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# Management of persistent hyperinsulinemia hypoglycemia of infancy

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**Abstract**--We describe a case of a 9-day-old boy weighing 3800 grams and experiencing recurrent hypoglycemia and seizures was referred to the hospital. The patient's condition improved when the medical staff administered a dextrose bolus. The laboratory test results showed hyperinsulinemia and hypo-ketonemia. Furthermore, the ultrasonography of the head indicates that the brain was impaired. The glucose infusion rate (GIR) was increased to 20 mg/kg BW/min. The medical staff administered a nifedipine and octreotide syringe pump to overcome this condition. According to the patient's response, the Octreotide syringe pump was replaced with subcutaneous injection, and the glucose infusion rate was decreased gradually. The patient was then discharged with no episode of hypoglycemia or seizure. Meanwhile, an experience of developmental and neurological sequelae was also confirmed.

**Keywords**---persistent hyperinsulinemia, hypoglycemia in infancy, hyperinsulinemia hypoglycemia.

## Introduction

Persistent Hyperinsulinemia Hypoglycemia Infancy (PHHI) is an uncommon hereditary disorder characterized by uncontrolled insulin secretion than hypoglycemia. The clinical manifestations of this condition vary widely, ranging from mild state to irreversible brain damage.<sup>1</sup> Because of the heterogeneous clinical presentation and the medical response of diffuse PHHI lesions, surgery is not considered the optimal treatment for this disorder. The first-line medication for PHHI often uses diazoxide, which is widely unavailable in some centres and institutions. However, octreotide can be utilized as an alternative therapy.<sup>2</sup> Near-total pancreatectomy, which removes 95–98% of the pancreas, was traditionally performed on patients with an unimproved medical condition or at high risk of developing adverse side effects. Several research with long-term patient follow-up indicate that near-total pancreatectomy is related to an increased risk of diabetes mellitus and malabsorption. Although most medically treated individuals are relaint on medication, clinical remission sometimes occurs.<sup>3</sup>

## Case Presentation

A 9-days-old male infant weighing 3800 grams was referred from a district hospital with the chief complaints of seizure and recurrent hypoglycemia in the first 48 hours of life. The patient experienced a seizure, which improved after dextrose administration. Furthermore, experiences of jitters, lethargy, cyanosis, and breathing problems were confirmed. According to the medical record, the infant was delivered by caesarian section at 38-39 weeks gestation from a 34 years old mother. The Apgar score, birth weight, and body length of the infant were reported to be 8-9, 3900 grams, and 51 cm, respectively.

At admission, the patient's heart rate, respiration rate, temperature, and oxygen saturation were 144 bpm, 45 per minute, 37°C, and 98%, respectively. Meanwhile, there was no experience of anaemia, jaundice, cyanosis, and dyspnea. The patient was alert with isochoric pupils, positive light, and normal physiological reflexes. There were no meningeal signs, lateralization, and pathological reflex. Additionally, snout, rooting, grasp, glabellar, and palmomental reflexes were positive.

The patient's body weight, height, and head circumference of 3,800 kg, 53 cm, and 36 cm, respectively. Furthermore, the laboratory test revealed that the fasting insulin, serum cortisol, ketone, sodium, potassium, calcium, chloride were 13.87 mU/L (<2 $\mu$ U/L), 68.448 nmol/L (119.23-618.24 nmol/L), 0.2 mg/dl (> 2mmol/L), 143 mmol/L (136-145 mmol/L), 4.0 mmol/L (3.5-5.7 mmol/L), 10.4 mmol/L (8.5-10 mmol/L), 105 mmol/L (98-107 mmol/L), respectively.

## Discussion

The patient was admitted with the chief complaints of seizure and recurrent hypoglycemia. HH-related Hypoglycemia can be caused by unregulated insulin secretion from pancreatic  $\beta$  cells, which could lead to persistent hypoglycemia,<sup>4</sup> and the most concerning outcomes are severe neuro-developmental abnormalities.

The patient experienced a low serum cortisol level (2.48 ng/ml). Furthermore, Hussain's research stated that HI sufferers tend to have inadequate serum cortisol counter-regulatory hormonal response. The individual also had hypoglycemia and hyperinsulinemia, meaning that glucose infusion with a GIR of 13 mg/kg/min is required. The diagnostic criteria for PHHI are a high fasting insulin level, an episode of non-ketotic hypoglycemia, and a more significant GIR requirement (GIR >10) to maintain euglycemia. As previously stated, the symptoms of 'Whipple Triad' include hypoglycemia and low plasma glucose, which can be alleviated by normalization.<sup>5</sup> The existence of detectable quantities of insulin and C-peptide during hypoglycemia is a crucial component of HH, diagnosed with the presence of glycemic response to glucagon or octreotide support<sup>4</sup>, as well as the presence of ATP-dependent potassium channels dysfunction in pancreas  $\beta$  cells. Therefore, focal PHHI is considered to correlate with *SUR* gene, potassium channel genes mutation, and loss of maternal in the hyperplastic islets.<sup>6</sup>

The two standard treatment options for HH are medical and surgery. Symptomatic hypoglycemia can be treated with the administration of intravenous dextrose "mini-bolus" followed by continuous intravenous glucose.<sup>7</sup> The initial GIR for full-term and premature infants are 4 to 6 mg/kg/min and 6 to 8 mg/kg/min<sup>8</sup>, respectively. The hypoglycemic patient was treated with continuous glucose infusion with GIR of 8 mg/kg/min and 10% dextrose ~ 2 ml/kg mini-bolus. Furthermore, the sufferer received Diazoxide ~ 10 mg/kg BW/day orally in 2 to 3 divided doses as the first-line agent in HH management. Previous research showed this medication acts as a strong  $\beta$  cell K channel opener. Meanwhile, stabilizing open KATP channels could interrupt the release of insulin. The therapy was discontinued, and an octreotide syringe pump was administered due to the shortage of medicine used in this research. The patient who does not respond to diazoxide can use octreotide, a long-acting somatostatin analogue, as a substitution treatment choice. Somatostatin has long been considered an inhibitor of insulin secretion through hyperpolarization of  $\beta$  cells and direct inhibition of VGCC.<sup>8</sup> Thornton used octreotide at a dose of 5 mcg/kg every 6 to 8 hours, which was then titrated to 40 mcg/kg/day.<sup>9</sup> The patient received ~5 mcg/kg/day of an octreotide syringe pump, which was then gradually down-titrated before switching to subcutaneous octreotide.

Nifedipine is a treatment option for patients who do not respond to diazoxide. Calcium channels are present in the  $\beta$  cells of the pancreas, which could allow calcium to enter the cell. This condition can lead to an increase in intracellular calcium, which stimulates insulin secretion. Therefore, a channel blocker is being used to inhibit insulin secretion<sup>10</sup>, and the patient could be successfully treated with nifedipine at a dose of 0.5 to 0.8 mg/kg/day<sup>8</sup>. In this case, the patient survived by maintaining a >40 mg/dl blood glucose level but developmental and neurological sequelae were experienced. Although previous Electroencephalography (EEG) examination revealed normal findings, EEG and head Magnetic Resonance Imaging (MRI) examination is needed to define the characteristics of cerebral lesions and monitor the treatment to prevent brain damage. The patient also has endocrinology management follow-up for therapeutic evaluation and monitoring clinical laboratories; pancreatic function,

thyroid function, and liver function. It is important to have a regular Denver developmental screening test and head circumference measurement to monitor neurodevelopmental delay. Furthermore, medical rehabilitation interventions can be carried out immediately to prevent more severe delays.

### Conclusion

PHHI Children had a higher risk in neurological problems due to hypoglycemia. The patients suffered the sequelae of developmental and neurological despite the discontinuation of the treatment.

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### References

1. Ackermann A, Palladino A. Managing congenital hyperinsulinism : improving outcomes with a multidisciplinary approach. *Res Rep Endocr Disord* 2015;103–17.
2. Angelika D, Etika, R, Utomo MT, Mirha S, Handayani KD, Ugrasena, IDG. The glucose infusion rate of parenteral nutrition in the first week of life in preterm infants: an observational study. *Ital J Pediatr* 2021;47(219): 1-9
3. Chandran S, Rajadurai VS, Alim A, Haium A. Current perspectives on neonatal hypoglycemia, its management, and cerebral injury risk. *Research and Reports in Neonatology* 2015;5:17–30.
4. Damanik ST, Netty EP, Gunawan K, Irmawati M, Harianto A, Indarso F. Subtotal Pancreatectomy for Persistent Hyperinsulinemia Hypoglycemia in Neonate (A Case Report). *Folia Medica* 2003; 39(4): 269-6
5. Fatema K. Persistent Hyperinsulinemic Hypoglycemia of Infancy-Case Report. *Ijsrm.Human* 2018;9: 106-11.
6. Goel P, Choudhury SR. Review Article Persistent hyperinsulinemic hypoglycemia of infancy: An overview of current concepts. *J Indian Assoc Pediatr Surg* 2012;17:99–103.
7. Güemes M, Shah P, Silvera S, Morgan K, Gilbert C, Hinchey L, et al. Assessment of Nifedipine therapy in Hyperinsulinemic Hypoglycemia due to mutations in the ABCC8 gene. *J Clin Endocrinol Metab* 2016; 1-2
8. Khidoyatova, M. R., Kayumov, U. K., Inoyatova, F. K., Fozilov, K. G., Khamidullaeva, G. A., & Eshpulatov, A. S. (2022). Clinical status of patients with coronary artery disease post COVID-19. *International Journal of Health & Medical Sciences*, 5(1), 137-144. <https://doi.org/10.21744/ijhms.v5n1.1858>
9. Li J, Ma Y, Lv M, Zhou J, Liu B, Dong K. Persistent hyperinsulinemic hypoglycemia of infancy : a clinical and pathological study of 19 cases in a single institution. *Int J Clin Exp Pathol* 2015;8:14417–24.
10. Miharja, M. ., Setiawati, S. ., & Lubis, A. L. P. . (2020). How dangerous the Indonesian recession due to COVID-19 pandemic: review policy and strategy to recovery. *International Journal of Social Sciences and Humanities*, 4(3),

- 121–129. <https://doi.org/10.29332/ijssh.v4n3.470>
11. Pan S, Zhang M, Li Y. Experience of Octreotide Therapy for Hyperinsulinemic Hypoglycemia in Neonates Born Small for Gestational Age : A Case Series. *Horm Res Paediatr* 2015;84:383–7.
  12. Senniappan S, Arya VB, Hussain K. Review Article The molecular mechanisms, diagnosis and management of congenital hyperinsulinism. *Indian J Endocr Metab* 2013;17:19-27
  13. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Get vaccinated when it is your turn and follow the local guidelines. *International Journal of Health Sciences*, 5(3), x-xv. <https://doi.org/10.53730/ijhs.v5n3.2938>