Postgraduate Journal of Pediatrics and Adolescent Medicine
Volume 1, Issue 1 - 2025, Pg. No. 59-61
Peer Reviewed & Open Access Journal

Interesting Cases

Transient Neonatal Hyperinsulinemia: Timely Diagnosis and Treatment

Megha P[1], Ashwini RC[2]

[1]Postgraduate, [2]Associate Professor, Division of Neonatology, Department of Paediatrics, Bapuji Child Health Institute, JJM Medical College & RC, Davangere, Karnataka, India.

I N F O

Corresponding Author:
Ashwini RC, Department of Paediatrics, Bapuji Child Health Institute, JJM Medical College & RC, Davangere, Karnataka, India.
E-mail Id:
dr.wini@gmail.com
Orcid Id:
https://orcid.org/0000-0002-2342-0759
How to cite this article:
Megha P, Ashwini RC. Transient Neonatal Hyperinsulinemia: Timely Diagnosis and Treatment. Postgrad J Pediatr Adol Med. 2025;1(1):59-61.

Date of Submission: 2025-11-27
Date of Acceptance: 2025-01-28

A B S T R A C T

Hyperinsulinism (HI) is the leading cause of persistent hypoglycaemia in newborns. Diazoxide inhibits the secretion of insulin and is the first-line drug for controlling hypoglycaemia secondary to prolonged transient hyperinsulinemia or permanent hyperinsulinemia, thus it prevents hypoglycaemia and the permanent neurological sequelae associated with hypoglycaemia. We report two neonates who presented with hypoglycaemia which was refractory. Investigations revealed hyperinsulinism and both neonates responded to treatment with oral diazoxide. Timely screening and prompt treatment of hypoglycaemia are recommended as it is linked to poor neuro developmental outcomes in the long term.

Keywords: Persistent Hypoglycaemia, Refractory Hypoglycaemia, Hyperinsulinism, Diazoxide

Introduction

Hypoglycaemia is defined as "blood glucose level (BGL) of less than 45 mg/dl" as per World Health Organization. In neonates, hypoglycaemia is the most commonly encountered metabolic disorder with incidence varying between 1.3-3 per 1000 neonates.[1] Most of these cases are transient episodes and may remain asymptomatic. It responds readily to treatment and is associated with an excellent prognosis.

Inadequately elevated insulin level due to inappropriate insulin secretion by pancreatic islet β cells in the presence of hypoglycaemia is defined as hyperinsulinism (HI). The inability to maintain normal levels of blood sugar in spite of glucose infusion rate of 12 mg/kg/min and failure to achieve euglycaemia even after 7 days of therapy is defined as refractory and persistent hypoglycaemia respectively.[2] In HI, at low Random Blood Sugar (RBS) levels (critical level), insulin levels > 2mIU/ml, low levels of plasma free fatty acids and ketones are seen. Symptomatic hypoglycaemia (including seizures) and HI causing persistent hypoglycaemia are associated with possible long term neurologic sequelae. A recent systematic review by McKinlay C et al. to assess neurodevelopmental outcomes in neonates exposed to neonatal hypoglycaemia concluded that it was associated with executive dysfunction and visual-motor impairment in early childhood and with numeracy skills, low literacy, and neurodevelopmental impairment later.[3] Thus, hypoglycaemia requires timely assessment and prompt treatment.

Though hyperinsulinism should be evaluated in case of persistent or refractory hypoglycaemia, especially among IUGR neonates, it is often missed. We here report two such neonates to highlight the importance of work up and timely initiation of treatment to ensure prompt glycaemic control and in the long-term, an intact neuro developmental survival of these neonates.

Case Reports

Case 1

A three-day-old male child born at a gestational age of 35 weeks to a non-consanguineously married primigravida mother by preterm vaginal delivery with a birth weight of 2100 gm, was received with complaints of lethargy, poor feeding, jitteriness, and hypoglycaemic episodes. Vitals and systemic examination were normal with admission GRBS of 34 mg/dl. Mother had hypothyroidism since 5th month of pregnancy. There was no history of gestational diabetes mellitus (GDM), preeclampsia (PE), or anaemia in the antenatal period. There was no family history of diabetes or hypoglycaemia or unexplained death in the early neonatal period. Antenatal scans were normal. Dextrose bolus was given and subsequently, GIR 6 mg/kg/min was started with a maximum GIR requirement of 8 mg/kg/min.

Blood gas analysis and workup for IEM were normal. Enteral feeds (30 ml/kg/day) at third hourly intervals were started on day 4 of life, with RBS monitoring feeds increased by 30 ml/kg/day. GIR was gradually tapered and stopped over the next 48 hours. The baby started accepting breastfeeds by day 7 of life. He again developed hypoglycaemia with a blood sugar of 45 mg/dl on day 8. The critical sample sent then showed lab sugar of 35 mg/dl and serum insulin of 2.4 mIU/L. The neonate was restarted on GIR of 6 mg/kg/min (total fluid rate of 90 mL/kg/day of 10% Isolyte-P) and feeds (60 mL/kg/day) were continued. In view of persistent hypoglycaemia due to hyperinsulinism (detectable insulin levels at low RBS records), tab diazoxide was started at a dose of 8 mg/kg on day 9 of life. Subsequent sugar values were within the normal range. GIR was tapered and once the baby reached full feeds (150 ml/kg/day), intravenous fluids were stopped. Gradually, tapering of dosage of diazoxide with sugar monitoring was begun from day 14 of life and stopped by day 23 of life. Subsequently, the neonate continued to be euglycaemic on breastfeeds in follow-up of 14 days and had normal developmental milestones appropriate for age at 3 months, 6 months, and 9 months follow-up.

Case 2

A term male neonate was born to a non-consanguineously married primigravida mother by caesarean section (indication: severe pre-eclampsia) with a birth weight of 2340 gm and no maternal history of GDM, hypothyroidism, or anaemia in the antenatal period was received. The antenatal scan showed pericardial effusion and Doppler showed reduced end-diastolic flow. There was no history of diabetes, hypoglycaemia or unexplained death in the family in the early neonatal period in 3 generation pedigree. The baby was received at 6 hours of life with jitteriness, decreased activity, and respiratory distress with ascites. Blood sugar at admission was 26 mg/dL. The neonate was started on GIR of 6 mg/kg/min. Complete haemogram, serum electrolytes, and RFT were normal. ABG was normal and lactate was 0.9 mmol/l. He was also evaluated for the cause of non-immune hydrops as there was no blood group incompatibility. Initial ultrasound abdomen and thorax showed minimal fluid. Ultrasound cranium was not suggestive of TORCH infections, 2D ECHO showed dilated all four chambers with no pericardial effusion. TORCH panel showed negative results. As the baby was not maintaining sugars, GIR was increased to 12.5 mg/kg/min by 64 hours of life to maintain euglycaemia which was administered through the central line. The critical sample sent at the time of low blood sugar showed a lab RBS value of 30 mg/dl with insulin level of 12.3 mIU/ml and low cortisol levels. He was started on injection hydrocortisone. Once he started maintaining sugar levels, GIR was gradually tapered and Inj hydrocortisone stopped after 3 days. In view of persistent hypoglycaemia with hyperinsulinism, oral diazoxide was started at a dosage of 8 mg/kg/day on day 6 of life. Once on full enteral feeds (150 ml/kg/day) by day 14 of life, the dose of diazoxide was gradually tapered over the next 5 days and then stopped. IEM screening panel was normal. Subsequently, all GRBS readings were within the normal range on direct breastfeeds and measured spoon feeds given second hourly. Blood glucose monitoring was continued for further two weeks period during which the baby continued to be euglycaemic. He is now 11 months old with age-appropriate developmental milestones.

Discussion

Both of our patients who presented with hypoglycaemia had risk factors such as late prematurity and term gestation with intrauterine growth restriction. They were noted to have hyperinsulinism which responded to a short course of oral diazoxide along with adequate breastfeeding and measured feeds.

Transient HI often occurs in the neonatal period and resolves within a few weeks to months of life.[1] Early management of HI is important for the prevention of neurological damage. Glycaemic control is achieved through glucose infusions and hydrocortisone. Diazoxide is used as a first-line treatment for long term therapy in HI or somatostatin analogues can be used in case of diazoxide unresponsiveness.[4]

Diazoxide is an FDA-approved first-line drug and it is the only oral therapy for hypoglycaemia caused by persistent HI with a dose range of 5 to 15 mg/kg/day. The dose should be gradually increased by 2.5-5 mg/kg/day if hypoglycaemia continues after 3-5 days. Once off diazoxide, RBS needs to be monitored closely for at least 5 days.[5] The adverse effects of diazoxide include tachycardia, oedema, hypertrichosis, hyperuricemia, leucopenia, feeding intolerance, heart failure, and pulmonary hypertension.[6] Thiazide diuretics can

be used to reduce the risk of fluid overload and pulmonary hypertension.

Hu S et al. reported in their study that out of 44 patients with congenital hyperinsulinism, the blood glucose level increased to normal gradually about 7-10 days after being treated with diazoxide in case of 36 patients. 8 subjects still had persistent hypoglycaemia when the diazoxide dose was raised to 15 mg/kg/day. It indicates that they were unresponsive to diazoxide.[7] Davidov AS et al. reported a good response to diazoxide therapy in neonates with prolonged hyperinsulinemic hypoglycaemia.[8] A recent RCT was conducted involving 30 small for gestational age newborns with hyperinsulinemic hypoglycaemia. They were given either diazoxide or placebo. The study revealed that the neonates who were given diazoxide attained control of hypoglycaemia faster and also needed a shorter duration of IV fluids.[9]

Conclusion

Early recognition of hypoglycaemia and quick treatment helps to prevent long-term neurological impairment. Cases with persistent or refractory hypoglycaemia should be promptly investigated to rule out hyperinsulinism. Diazoxide should be used as an early treatment option to ensure an intact long term neurodevelopmental outcome.

Conflict of Interest: None

References

1. Kallem VR, Pandita A, Pillai A. Infant of diabetic mother: what one needs to know? J Matern Fetal Neonatal Med. 2020;33:482-92. [PubMed] [Google Scholar]
2. Jain A, Aggarwal R, Jeevasanker M, Agarwal R, Deorari AK, Paul VK. Hypoglycemia in the newborn. Indian J Pediatr. 2008;75:63-7. [PubMed] [Google Scholar]
3. Shah R, Harding J, Brown J, McKinlay C. Neonatal glycemia and neurodevelopmental outcomes: a systematic review and meta-analysis. Neonatology. 2019;115:116-26. [PubMed] [Google Scholar]
4. Falzone N, Harrington J. Clinical predictors of transient versus persistent neonatal hyperinsulinism. Horm Res Paediatr. 2020;93:297-303. [PubMed] [Google Scholar]
5. Brar PC, Heksch R, Cossen K, De Leon DD, Kamboj MK, Marks SD, Marshall BA, Miller R, Page L, Stanley T, Mitchell D, Thornton P. Management and appropriate use of diazoxide in infants and children with hyperinsulinism. J Clin Endocrinol Metab. 2020;105:543. [PubMed] [Google Scholar]
6. Gray KD, Dudash K, Escobar C, Freel C, Harrison T, McMillan C, Puia-Dumitrescu M, Cotton CM, Benjamin R, Clark RH, Benjamin Jr DK, Greenberg RG; Best Pharmaceuticals for Children Act-Pediatric Trials Network Steering Committee. Prevalence and safety of diazoxide in the neonatal intensive care unit. J Perinatol. 2018;38:1496-502. [PubMed] [Google Scholar]
7. Hu S, Xu Z, Yan J, Liu M, Sun B, Li W, Sang Y. The treatment effect of diazoxide on 44 patients with congenital hyperinsulinism. J Pediatr Endocrinol Metab. 2012;25:1119-22. [PubMed] [Google Scholar]
8. Davidov AS, Elkon-Tamir E, Haham A, Shefer G, Weintrob N, Oren A, Lebenthal Y, Mandel D, Eyal O. Higher C-peptide levels and glucose requirements may identify neonates with transient hyperinsulinism hypoglycemia who will benefit from diazoxide treatment. Eur J Pediatr. 2020;179:597-602. [PubMed] [Google Scholar]
9. Balachandran B, Mukhopadhyay K, Sachdeva N, Walia R, Attri SV. Randomised controlled trial of diazoxide for small for gestational age neonates with hyperinsulinaemic hypoglycaemia provided early hypoglycaemic control without adverse effects. Acta Paediatr. 2018;107:990-5. [PubMed] [Google Scholar]