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A Case Study on Neurological Outcome in Persistent Neonatal Hypoglycemia in Upper Middle-Income Country

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Abstract

In Indonesia, comprehensive management and monitoring of persistent neonatal hypoglycemia, is rarely reported. Despite the fact that there are studies highlighting the risk of neurodevelopmental disorders in neonates with hypoglycemia, there seems to be limited comprehensive case reports detailing both the early diagnosis and the long-term growth and development monitoring in these neonates. A unique case report of a 10-day-old male baby, born at a term weeks gestation via caesarean section, diagnosed with persistent hypoglycemia and suspect of hyperinsulinemia is presented in this study. At birth, the neonate exhibited hypoglycemia with a blood glucose level of 25 mg/dL, accompanied by a one-minute seizure characterized by upward gaze and stiffening of the extremities. The neonate cried after seizure and there was no loss of consciousness and was admitted to the NICU due to worsening respiratory distress. Based on the thoracic X-ray examination, he was diagnosed with transient tachypnea of newborn (TTN). Blood glucose levels were monitored every four hours, and tests for cortisol, thyroid and growth hormone and routine urinalysis were planned. Total parenteral nutrition (TPN) were given with intravenous antibiotics. At 6 months of age, the infant was diagnosed with intellectual disability by the growth and development social pediatric unit. At 7 months, the infant began undergoing physiotherapy. This case was followed for 7 months in total and the findings highlight the challenges in managing neonatal persistent hypoglycemia and the potential long-term developmental implications in neonates with early-life hypoglycemia, emphasizing the need for continual growth and development monitoring.

Keywords: Blood glucose, neonatal, neurodevelopmental, persistent hypoglycemi

Introduction

Hypoglycemia is one of the most common metabolic disorders in neonates, with an incidence ranging from 1 to 5 per 1,000 live births. Several risk factors have been identified in relation to neonatal hypoglycemia, including small or large for gestational age (SGA/LGA), intrauterine growth restriction (IUGR), prematurity, asphyxia, treatment in an intensive care unit, congenital syndromes such as Beckwith-Wiedemann, congenital hyperinsulinism, maternal diabetes mellitus (DM), and genetic familial hypoglycemia disorders.[1,2] A study in Bangalore, India, showed that the incidence of asymptomatic hypoglycemia in term neonates was 10%. Another study in Turkey found that the incidence of hypoglycemia in term neonates in the NICU was 7.6%, which is twice as high as in preterm neonates (15.3%). Persistent hypoglycemia can lead to damage to the central nervous system, with a continuous risk of neurodevelopmental disorders as a long-term consequence.[3,4]

Glucose levels <47 mg/dL are considered the cutoff, as defined by the American Academy of Pediatrics (AAP), based on a follow-up study of premature infants weighing <1,850 grams who developed neurodevelopmental disorders.[5,6] A prospective study in New Zealand found that neonates with a history of hypoglycemia had 2 to 3 times higher risk of impaired executive function and poor visual-motor skills at 4,5 years old. The research in Swedia showed that neonates with transient hypoglycemia have a 50% higher risk

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of neurodevelopmental disorder. Moreover, the group of neonates with hypoglycemia is 2 times higher had motor delay and 3 times higher had a delay in the development of cognitive function.[7]

This case report details the diagnosis, initial and follow-up management, blood glucose monitoring, and clinical improvement of a neonate diagnosed early with persistent hypoglycemia.[8] Additionally, the report includes the monitoring of the patient's growth and development. Written informed consent was obtained from the patient's parents for the publication of this case report, including the use of their photograp.

Case

A 10-day-old male neonate was born to a mother with a G4P3A1 status, at term gestation, via cesarean section due to twin pregnancy. The baby was diagnosed with persistent hypoglycemia, with suspected hyperinsulinemia.

The mother's pregnancy history was complicated by severe preeclampsia, with a blood pressure of 180/110 mmHg, and premature rupture of membranes for 16 hours. The APGAR scores at 1 and 5 minutes were 6 and 8, respectively. The patient's birth weight was 2,889 grams, with a body length of 49 cm and a head circumference of 34 cm. These measurements were appropriate for gestational age (SGA), based on the Lubchenco curve. During monitoring, the baby exhibited rapid breathing, with a down score (DS) of 2. Current Blood Glucose Serum levels are low at birth at 25 mg/dL. The patients also found a one-time seizure in the form of eyes looking up, stiff hands and feet with a duration of 1 minute. The patient cried following the seizure and showed no loss of consciousness. As respiratory distress worsened, the patient underwent endotracheal intubation, ventilator support, and was transferred to the NICU for further treatment. Serum blood glucose levels on day 1 were 3 mg/dL and 1 mg/dL, while peripheral blood glucose was undetectable. Chest X-rays revealed reticulonodular patterns in both lung fields, consistent with neonatal pneumonia, and the patient was diagnosed with transient tachypnea of the newborn (TTN). The patient was started on total parenteral nutrition (TPN) with a glucose infusion rate (GIR) of 12 mg/kg/min, intravenous antibiotics, and periodic blood glucose monitoring. At 3 days of age, the patient experienced two seizures with the same pattern as the previous ones. At that time, peripheral blood glucose levels were measured at 30 mg/dL, and respiratory distress showed improvement. Interventions included increasing the glucose infusion rate (GIR) above 12 mg/kg/min and close monitoring of blood glucose levels. On day 5 of treatment, there were no clinical signs of seizures, but serum blood glucose levels remained low at 43 mg/dL, with intravenous fluid GIR set to 19 mg/kg/min and dextrose at 22.5%. The patient was diagnosed with persistent hypoglycemia and was referred for consultation with the endocrinology division. The patient received 2 mg of hydrocortisone every 8 hours (30 mg per body surface area via sonde). After 5 days of ventilator support, the patient was successfully extubated and transitioned to continuous positive airway pressure (CPAP) for 2 days. DDuring subsequent observations, no further seizures were observed. At 6 days of age, the patient was tested for insulin, which returned

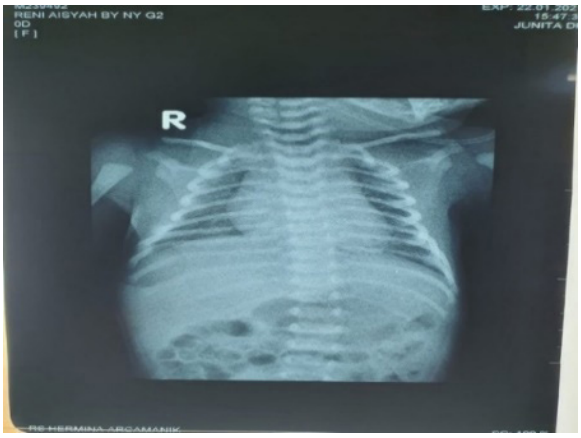
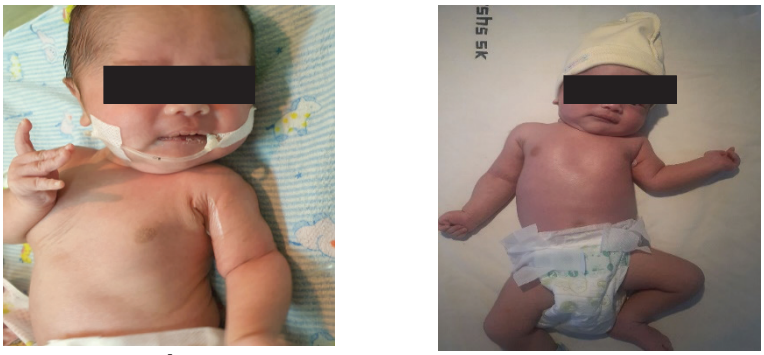


Figure 1 Thoracic X-ray of the Patient



A **B**

Figure 2 Clinical Photos of the Patient

a result of 28.4 nIU/mL. Additional treatment with octreotide (8 µg every 8 hours, 6 µg/kg body weight per day) was initiated subcutaneously. Despite the administration of octreotide and hydrocortisone, the patient experienced one episode of hypoglycemia, with a blood glucose level of 38 mg/dL. The patient responded well to octreotide, with no further episodes of hypoglycemia. At 7 days of age, a quantitative CRP test was performed, which returned a result of 164 mg/L. The patient was diagnosed with neonatal sepsis, and the antibiotic regimen was switched to meropenem (90 mg every 8 hours, 30 mg/kg body weight per day) administered intravenously. The glucose infusion rate was gradually reduced, and periodic blood glucose monitoring continued.

Upon arrival at Dr. Hasan Sadikin General Hospital Bandung, the patient appeared active with no signs of seizures, respiratory distress, or desaturation. The patient had been fed via a residual oral tube. A physical examination showed a State 5 status, with vital signs within normal limits. The anthropometric measurements at 10 days of age were: body weight of 3,150 grams, body length of 49 cm, and head circumference of 34 cm. The physical examination was otherwise within normal limits, and no hypoglycemic episodes were detected during peripheral blood sugar level monitoring. The management included fluid infusion with a GIR of 3.5 mg/kg/min, feeding formula milk (8 grams carbohydrates/100 mL, 65 kcal/100 mL) at 45 cc every 3 hours orally (120 mL/kg BW/day), continued meropenem antibiotics (day 6), hydrocortisone 2 mg every 8 hours, a decrease in octreotide dose to 5 µg every 8 hours (5 µg/kg BW/day) subcutaneously, and hydrochlorothiazide 7.5 mg every 12 hours orally. Patients are monitored for blood sugar

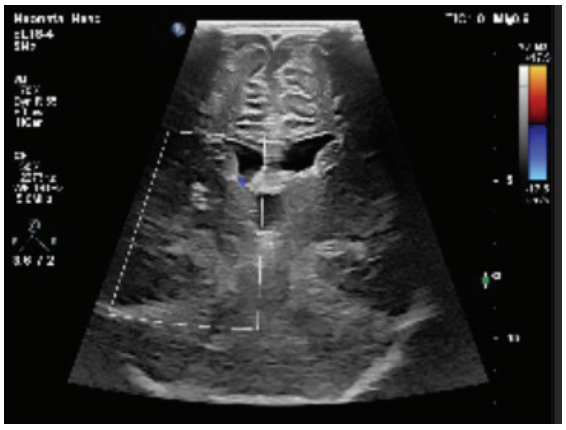


Figure 3 Patient Ultrasound Results

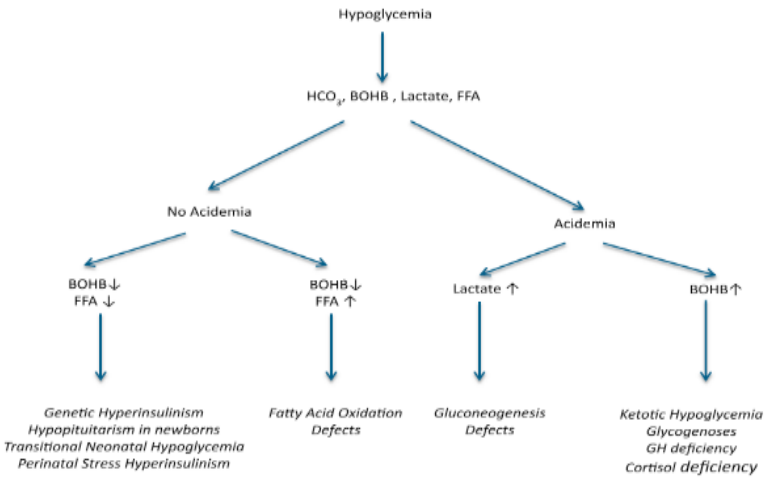


Figure 4 Hypoglycemia Diagnosis Algorithm Based on Clinical Information
Source: Thornton et al.[14]

levels every 4 hours, a plan to examine cortisol, thyroid hormone, growth hormone, and routine urinalysis.

Fluid infusion was discontinued on day 2 of treatment at the hospital, and the patient was transitioned to full oral feeding, receiving 60 cc every 8 hours (150 ml/kgBW/day). he results of the morning serum cortisol test were 1.8 µg/dL (normal range: 4.3–22.4 µg/dL), and the afternoon cortisol level was 1.9 µg/dL (normal range: 3.09–16.66 µg/dL). thyroid hormones (T3, FT4, TSHs) normal and ketones in negative urine. *Thyroid hormones* (T3, FT4, TSH) were within normal limits, and urine ketones were negative. Growth hormone testing could not be performed due to cost constraints. The planned octreotide dose was reduced to 0.5 µg/kgBW/day when blood glucose levels were >60 mg/dL. On day 2, the octreotide dose was reduced to 4.5 µg/kg BW/day and maintained for the next 3 days.

However, due to monitoring results showing two instances of blood glucose levels below 60 mg/dL (58 mg/dL and 41 mg/dL), the octreotide dose was increased back to 5 µg/kg BW/day and maintained until the end of treatment. The patient was treated in the intensive care unit for 8 days and was discharged with significant improvements. Upon discharge, the patient's weight was 3,150 grams. The patient's parents were educated on how to administer subcutaneous octreotide injections at home. Discharge medications included 2 mg of hydrocortisone every 8 hours, 5 µg of octreotide every 8 hours, and 7.5 mg of hydrochlorothiazide every 12 hours. A photo of the thoracic X-ray examination of the patient during treatment can be seen in Figure 1. Clinical photos of the newborn, taken during treatment at the hospital and at home, are shown in Figures 2a and 2b.

The patient was treated in NICU Level II (for neonates with stable medical conditions requiring ongoing monitoring) for 8 days and was discharged with improvements. After discharge, the patient was closely monitored and, at a 2-month follow-up, consulted a pediatric neurologist at Dr. Hasan Sadikin General Hospital. The assessment indicated the patient was a high-risk infant. The Hammersmith Infant Neurological Examination (HINE) tool was used, where a score of less than 50 categorizes an infant as high-risk. High-risk infants require early intervention programs for developmental stimulation, continuous monitoring, and comprehensive parental guidance and support. In 6th month the patient controlled social pediatric growth and development and had an impression with respect to intellectual disability and in the 7th months the patient underwent physiotherapy. The tools of monitored examination used KPSP *(Kuesioner Pra Skrining Perkembangan)*/developmental pre-screening questionnaire where a score is equal or less than 6, there is a possibility of developmental deviation, PEDS (Parents' Evaluation of Developmental Status) with the presence of two or more significant concerns in predictive domains (such as expressive language, receptive language, motor skills, self-help, or school skills) represent high concern, Denver II (Denver Developmental

Screening Test) with one/more delays or two/more cautions represent suspect for intellectual disability, CAT-CLAMS (Clinical Adaptive Test/Clinical Linguistic and Auditory Milestone Scale), DQ (Developmental Quotient) CAT where score below 70 suggesting developmental delay, DQ CLAMS where score below 70 suggesting developmental delay, and FSDQ where score below 70 suggesting developmental concerns.

Discussion

The Neonatology Coordination Working Unit of the Indonesian Pediatric Society (IDAI/I*katan Dokter Anak Indonesia*) defines hypoglycemia in neonates as a blood glucose level of <45 mg/dL. The World Health Organization (WHO) also uses a similar cut-off for defining hypoglycemia. According to the Pediatric Endocrine Society (PES), blood glucose levels <50 mg/dL are considered hypoglycemic in neonates during the first 48 hours of life, while blood glucose levels >60 mg/dL are recommended for neonates older than 48 hours. The American Academy of Pediatrics (AAP) recommends plasma glucose levels >45 mg/dL before feeding neonates. Immediate intervention should be carried out for neonates with plasma glucose levels <40 mg/dL if symptomatic, and for asymptomatic neonates, intervention is suggested for blood glucose levels <40 mg/dL (age <4 hours) or <50 mg/dL (age 4–24 hours).[5,9] Diagnosis of hypoglycemia can be done by examination of plasma blood sugar levels. A single examination of capillary blood sugar levels using a glucometer cannot diagnose hypoglycemia. The results of the examination of plasma blood sugar levels at the age of > 48 hours before getting the intervention are always below 45 mg/dL.[9] Based on plasma blood sugar levels, hypoglycemia criteria are met in neonates.

Newborns are particularly vulnerable to hypoglycemia due to the abrupt cessation of glucose supply from the placenta, while insulin production continues. In response to this transition, the body initiates a series of physiological mechanisms, including the release of counter-regulatory hormones such as cortisol and glucagon. These hormones stimulate processes like gluconeogenesis, glycogenolysis, and ketogenesis to restore blood glucose levels to normal ranges. Neonates less than a month, Small Gestational for Age, or *intrauterine growth restriction* (IUGR) have a risk of hypoglycemia due to limited fat and glycogen reserves and metabolic ability that has not matured.[1,10] Hypoglycemia that occurs in neonates who experience sepsis, asphyxia and perinatal stress is caused by an increase in metabolic processes and an increase in the need for glucose.[11] In this case the risk factors for hypoglycemia are not obtained. Hypoglycemia is possible in 10 % of babies of enough months at the age of 24–48 hours and is transitional.[5] A history of severe preeclampsia in the mother can be a provoking factor for the occurrence of neonatal hypoglycemia. Studies in Texas suggest neonates born to preeclampsia mothers have a greater risk of developing hypoglycemia (27.3%, p=0.003). This is related to the condition of placental hypoperfusion and the side effects of drugs used in cases of preeclampsia such as labetalol.[12] Newborns are prone to hypoglycemia in the first 24 hours of life and the majority are transitional. Clinical hypoglycemia varies from asymptomatic, the appearance of symptoms involving the autonomic (neurogenic) nervous system to brain dysfunction (neuroglycopenia). Signs and symptoms of neuroglycopenia are apnea, hypotony, seizures, weak suction reflexes, loss of consciousness to coma which can lead to death. Hypoglycemia is said to be persistent when blood sugar levels are abnormal by giving glucose *infusion fluid with a glucose infusion rate* (GIR) of 12 mg/kg/minute or lasting ≥5–7 days.[1,2,5]

Transient hyperinsulinemia typically resolves on its own within one week to several months after birth. In contrast, congenital hyperinsulinemia is caused by genetic mutations, most commonly in the ABCC8 and KCNJ11 genes, which disrupt the potassium-adenosine-triphosphate (K-ATP) channels, as well as in the glutamate dehydrogenase 1 (GDH) gene. Congenital hyperinsulinemia is often associated with macrosomia, while neonates with small for gestational age (SGA) are more likely to experience the transient form of hyperinsulinemia. However, a retrospective study conducted in Toronto suggests that 26.1% of neonates who experience transient hyperinsulinemia do not have common risk factors, such as being small for gestational age (SGA), having diabetic mothers, or experiencing fetal distress.[13-15] The diagnostic criteria for persistent hyperinsulinemia and hypoglycemia include insulin levels >3 mU/L, low β-hydroxybutyrate levels (<1.8 mmol/L), low free fatty acid levels (<1.7 mmol/L), and an increase in blood glucose levels >30 mg/dL following the administration of 1 mg of glucagon.[16,17]

In the case of hypoglycemia, it remains

unresolved after the age of 48 hours and the patient has also received intervention in the form of intravenous fluid administration with a GIR of >12 mg/kgBW/minute so that it is considered a persistent hypoglycemia.

The diagnosis in this case was confirmed through insulin level testing conducted during the hypoglycemia period, which showed very high levels (28.4 mIU/mL). During monitoring, a re-examination of fasting insulin levels was performed at 5 months of age, with results showing fasting insulin levels <1 uIU/mL, indicating improvement. Based on these findings, it can be concluded that the hyperinsulinemia experienced by the patient was transient.

Physiologically counter-regulatory hormones such as cortisol will increase in response to overcoming hypoglycemia conditions. A case report stated that children aged <3 months produced a poor cortisol response regardless of gestational age or insulin levels. Based on the results of a study in Toronto, low cortisol levels were also found in the group with transient hyperinsulinemia. The pathogenesis of this is still unclear, but it is suspected that in conditions of persistent hypoglycemia, there is a disruption of the counter-regulatory hormonal response.[15,18] Patients also found low cortisol levels at the beginning, namely 1.8 ug/dL (morning) and 1.9 ug/dL (afternoon). Cortisol parameters return to normal when evaluated at the age of 5 months.

Severe hypoglycemia (Blood sugar levels <45 mg/dL) and prolonged (>1 hour) I associated with the incidence of brain injury commonly referred to as hypoglycemia-induced brain injury (HIBI). The pathogenesis that plays a role is a decrease in the production of adenosine triphosphate (ATP) so that the Na+/K+ ATPase pump becomes inactive and depolarization of neuron cells occurs. Furthermore, there will be excessive release of the neurotransmitter glutamate, calcium influx into cells, and production of reactive oxygen species (ROS). Exposure to ROS will cause the formation of jejas on neuron cells.[19] The predilection areas of HIBI are the basal ganglia, thalamus, brainstem, sensorimotor cortex, and corticospinal jaras. As many as 25–50 % of neonates with HIBI experience permanent brain structure damage and cause sequelae of *neurodevelopmental* disorders. The most commonly found disorders are psychomotor delays, visual impairments and epilepsy.[20] Research in New Zealand states neonates with a history of hypoglycemia are 2–3 times more at risk of having a poor executive function and visual motor skills at the age of 4.5 years associated with attention deficit hyperactivity disorder (ADHD) and learning disorders later in life. Other research in Sweden shows that neonates with hypoglycemia transients have a 50% higher risk of developing neurodevelopmental disorders in the form of epileptic events, stereotypical behavior, and ADHD as much as 30–50%. In addition, this research states that the neonate group with hypoglycemia has a 2 times greater risk of developing motor delays in cognitive function.[7,8] Types of developmental disorders found in neonates with a history of hypoglycemia hyperinsulinemia vary including neurosensory disorders, impaired executive function, and impaired visual motor function.[2]

In this case, progression screening was carried out using the Denver Developmental Screening Test II. Patients are advised to be suspicious of three aspects, namely gross motor, fine motor, and language. Assessment with CAT/CLAMS was also carried out with the results of DQ CAT 65, DQ CLAMS 83.3, FSDQ 74.2 with the impression of intellectual disability suspects. Cognitive Adaptive Test (CAT)/Clinical linguistic and Auditory Milestone Scales (CLAMS) can be used to determine cognitive (language and visual-motor) development in children up to 36 months of age. In this application, CAT/CLAMS has proven to be easy to use and has validity equivalent to Bayley Scales of Infant Development is the gold standard. This tool has been used widely to assess neurodevelopmental with a sensitivity of 88 % and a specificity of 98 %. [21]

Supporting examinations are essential in patients with hypoglycemia. Ultrasound of the head in neonates with hypoglycemia often shows hyperechogenicity in the posterior subcortical white matter and cortex. In cases of congenital abnormalities, such as Kabuki syndrome, ventricular enlargement may also be observed. A study in China found that 30% of 66 neonates with hypoglycemia had abnormal cranial sonography results. Additionally, MRI scans may reveal extensive thinning of the cortex, particularly in the occipital lobe. The cortex of the posterior and occipital parietal lobes is especially vulnerable to damage in cases of neonatal hypoglycemia.[22]

In patients, it was also found that the failure to thrive was characterized by insignificant weight gain at the 5th to 6th month. Failure to thrive is associated with the incidence of hypoglycemia caused by inborn errors of metabolism such as glycogen storage disorders or abnormalities in the glycosylation process. In patients with hypoglycemia, the deficiency of essential calories

needed for growth increases the risk of nutritional disorders. In this case, the patient did not receive exclusive breastfeeding. Additionally, the patient was at an age where transition to complementary foods occurs, which further heightens the risk of acute nutritional disorders.[23]

Giving octreotide to neonates can increase the risk of growth disorders from side effects in the form of decreased *sec*retion of growth hormones, especially in premature babies. Another side effect is the possibility of necrotizing enterocolitis due to impaired splanchnic blood circulation.[16] The condition of hypocortisol in patients is overcome by the administration of hydrocortisone.[24] Growth disorders in patients can also arise from prolonged use of hydrocortisone. The patient underwent a vision function assessment, which showed normal results.

In conclusion, despite initial management with glucose infusion and hydrocortisone, the patient continued to experience hypoglycemia and seizures, necessitating further treatment with octreotide. Long-term follow-up revealed potential developmental concerns, emphasizing the need for continuous monitoring and early intervention in neonates with severe and persistent hypoglycemia. This case underscores the complexity of managing neonatal hypoglycemia and highlights the importance of a multidisciplinary approach to achieve optimal outcomes.

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