Case Report

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Paediatrics Section

Congenital Hyperinsulinemic Hypoglycaemia of Infancy- A Case Report

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ABSTRACT

The most common cause for neonatal persistent hypoglycemia is Congenital Hyperinsulinism (CH) which is characterised by low blood glucose with an inappropriately higher insulin level. A one-day-old male baby, third born to non consanguineous parents delivered at term, small for gestational age, detected to have hypoglycaemia at 24 hours of life. He was established on breastfeed. Glucose infusion was started initially with Glucose Infusion Rate (GIR) of 4 mg/kg/min and increased according to the blood glucose values. Euglycaemic state was achieved with GIR of 14 mg/kg/min and intravenous hydrocortisone. Critical blood samples were sent when GIR was at 8 mg/kg/min which showed detectable insulin with high ammonia and normal cortisol levels. Hence, the diagnosis of transient hyperinsulinemic hypoglycaemia of infancy with hyperammonemia was considered and treated with oral diazoxide and sodium benzoate. GIR could be tapered and was discharged on breastfeed and medications. During follow-up at three months of age, the medications were stopped under glucose monitoring. He had normal growth and development at 12 months of age. Neonatal hypoglycaemia should be aggressively managed to prevent neuroglycopenia and its resultant neurodevelopmental disability. When GIR is more than 8 mg/kg/min, hyperinsulinism should be suspected for appropriate therapy.

Keywords: Glucose infusion rate, Hyperammonemia, Newborn

CASE REPORT

A one-day-old male baby shifted on day 1 of life from postnatal ward to intensive care for asymptomatic hypoglycaemia detected on routine sugar monitoring since baby was small for his gestational age. He was born to a low risk G3P2L2 mother at 37 weeks by vaginal delivery with birth weight of 2270 grams and with good Apgar scores (8 and 9 at 1 and 5 minutes respectively). Direct breastfeeding was established within one hour of delivery and he was on capillary blood sugar monitoring since two hours of life. He had normal general and systemic examination with no dysmorphism. Midline defects such as cleft lip and cleft palate were absent and no neurocutaneous markers. Examination of external genitalia revealed normal penile length and bilateral descended testis.

At 24 hours of life his capillary sugar was low (32 mg/dL). Despite a trial of breastfeeding, child had low capillary sugar. Simultaneously estimated Random Blood Sugar (RBS) was 30 mg/dL hence glucose infusion was started at the rate of 4mg/kg/min. GIR was titrated according to serial RBS monitoring. He required intravenous glucose up to 14 mg/kg/min and intravenous hydrocortisone 5 mg/kg/day to maintain euglycaemia (maximum RBS was 54 mg/dL) at 84 hours of life. Critical samples were sent when RBS was 30 mg/dL and requiring GIR of 8 mg/kg/min at 36 hours of life which showed detectable insulin levels (4.11 IU/L), high ammonia (518.3 mcg/dL), normal cortisol (3.8 mcg/dL) and absent ketones in urine. His metabolic work-up revealed normal lactate, blood gas and no detectable abnormal metabolites in the blood and urine by Tandem Mass Spectrometry and Gas Chromatography Mass Spectrometry (TMS/GCMS) [1]. Hence, the diagnosis of transient hyperinsulinemic hypoglycaemia of infancy with hyperammonemia was considered. C-peptide level was 1.41 ng/mL and Insulin: C-peptide ratio was more than 1, ruling out insulinoma. Abdomen ultrasound scan showed normal pancreas. Oral diazoxide 15 mg/kg/day and oral sodium benzoate (250 mg/kg/day) was started on day 11 of life and hydrocortisone was stopped. Subsequently he became euglycaemic with serial blood sugar values above 70 mg/dL and maximum sugar recorded being 114 mg/dL. GIR could be tapered gradually by 2 mg/kg/min every 4 hours with glucose monitoring. Day 13 he remained euglycaemic on direct breastfeed, oral diazoxide and sodium benzoate.

Baby was discharged on day 14 of life. On follow-up at three months of life, baby was readmitted for tapering diazoxide under sugar monitoring which was successful. Diazoxide was decreased to 10 mg/kg/day and then to 5 mg/kg/day and stopped over next three days. Duration of re-admission was 8 days during which he was monitored for glucose every 6th hourly. Parents were educated about warning signs of hypoglycaemia and home monitoring of sugars. At 3, 6 and 12 months of age, his growth and development were appropriate for age. Plan was to perform Magnetic Resonance Imaging (MRI) brain and genetic testing in follow-up but couldn't be done due to COVID-19 pandemic.

DISCUSSION

The foremost cause of persistent hypoglycemia in newborn is CH which is characterised by detectable levels of insulin during hypoglycaemia [2,3]. It is caused by mutations in one of at least eight different genes responsible for beta-cells function in glucose homeostasis leading to profound and recurrent hypoglycaemia [4]. CH manifests as persistent hypoglycaemia with absent ketonemia. Defect of signal transduction pathway coupled with unregulated insulin secretion occurs as the result of mutation in two subunits of Adenosine Triphosphate (ATP) sensitive potassium channel (KATP). Hyperammonemia occurs due to defect in glutamate dehydrogenase activity [4,5]. The second most common form of CH is Hyperinsulinemic hyperammonemia (HI/HA) [5]. This report aims to create awareness on this condition and update its management. HI can be classified as transient (THHI) that resolves within six months of age and persistent (PHHI) that persists beyond six months. The latter variety is usually linked with Beckwith-Wiedemann syndrome, Kabuki syndrome and Soto syndrome [6].

HI should be considered when hypoglycaemia occurs while infant is already on glucose infusion. In these infants, beta cells in the pancreas secrete insulin regardless of the blood glucose concentration resulting in hypoglycaemia particularly when fasting. This hypoglycaemia is devastating as the brain is deprived of the fuels (glucose, ketones, and lactate) on which it is critically dependent. Also, HI prevents glycogenolysis, gluconeogenesis and ketogenesis which are the compensatory mechanisms for hypoglycaemia. Such deprivation with absent homeostasis leads to cell damage and the resultant features are seizures and coma. Infants manifest with neurodevelopmental disorders like seizure disorder, learning disabilities, cerebral palsy, visual and hearing defects. Mortality is seen in unrecognised cases [7,8].

This case report discloses the clinical presentation of CH, its diagnosis and highlights on the early diagnosis and early interventions done to reduce the risk of neurological long term sequalae. Challenges in diagnosis and management of CH like availability of diazoxide and access for genetic analysis were highlighted by the researchers in their report [9]. Sáeza J et al., have reported a case of refractory hypoglycaemic neonate who underwent surgical resection of pancreatic focus to maintain euglycaemia [10]. This report is on asymptomatic neonate. Several authors have analysed genetic component for CH which was not possible in the reported infant [11-13]. The cornerstone of treatment of hyperinsulinism is involving either one of the following: inhibitors of insulin secretion (diazoxide, somatostatin, epinephrine or calcium channel inhibitors), antagonists for insulin effect on tissues (glucocorticoids, epinephrine, glucagon, or growth hormone), and destruction of islet cells (surgery) [14]. Surgical treatment is usually chosen after unsuccessful medical management. First line and the only drug approved by Food and Drug Administration (FDA) is diazoxide for treatment of persistent hypoglycemia caused by hyperinsulinism [15]. This drug acts by binding to the Sulphonyl Urea Receptors (SUR2) subunit of the KATP channel that are present mainly in cardiac, smooth and skeletal muscles, and also in the brain. Hyperammonemia is a feature of many inborn errors of metabolism such as urea cycle enzyme defects, organic aciduria and fatty acid oxidation defects [16]. In this infant, hyperammonemia was asymptomatic and reduced by administering sodium benzoate. Prognosis of THHI or PHHI depends essentially on early and correct diagnosis, and on immediate therapy for treatment of hypoglycaemia. Prompt surgical treatment may also be necessary. Infants with persistent hypoglycaemia should be promptly evaluated in whom the primary objective is to attain optimal glycemic control at the earliest and to be maintained for prevention of neurological disabilities. Genetic analysis in such cases guides in management, predicts long term prognosis, and helps the clinician to be vigilant in identifying associated co-morbidities like epilepsy. Also, it allows for screening of asymptomatic family members and offer appropriate genetic counselling.

CONCLUSION(S)

The HI/HA stands as one of the causes for persistent hypoglycaemia. Ammonia should be included in the critical samples and if hyperammonemia is noticed HI/HA needs to be considered if other causes of elevated ammonia levels are ruled out. Currently, available oral formulations of diazoxide are difficult to administer in newborns and hence the authors recommend preparation of formulations that facilitate easy administration.

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