypoglycemia during the first week of life [1, 2]. Factors that further lead to hypoglycemia are prematurity, perinatal asphyxia, small for gestational age (SGA) and infant of diabetic mother (IDM). Insulin secretion depends upon the activity of potassium channels in pancreatic beta cells, which are influenced by fluctuations in blood glucose levels. Persistent hyperinsulinemic hypoglycemia of infancy (PHHI), a disorder of glucose metabolism is an important cause for refractory hypoglycemia in infants. It is characterized by inappropriate hyperinsulinemia and persistent hypoglycemia. Unregulated hyperinsulinemia despite hypoglycemia is a hallmark of PHHI [3], which usually manifests within the first three months of life. PHHI has both autosomal recessive inheritance (1:40,000–50,000 live births) and sporadic occurrence [3, 4]. McQuarrie first described PHHI [5, 6]. Hyperinsulinemic-hyperammonemia (HI/HA) syndrome, a rare disorder of Glutamate dehydrogenase mutation, leads to recurrent hyperinsulinemic-hypoglycemia and this has autosomal dominant mode of inheritance [7]. Early recognition and prompt intervention is crucial, as uncorrected hypoglycemia in neonatal period can lead to occipital cortical damage and subsequent cortical blindness.

CASE REPORT

A 1300 grams, 30 weeks, male neonate born by C-section, had normal extra-uterine transition (APGAR score: 6 and 7 @ 5 and 10 minutes), but developed respiratory distress soon after birth requiring mechanical ventilation (MV) for 10 days. Chest X-ray showed congenital pneumonia. On 11th day of life, the neonate had recurrent apneic episodes, jitteriness and seizures. On initial evaluation, blood sugar levels were low (20 mg/dL) and remained low despite high glucose infusion rate (GIR 12 mg/kg/min).

Hypoglycemia was attributed to prematurity, the very low birth weight (VLBW) status and sepsis. There was no

facial dysmorphism, ambiguous genitalia or micropenis. However, the hypoglycemia persisted despite adequate antimicrobial coverage and the neonate was investigated for refractory hypoglycemia.

Important clinical conditions that lead to persistent hypoglycemia are congenital adrenal hyperplasia (CAH), hyperinsulinemic conditions (PHHI), inborn errors of metabolism (IEM) and pituitary insufficiency (genetic, metabolic, endocrinal). Hence, the neonate was evaluated for refractory hypoglycemia and these conditions. There was no hyponatremia, no hyperkalemia and 17 OHP levels were normal, thus ruling out congenital adrenal hyperplasia. Further evaluation showed normal serum cortisol (12.7 µg/dL), growth hormone (29.3 ng/mL) and thyroid profile ruling out adrenal insufficiency, hypopituitarism and hypothyroidism. Similarly, metabolic screening for IEM was normal. Paper chromatography of the urine in butanol acetic acid and water, showed normal excretory pattern. Ferric chloride test, 2,4-dinitrophenyl hydrazine test and nitroprusside screening for homocysteine test were negative. There was no metabolic acidosis in arterial blood gas analysis. There was hyperammonemia (serum NH₃ levels 273 µg/dL (normal ammonia levels 40–80 µg/dL)) along with hyperinsulinemia. However, blood lactate levels were normal (lactate 14.4 mg/dL). Serum insulin levels during hypoglycemic episode were 0.7 milli units/L. Detectable insulin levels during hypoglycemic episode is an inappropriate insulin response, often seen in PHHI. Hence, abdominal imaging with ultrasound and contrast-enhanced CT scan was done to look for pancreatic hyperplasia and insulinomas. However, the imaging did not reveal pancreatic hyperplasia. However, micro insulinomas could not be ruled out in this case. Persistent hypoglycemia, hyperinsulinemia along with hyperammonemia could suggest hyperammonemic hyperinsulinemic syndrome in this neonate. Cranial ultrasound was done to screen for any intracranial pathology which was normal. The child was started on oral diazoxide, 10 mg/kg/day in three divided doses, in view of hyperinsulinemic hypoglycemia and the infant showed response within a week of initiating the therapy. Blood sugar levels were maintained well above 60 mg/dL. At sixth month, the infant was maintaining blood glucose levels on oral diazoxide. The infant required laser photocoagulation for retinopathy of prematurity at one month of life, but the brain stem evoked auditory potentials were normal at sixth month, indicating intact hearing mechanism. The patient was continuously followed-up for sixth months and had no major developmental abnormalities.

DISCUSSION

Hypoglycemia is one of the common neonatal complication in the first few days of life and is associated with long-term neuromorbidity [1, 2]. Small for gestation

(SGA) premature neonates, infants born to diabetic mothers and those with perinatal asphyxia are at further risk for neonatal hypoglycemia. Index case had these known risk factors like prematurity, SGA status although there was no maternal diabetes. Glucose diffusion through the placenta takes place along the concentration gradient, resulting in 70–80% of glucose concentration in the fetus when compared to the mother [8]. As insulin cannot cross the placenta, the fetus secretes insulin independently [9]. When the umbilical cord is clamped, the glucose supply to the neonate is stopped, but the insulin production continues, leading to transient hyperinsulinemia coupled with lower plasma glucose levels. This response results in secretion of counter regulatory hormones (glucagon and cortisol), which enhance glucose production by glycogenolysis and gluconeogenesis [9]. As an adaptation to persistent hypoglycemia, the brain utilizes alternate substance like ketones.

Persistent hyperinsulinism, also known as persistent hyperinsulinemic hypoglycemia of infancy (PHHI), often manifests during first three months of life and is associated with inappropriately high insulin levels for the degree of hypoglycemia. It results from genetic defects in insulin production and pancreatic beta cell dysfunction [7, 10]. Plasma membrane sulfonylurea receptor (SUR1) and potassium channel (KIR6.2) mutations are autosomal recessively inherited [3] while glucokinase gene mutations have autosomal dominant inheritance. The hyperinsulinism hyperammonemia syndrome (HI/HA), an IEM, described by Zammarchi et al. in 1996 is a form of PHHI [11]. PHHI can also be associated with diffuse or focal adenomatoid pancreatic beta cell hyperplasia. This is often associated with absent ketone production. As the index case had refractory, symptomatic hypoglycemia, causes other than prematurity, very low birth weight status and sepsis were considered. Hence, the neonate was investigated for congenital adrenal hyperplasia (CAH), inborn errors of metabolism (IEM) and endocrinal causes like pituitary insufficiency. As these were ruled out, the infant was further evaluated for PHHI, which revealed hyperinsulinemia along with hyperammonemia. Hence, autosomal dominant variant of PHHI (HI/HA) was considered. This HI/HA syndrome often results from glutamate dehydrogenase (GDH)-GLUD1 gene mutation [7, 12] and is associated with persistently elevated serum ammonia levels (2–5 times over normal limit). However, the hyperammonemia is not associated with lethargy, irritability or altered sensorium, as in the index neonate. The infant was treated with oral diazoxide (10 mg/kg/day), as this is the treatment of choice for HI/HA syndrome. However, GLUD 1 gene mutations could not be done due to financial constraints. Though the effectiveness of diazoxide in neonatal period is not optimum [13], the index infant showed response to oral diazoxide and the glucose levels attained normally within few days of therapy. As PHHI can also be associated with diffuse or focal adenomatoid pancreatic beta cell hyperplasia, the index neonate was subjected to

abdominal imaging with ultrasound and CT scan, which did not reveal any pancreatic hyperplasia. Octreotide scan, the definitive diagnostic tool was not feasible due to financial limitations. Hypoglycemia, whether symptomatic or asymptomatic leads to permanent brain damage. Hence the aim of treatment is to maintain blood sugar levels (above 60 mg/dL), irrespective of its etiology. Therefore, the index infant was treated accordingly and did not have major developmental abnormalities at sixth month.

CONCLUSION

A preterm, 30 weeks, VLBW male neonate manifesting with refractory hypoglycemia and inappropriately elevated insulin levels, suggestive of persistent hyperinsulinemic hypoglycemia of infancy (PHHI). Presence of hyperammonemia along with hyperinsulinemia with response to oral diazoxide therapy, could suggest a rare entity of hyperinsulinemic-hyperammonemia (HI/HA).

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Author Contributions

Jillalla Narsing Rao – Substantial contributions to conception and design, Acquisition of data, Analysis & interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Swathi Chacham – Substantial contributions to conception and design, Acquisition of data, Analysis & interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Uppin Narayan Reddy – Substantial contributions to conception and design, Acquisition of data, Analysis & interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Janampally ravikiran – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Mohd Ahmeedulla Khan – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Jakkampudi Nagasravani – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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REFERENCES

1. Cornblath M, Odell GB, Levin GY. Symptomatic neonatal hypoglycemia associated with toxemia of pregnancy. *J Pediatr* 1959 Nov;55:545–62.
2. Collins JE, Leonard JV. Hyperinsulinism in asphyxiated and small for dates infant with hypoglycemia. *Lancet* 1984 Aug 11;2(8398):311–3.
3. Otonkoski T, Ammala C, Huopio H, et al. A point mutation inactivating the sulfonylurea receptor causes the severe form of persistent hyperinsulinemic hypoglycemia of infancy in Finland. *Diabetes* 1999 Feb;48(2):408–15.
4. Daneman D, Ehrlich RM. The enigma of persistent hyperinsulinemic hypoglycemia of infancy. *J Pediatr* 1993 Oct;123(4):573–5.
5. Wolfsdorf J. Hypoglycemia in infants and children: A pathophysiologic approach to diagnosis. *Pediatr Med* 1998;8–14.
6. Stanley CA. Hyperinsulinism in infants and children. *Pediatr Endocrinol* 1997;44:363–73.
7. Weinzimer SA, Stanley CA, Berry GT, Yudkoff M, Tuchman M, Thornton PS. A syndrome of congenital hyperinsulinism and hyperammonemia. *J Pediatr* 1997 Apr;130(4):661–4.
8. World Health Organization. Hypoglycemia of the newborn: review of the literature. Geneva, Switzerland: World Health Organization 1997. http://www.who.int/child_adolescent_health/documents/chd_97_1/en/index.html. Accessed April 24, 2013.
9. Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: A new look. *J Pediatr* 1986 Jul;109(1):114–7.
10. Schwitzgebel VM, Gitelman SE. Neonatal hyperinsulinism. *Clin Perinatol* 1998 Dec;25(4):1015–38.
11. Zammarchi E, Filippi L, Novembre E, Donati MA. Biochemical evaluation of a patient with a familial form of leucine-sensitive hypoglycemia and concomitant hyperammonemia. *Metabolism* 1996 Aug;45(8):957–60.
12. Stanley CA, Lieu YK, Hsu BY, et al. Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene. *N Engl J Med* 1998 May 7;338(19):1352–7.
13. Touati G, Poggi-Travert F, Ogier de Baulny H, et al. Long-term treatment of persistent hyperinsulinaemic hypoglycemia of infancy with diazoxide: A retrospective review of 77 cases and analysis of efficacy-predicting criteria. *Eur J Pediatr* 1998 Aug;157(8):628–33.

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