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Transient Hyperinsulinemic Hypoglycemia in Small for Gestational Age Infants in a Tertiary Care Hospital - A Retrospective Analysis

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Abstract: ***Aim: To study the clinical profile and course of hyperinsulinemic hypoglycemia (HH) in small for gestational age (SGA) infants. Methods: A Retrospective analysis of all SGA infants admitted in the neonatal unit of our hospital between February 2023 and June 2024 was done. The cases were SGA infants diagnosed with hyperinsulinemia (HI), and these were compared with the other SGA infants without HI. The antenatal and birth characteristics of the groups were compared, and the clinical profile and outcomes of the HH infants were described. Results: Seven cases of HH were identified among 174 hypoglycemic SGA infants (4%). The mean gestational age of the HH group was 38weeks and birth weight 1926grams, whereas the mean gestational age and birth weight of the other SGA infants was 37weeks and 2030grams respectively. There was no difference in the antenatal and birth characteristics of the 2 groups. The HH infants developed hypoglycemia (blood glucose < 40 mg/dl) from <1 hour to 50 hours of life. These infants were evaluated for hyperinsulinemia when the need for glucose infusion was > 6 mg/kg/min and persisted for >7 days. Hyperinsulinemia was diagnosed if plasma insulin levels was >2µU/ml when plasma glucose was <50mg/dl. The mean insulin level was 19.7µU/ml during hypoglycemia. Three infants received diazoxide and one received octreotide. Infants receiving drug therapy were weaned off intravenous glucose between 2.5 and 7 days after starting therapy and drugs were successfully withdrawn between 15 and 48 days of life (mean 31.5 days). In 3 infants, glucose requirement spontaneously decreased between 8.5 and 12 days, without requiring specific drug therapy. Conclusion: This study on transient HH in SGA infants, suggests that hyperinsulinemia in hypoglycemic SGA infants is not uncommon. No difference in the antenatal and birth characteristics were seen in the HH infants compared to the other SGA infants. Response to diazoxide/octreotide could indicate transient HH and successful withdrawal of drug therapy could be made.***

Keywords: Infant, Small for Gestational Age, Hyperinsulinism, Hypoglycemia, Diazoxide, Octreotide

Abbreviations:
SGA – small for gestational age
AGA – appropriate for gestational age
HI – Hyperinsulinemia
HH – hyperinsulinemic hypoglycemia
TNHI – transient neonatal hyperinsulinemia
IV - Intravenous

1. Introduction

Neonatal hypoglycemia is a common problem in small for gestational age (SGA) infants with a reported incidence varying from 24% to 36% (1 - 3). The cause of hypoglycemia has been variably attributed to lack of exogenous substrate supply, glycogen and adipose tissue depletion, immature gluconeogenesis and ketogenesis, adrenocortical insufficiency, failure of counter - regulatory hormone response and peripheral insensitivity to hormone action (4 - 5). Hyperinsulinemia (HI) is another cause that is well recognized since 1954 (6), but nevertheless is still widely regarded as being relatively uncommon. HI can be transient, prolonged or persistent. Hyperinsulinemia as a cause of hypoglycemia in SGA infants has been sparsely reported (7 - 10) and the reason for hyperinsulinemia in these infants has been attributed to perinatal stress. Neonatal onset hyperinsulinemic hypoglycemia (HH) is a major risk factor for neurodevelopmental impairment (11, 12) and has to be aggressively managed. We report a series of SGA infants presenting with hypoglycemia and who were subsequently diagnosed with hyperinsulinemia and compared them with the other SGA infants in the study

2. Methodology

This study was done in the neonatal unit of a tertiary care hospital in Southern India. Institutional ethical approval and informed consent were taken. During the study period of 16 months (February 2023 and June 2024), 174 SGA infants with hypoglycemia were identified. Seven among these 174 infants (4%) were diagnosed to have associated HI. Hypoglycemia was defined as blood glucose less than 40 mg/dl and was detected bedside by testing capillary whole blood, obtained by heel lancing, using an Optium Xceed glucometer (MediSense, Abbott Diagnostics, Bedford, MA). Laboratory confirmation of hypoglycemia was done in all the 7 study infants using a simultaneously drawn venous sample at the point of detection of hypoglycemia. All efforts were made to process the blood sample for glucose estimation as early as possible to minimize the time bound changes that may occur in the blood glucose value. Infants were classified as SGA if their birth weight (in grams) was greater than 2 SD below the mean for the corresponding

gestational age as per Modified Fenton's growth chart (13). The antenatal and neonatal characteristics of the SGA with or without HH is shown in table 1. The demographic characteristics of the HH infants are depicted in table 2.

Comparison of demographic characteristics of HH SGA with other SGA infants shows comparable gestational age and birth weight. The mean (SD) gestational age of the HH infants was 38 (1.9) weeks and the mean (SD) birth weight was 1926 (235) grams and this was comparable with the other SGA infants. The antenatal morbidities like diabetes and hypertensive disorders complicating pregnancy as well as the exposure to antenatal steroids and other medications with potential to alter the fetal neonatal glucose homeostasis, were also similar between the 2 groups. None of the HH infants required prolonged resuscitation at birth or had culture proven sepsis predating diagnosis of HH.

Thirty - seven (22.1%) infants in the non HH SGA group developed hypoglycemia during hospital stay. The infants were diagnosed during routine glucose monitoring by mean (SD) age of 14 (1.2) hours and none were symptomatic and required IV dextrose for > 3 days for maintaining euglycemia. In the HH group, the mean (SD) age of diagnosis of hypoglycemia was 20.7 (21.7) hours with infants developing hypoglycemia as early as 1 hour to as late as 50 hours of age.4 infants were inborn and the other 3 were referred for management of hypoglycemia at postnatal ages ranging between 5 and 11 days.

Outborn HH infants

The mean (SD) gestational age of the out born infants was 39.7 (0.6) weeks and the mean (SD) birth weight was 2067 (57.7) grams. Hypoglycemia was detected at a mean (SD) of 43 (7) hours in these infants and they were on a mean intravenous (IV) glucose infusion of 10.7 mg/kg/minute at referral. Out of the 3 infants referred, 2 were detected to have hypoglycemia while being evaluated for certain non - specific symptoms like lethargy and poor feeding whereas seizures prompted the detection in the third infant. But subsequently all the 3 infants had manifested seizures associated with recurrent hypoglycemic episodes before being referred to our hospital. Prior to the detection of hypoglycemia all the three infants were on exclusive breast feeding. One infant had documented high plasma insulin levels of 28.4 µU/ml and 13.6 µU/ml detected on day 4 and 9 of life with corresponding blood glucose levels of 33 mg/dl and 42 mg/dl respectively. This infant was initiated on oral diazoxide therapy at a dose of 20 mg/kg/day in 3 divided doses and was referred due to poor response to the drug.

Inborn HH infants

The mean (SD) gestational age of the inborn infants was 36.8 (1.5) weeks and the mean (SD) birth weight was 1821.2 (272) grams. Hypoglycemia was detected at a mean (SD) postnatal age of 3.7 (2.7) hours in these infants. Hypoglycemia was detected in all during routine screening and they were asymptomatic at the point of detection. All the study infants were on a pre - measured volume of expressed breast milk fed through spoon. Their breast milk was supplemented with formula milk in some cases where the breast milk output was considered to be less than adequate by the treating team.

Course in hospital of HH infants

All infants required high IV glucose infusion, ranging from 12 to 18 mg/kg/min. According to the unit's policy, investigations for persistent hypoglycemia were initiated once the requirement for IV glucose reached 8mg/kg/minute and persisted for greater than 7 days. During a subsequent hypoglycemic episode, plasma insulin levels were measured for hyperinsulinemia (HI) by chemiluminescence microparticle assay. Hyperinsulinemia was diagnosed in the presence of any detectable level of plasma insulin in the face of hypoglycemia (blood glucose <40 mg/dl). Apart from plasma insulin levels, plasma cortisol, thyroid hormone profile, serum ammonia and urine for reducing substances and ketone bodies were also investigated in the study infants. Samples for plasma cortisol assay were obtained before starting the infant on hydrocortisone. Additional investigations like amino acid profile assay and screening for organic acidemias was done in 3 infants due to the associated metabolic acidosis and inborn errors of metabolism were excluded in them.

Table 3 shows the blood profiles documented during hypoglycemia. The plasma insulin was inappropriately high during hypoglycemia and the plasma ammonia levels normal in all infants. Plasma cortisol levels were found to be high in the 3 outborn infants, who had received hydrocortisone in the referring hospital and had cortisol measured only after referral. Among the other infants, 2 had normal levels and 2 had low values. The other investigations were normal in all infants.

Following the diagnosis of HI, diazoxide was started in three infants, two of whom, responded with a decrease in intravenous glucose infusion requirement within the next 48 hours. The third infant required subcutaneous octreotide to be started simultaneously that resulted in a rapid reduction of glucose infusion rate within the next 24 hours. The fourth infant was started on subcutaneous octreotide directly due to non - availability of diazoxide. All the 4 infants were off intravenous glucose infusion between 3 and 7 days after institution of therapy and off diazoxide and / or octreotide between 15 and 48 days from the start of therapy.

In the rest of the infants, who were not initiated on any specific pharmacological therapy, the intravenous glucose requirement decreased spontaneously between 8.5 and 12 days from the onset of hypoglycemia. Two infants had recurrence of hypoglycemia following culture proven sepsis but responded well to antibiotics and were successfully weaned off glucose infusion in the next 48 hours.

3. Results and Discussion

Hyperinsulinemia (HI) in infants is arbitrarily divided into transient and persistent based entirely on the underlying etiology. Transient forms of HI generally recover within 1 month and have been well described in infants of diabetic mothers (15), perinatal asphyxia (16), in those born with Beckwith - Wiedemann syndrome (17), and following rhesus hemolytic disease (18). In this study, we have

described the transient nature of the clinical course of 7 SGA infants with hyperinsulinemic hypoglycemia (HH) emphasizing the existence of a syndrome of transient neonatal hyperinsulinemia (TNHI) in SGA infants.

In the current report, we did not detect any significant differences in the antenatal and neonatal demographic characteristics of the HH - SGA and the non - HH SGA infants. Non - HH SGA infants were diagnosed earlier with hypoglycemia compared to HH - SGA infants (14 hours vs.20.7 hours). Otherwise, we did not detect any significant differences in the antenatal and neonatal demographic characteristics of the HH - SGA and the non - HH SGA infants.

Lonlay et al (11) reported the largest data series on HI with 98 out of the 175 reported cases presenting in the neonatal period. The HI in 12 of their infants completely recovered within 1 month suggestive of TNHI. Although limited information is available in the report about those 12 infants (mean birth weight 3533g, gestational age not specified), 9 of them did not require diazoxide, while the other three were sensitive to diazoxide. Yap et al (19) reported 2 AGA infants without any known risk factors for hypoglycemia, who developed HI within 6 hours of life, requiring high IV glucose infusion rates. Both these cases responded well to diazoxide and drug therapy was discontinued in one case at day 12 of life. Apart from the transient nature of HI in some infants, both these reports also suggest that response to diazoxide can predict early resolution of HI.

An earlier study from north India had shown that HI is an important cause of hypoglycemia in SGA infants (20). Although prolonged HI has been reported more commonly in SGA infants (9, 21 - 24), the literature is sparse on transient forms of HI in such infants. Collins and Leonard reported hyperinsulinemic hypoglycemia within 2 days of life in three SGA infants, requiring diazoxide for 2 months before complete recovery (7). In a subsequent study, these investigators observed evidence of HI in 5 out of 27 SGA infants, suggesting that the disorder is not uncommon (8). Nili also reported HI in an asphyxiated SGA baby, in whom complete recovery occurred at 35 days of life without institution of any drug therapy (25). Apart from these case reports, this syndrome of TNHI in SGA infants has largely been under recognized.

In the current study the HH - SGA out born infants were not similar to the inborn infants. Two out of the 4 inborn infants had low Apgar scores at birth suggesting that perinatal asphyxia could be playing an important role in the persistence of hypoglycemia. Moreover, in comparison to the out born infants, 2 out of 4 inborn study infants were premature raising the possibility of prematurity induced HI, which has been previously reported (26). Contrary to the asymptomatic presentation in inborn infants, the out born infants had manifested with seizures. This could be due to intensive monitoring leading to hypoglycemia being picked up and treated early and aggressively in inborn infants, which often does not happen in referred babies. The association of HI with maternal gestation hypertension and intra - partum glucose administration has also been reported earlier (20, 23). Three infants received steroids before being referred to our institution. Poor response to steroids was seen in all 3 infants, again suggesting HI, where steroid responsiveness is not generally seen. In 3 infants, complete recovery was seen even without drug therapy. This is not unusual because there have been earlier reports where complete resolution had occurred even without drug institution (19, 23, 25). This could also be because of our policy of investigating for HI when need for high glucose infusion persists for > 7 days and not earlier. But all these 3 infants had received prolonged IV glucose infusion, when it could have been stopped earlier had diazoxide been started. Considering the requirement for high glucose infusion rates, limitations with peripheral venous access in small infants and the risk of infections with central venous catheters, our goal should be early withdrawal of IV glucose, which could only be achieved if diagnosis and appropriate drug therapy is started earlier. Thus, it might be prudent investigating any case of hypoglycemia for HI, in otherwise well SGA infants, if there is a high glucose requirement (> 8 mg/kg/min) and irrespective of post natal age, as proposed by some experts (27).

All infants in our study had plasma cortisol measured. The three outborn infants had received steroids for hypoglycemia from referring hospitals. Hence, they had manifested with high cortisol levels. Among the infants who did not receive steroids, two had low plasma cortisol levels. This could be explained by the fact that infants with hyperinsulinemic hypoglycemia fail to generate an adequate serum cortisol counter - regulatory hormonal response in response to falling blood glucose. This appears to be related to the lack of drive from the hypothalamic - pituitary axis, with inappropriately low plasma ACTH concentrations at the time of hypoglycemia (28). Apart from this, all the study infants had a normal plasma ammonia concentration, excluding the possibility of syndrome of hyperinsulinemic hyperammonemic hypoglycemia (29). The fact that the infants responded to diazoxide implies that the K^+ATP channel must be intact and the excessive insulin secretion must originate through another mechanism. A genetic defect is unlikely considering the transient nature of hypoglycemia. A more likely cause could be a transient alteration in β - cell regulation of insulin secretion induced by perinatal stress, although it remains only a hypothesis.

The symptomatic presentation of hypoglycemia in outborn infants highlights the failure of recognition of hypoglycemia as an important entity in SGA infants. The subsequent clinical course of the infants in our series has shown that syndrome of TNHI in SGA infants is an important hypoglycemic disorder that appears to be more common than generally recognized. Hence it is always necessary to entertain the possibility that hyperinsulinemic hypoglycemia in SGA infants will resolve completely and spontaneously. It is difficult to exclude the relative contributions of birth asphyxia and prematurity in the pathogenesis of HI in some of the infants. However, the course in the other infants who did not have these risk factors, suggests that being SGA is in itself a peril. In our infants, follow - up fasting tests to document full resolution of the HI were not done. Also follow up neurological monitoring of these infants should de done to detect any neuro - developmental sequelae.

4. Conclusion

In conclusion, hyperinsulinemia should be considered in case of prolonged hypoglycemia in SGA infants. Onset is later than in other SGA infants and the requirement of GIR > 8mg/kg/min and persisting > 7 days, increases the likelihood of hyperinsulinemic hypoglycemia. Diazoxide sensitivity is likely to differentiate this syndrome from other persistent forms of HI in SGA infants.

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Table 1: Antenatal and neonatal characteristics of SGA infants with or without HH

Parameter	HH SGA (n=7)	Other SGA (n=167)	p
Antenatal Characteristics			
Age of mother in years, Mean (SD)	27.1 (2)	28.3 (2.9)	0.25
Gestational diabetes n requiring medical treatment n (%)	1 (14)	35 (20.9)	0.10
Exposure to beta blockers	Nil	Nil	NA
Hypertensive disorders complicating pregnancy n (%)	4 (57)	75 (44.9)	0.39
Antenatal steroid exposure n (%)	1 (14)	40 (23.9)	0.19
Birth and Neonatal Characteristics			
Mode of delivery n (%) LSCS	6 (85.7)	138 (82.6)	0.26
Gestational age in weeks Mean (S. D)	38 (1.9)	37.1 (2.8)	0.18
Birth weight in grams Mean (S. D)	1926 (235)	2030 (186)	0.34
APGAR scores 5 minutes Mean (S. D)	7 (1)	8 (0.8)	0.48
Required prolonged resuscitation at birth n (%)	2 (28.5)	32 (19.1)	0.09
Culture positive sepsis in first week of life n (%)	Nil	15 (8.9)	NA
Died n (%)	Nil	4 (2.3)	NA

Table 2: Demographic profile of HH SGA study infants

	1	2	3	4	5	6	7
Place of birth	Outborn	Outborn	Outborn	Inborn	Inborn	Inborn	Inborn
Gestational age (wks)	41	39	40	35	38	36	38
B. Wt (g)	2100	2000	2100	1540	1954	1656	2135
Sex	M	M	M	M	F	F	M
Maternal problems	Gestational HTN	NK	NK	Gestational HTN	Heart disease	Gestational HTN	Antiphospholipid antibody syndrome
Mother received IV glucose during labour	Yes	No	No	Yes	Yes	No	Yes
Apgars (1min, 5 min)	NK	NK	NK	3, 7	8, 9	5, 8	9, 9
Onset of hypoglycemia (hours)	44	36	50	< 1 hour	2	6	6
Level of Illness	Well	Well	Well	Well	Well	Well	Well
Presentation	Symptomatic	Symptomatic	Symptomatic	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic
SGA status	Asymmetric	Asymmetric	Asymmetric	Asymmetric	Asymmetric	Asymmetric	Asymmetric
Drug treatment	Steroid, diazoxide, octreotide	Steroid	Steroid, diazoxide	No therapy	Diazoxide	Diazoxide	No therapy
Postnatal age at which pharmacotherapy was discontinued (d)	48	NA	20	NA	15	43	NA
Post natal age at which IV glucose infusion stopped (d)	19	11	13	8.5	9.5	18	14.5

HTN – hypertension; NA – not applicable; NK – not known; M - male; F - female

Table 3: Blood and urine chemistry of HH - SGA study infants

	1	2	3	4	5	6	7
Insulin µU/ml	25.4	11.8	16.2	13.4	23.1	29.7	18.3
Plasma glucose (mg/dl)	42	45	38	33	18	11	46
Serum Cortisol (µmol/l)	893	1027	689	263	47	68	189
Ammonia (µmol/l)	56	26	30	42	18	12	41
Urine reducing substances	Negative for all						
Urine ketone bodies	Negative for all						