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Asymptomatic Hyperinsulinemic Hypoglycemia and Grade 4 Intraventricular Hemorrhage in a Late Preterm Infant

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Abstract

Hyperinsulinemic hypoglycemia (HH) has the potential to cause acute neurologic dysfunction and neurodevelopmental impairment. Parieto-occipital neuronal injuries have been reported in hypoglycemic infants, but intraparenchymal hemorrhage is rare. On day 5 of life, a late preterm infant was transferred to our care with recurrent asymptomatic hypoglycemia. Prior to arrival, plasma glucose levels were at a median of 1.25 mmol/L (22.5 mg/dL) in the first 6 hours of life, and he required a glucose infusion rate (GIR) of 22.6 mg/kg/min. Hyperinsulinism was confirmed in the presence of detectable insulin, low ketones, and fatty acid when hypoglycemic. A left grade 4 intraventricular hemorrhage (IVH) was noted in the cranial ultrasound scan during the workup for sepsis on the day of admission. However, magnetic resonance imaging of the brain on day 7 of life revealed extensive bilateral IVH. On day 9, he was initiated on diazoxide, and HH resolved within 48 to 72 hours, allowing increment of feeds while weaning GIR. Ventricular drain for post-hemorrhagic ventriculomegaly was advised but not performed. At 3 months, post-hemorrhagic ventriculomegaly was stable, and there were early signs of neurodevelopmental delay. After discontinuing diazoxide at 4 months of age, he passed an 8-hour fasting study confirming the resolution of HH. Severe hypoglycemia has been associated with cerebral hyperperfusion in preterm infants and potentially could cause IVH. Close monitoring and prompt intervention in preterm infants to prevent severe hypoglycemia are paramount. In addition to long-term neurodevelopmental follow-up, infants with recurrent hypoglycemia may benefit from neuroimaging and thereby early intervention if required.

Keywords

prematurity, hypoglycemia, hyperinsulinism, intraventricular hemorrhage, cerebral injury

Introduction

Hypoglycemia is a common neonatal metabolic problem, and the fetal-neonatal glucose transition is challenging for infants at risk of hypoglycemia, including infants of diabetic mothers (IDM), small for gestational age (SGA), and large for gestational age (LGA), and preterm infants. Even though the term neonatal hypoglycemia has existed for more than 80 years, the definition remains controversial and lacks rational evidence.[1] Term well infants navigate through the physiological nadir of 1.4 to 1.7 mmol/L (25.2-30.6 mg/dL) at 1 hour of age[2] utilizing hepatic glycogen stores, counter-regulatory hormone response, and complimentary milk feed. Earlier pathological studies by Banker[3] and Anderson et al[4] enlightened us on the distinct patterns of hypoglycemic brain injury, with a predisposition for parieto-occipital cortex and subcortical white matter involvement. Burns et al[5] described more varied patterns of cerebral injury. In addition to white matter injury of posterior regions, authors reported hemorrhage, middle cerebral artery infarction, basal ganglia abnormalities, and wider cortical involvement. Grade 4 intraventricular hemorrhage (IVH) in a hypoglycemic infant was only once reported in the literature.[6] We present this case to highlight the importance of measures to facilitate glucose homeostasis in infants at risk of hypoglycemia to prevent neuronal injury.

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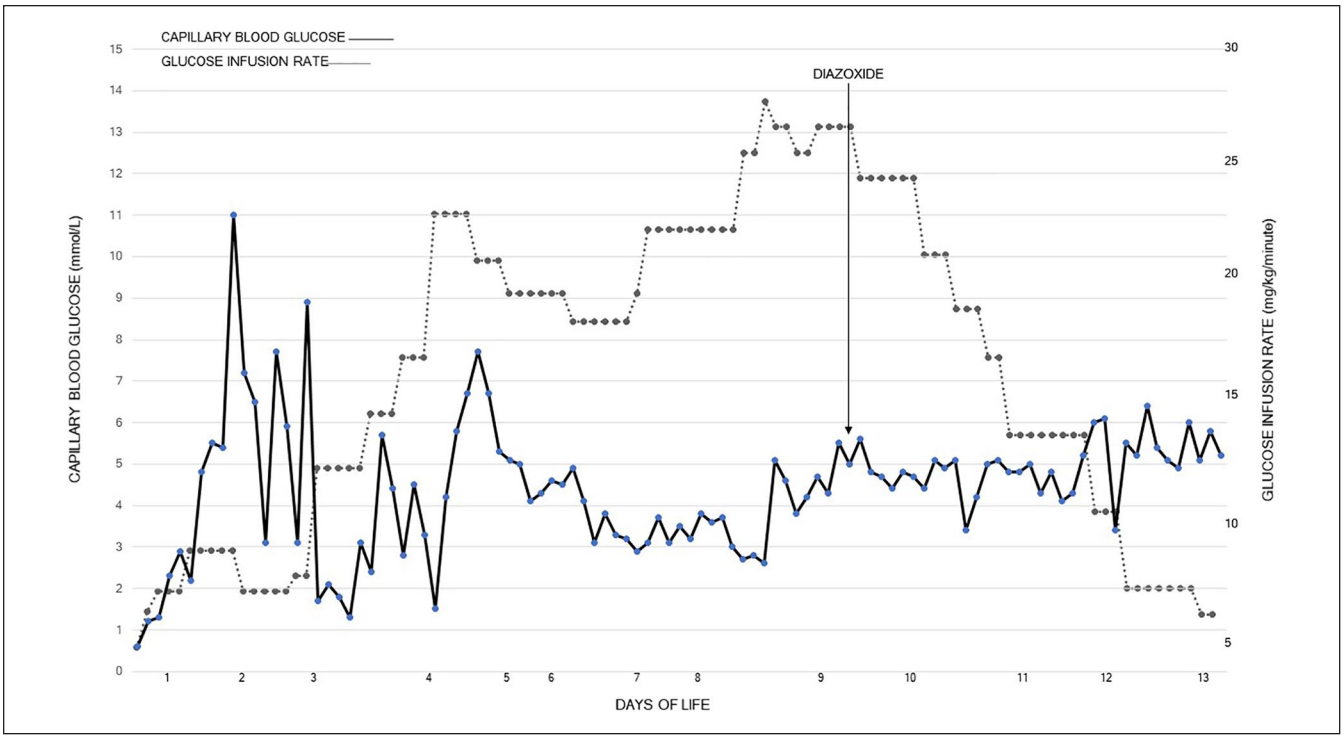

Figure 1. Blood glucose recordings and glucose infusion rate required for the infant from birth to day 13 of life, till optimal glucose control was obtained with diazoxide.

This case also raises the question of the need to do brain imaging of infants who had recurrent asymptomatic hypoglycemia.

Case Report

A male preterm infant was born elsewhere at 35^{+5} weeks gestation via normal vaginal delivery with a birth weight of 2238 g (27th centile) and head circumference of 32 cm (52nd centile). Apgar scores at birth were 9 at 1 and 5 minutes of life, respectively. There was no maternal history of diabetes, and her serologies were unremarkable. Antenatal scans were normal. Fetal cardiotocography (CTG) was unremarkable during labor.

The infant developed mild respiratory distress soon after birth and required headbox oxygen for the first 6 hours of life. His blood gas showed a pH of 7.42, PCO_2 of 31, BE −4, and lactate of 2 mmol/L. Chest X-ray was consistent with a diagnosis of transient tachypnea of the newborn. Ampicillin and gentamicin were initiated for presumptive sepsis. Blood counts and C-reactive protein (CRP) were unremarkable. Blood culture was sterile after 48 hours, and antibiotics were discontinued on day 3.

Milk feeds were offered soon after birth. Asymptomatic hypoglycemia with plasma glucose (PG) of 0.6 mmol/L (10.8 mg/dL) was detected at 2 hours of life. Dextrose infusion was initiated at a glucose infusion rate (GIR) of 6 mg/kg/min, after a mini bolus of 10% dextrose. He continued to remain hypoglycemic with a median PG level of 1.25 mmol/L (22.5 mg/dL) in the first 6 hours of life, and the GIR was progressively increased up to 22.6 mg/kg/min by day 4 of life (Figure 1). A serum insulin level of 7.6 mU/L was recorded on day 3 of life at the time of hypoglycemia (PG, 1.3 mmol/L [23.4 mg/dL]), consistent with a diagnosis of hyperinsulinism.

The infant was transferred to our tertiary level care hospital for Women and Children on day 5 of life to manage recurrent hypoglycemia. On admission, physical examination showed an alert male infant with intermittent tachypnea, and an isolated left bifid thumb with no other dysmorphic features. His capillary glucose level on admission was 4.2 mmol/L (75.6 mg/dL) on a GIR of 22.6 mg/kg/min. Attempts to wean the GIR resulted in hypoglycemic episodes requiring further escalation of GIR to 26 mg/kg/min on day 8 of life. Critical blood samples were obtained during an episode of hypoglycemia and confirmed hyperinsulinemic hypoglycemia (HH). Biochemical response included detectable insulin 10 mU/L (<1.6 mmol/L) while PG was 2.3 mmol/L (41.4 mg/dL) with low ketones 0.1 mmol/L (>0.6 mmol/L) and fatty acid <0.1 mmol/L (>0.5 mmol/L) levels. Adequate cortisol and growth hormone responses were obtained. Hepatic and renal function tests were unremarkable, and a cardiac evaluation before diazoxide initiation was reported as normal. On day 9, he was started on diazoxide at a dose of 3 mg/kg/day with hydrochlorothiazide (1 mg/kg/dose twice daily) to mitigate the water-retaining side effect of diazoxide.

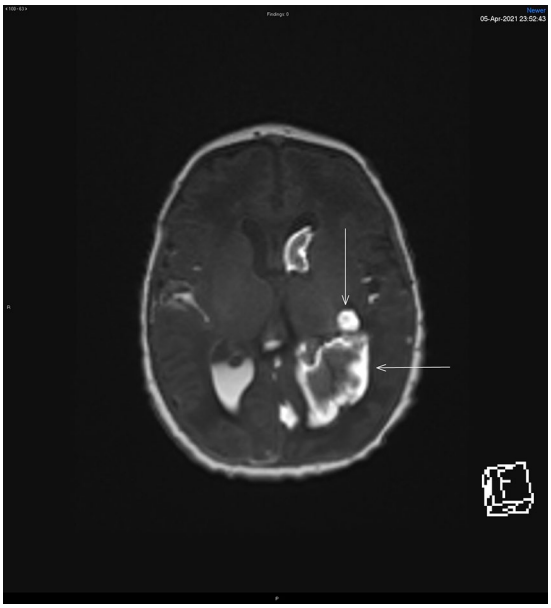

Figure 2. This T1-weighted axial magnetic resonance image shows the presence of blood in the lateral ventricles. The posterior horn of the left lateral ventricle is dilated with the blood products (horizontal arrow). Blood is noted extending from the left lateral ventricle to the cerebral parenchyma in keeping with a grade 4 hemorrhage (vertical arrow).

The infant's glucose profile stabilized within 48 to 72 hours, allowing weaning GIR to increase milk feeds (Figure 1).

He became febrile (38.2°C) on day 6 of life and was initiated on intravenous cloxacillin and amikacin. The full blood count showed a hematocrit of 48%, a white blood cell count of 11 000/10^9/L, and a platelet count of 224 $\times$ 10^9/L. Blood culture was sterile after 48 hours. On day 7 to 8 of life, due to recurrence of pyrexia, initiated further septic workup, and the antibiotic was escalated to cefotaxime. Blood counts and CRP were unremarkable, and a repeat blood culture was sterile. Surface swab cultures did not show any bacterial growth. Lumbar puncture was recommended, but parents declined. No dyselectrolytemia was noted in the birth hospital or in our center. Abdominal ultrasound scan (USS), done as part of septic workup, was negative. Cranial USS showed left IVH involving the left periventricular brain parenchyma (grade IV) with a sub-centimeter right germinal matrix hemorrhage.

Magnetic resonance imaging (MRI) of the brain on day 7 of life revealed extensive IVH involving lateral ventricles, left more than the right. On the left, it affects almost the entire left ventricle, and on the right, it involves the germinal matrix, with extension into the anterior horn. There is layering of blood in the right occipital horn (Figure 2). Hemorrhage was noted in the third and fourth ventricle. Hydrocephalus was noted in the left more than the right lateral ventricle. There was an intraparenchymal extension of the hemorrhage into the posterior limb of the left internal capsule and the left occipital lobe. There were areas of restricted diffusion in the bilateral periventricular regions representing ischemia/infarct. Magnetic resonance angiography (MRA) did not reveal flow-limiting stenosis in the anterior and posterior circulations. Neither the infant had clinical seizures nor abnormal cerebral function monitor record. Except for intermittent tremulousness, the infant was comfortable.

Occipitofrontal circumference (OFC) monitoring showed a progressive increase in size, and serial cranial USS demonstrated worsening ventricular indices (>97th centile) of bilateral lateral ventricles (Figure 3). Neurosurgical review advised placement of a Rickham reservoir but was declined by parents. Hence, the ventriculomegaly was managed conservatively and continued periodic assessment by the neurosurgeon with serial cranial USS.

Hematology review to identify an attributable cause for the extensive IVH advised coagulation studies (APTT/PT/INR), fibrinogen, Factors VIII, IX, XI, XIII, and vWF, and platelet function studies (CD41, 61) which were within normal limits.

Hyperinsulinism/hyperammonemia (HI/HA) syndrome was considered in the differential diagnosis. Metabolic workup including the serum ammonia, plasma lactate, serum amino acids, acylcarnitine profile, and urine organic acid was not suggestive of HI/HA or inborn errors of metabolism. He passed a universal newborn hearing screening.

Normoglycemia (3.5-7.0 mmol/L [63-126 mg/dL]) was maintained with oral diazoxide. He reached full enteral feeds by day 16 of life and was discharged home stable on day 34 of life on diazoxide after a successful 6-hour safety fasting study. Home capillary blood glucose (CBG) monitoring was advised, and the hypoglycemia team provided parental support. He passed an 8-hour resolution fasting study at 4 months of age after discontinuation of diazoxide.

Discussion

Grade 4 IVH is a serious complication of extreme prematurity. The case presented was a late preterm infant who had grade 4 IVH with recurrent asymptomatic hypoglycemia. To the best of our knowledge, this is the second report of neonatal severe parenchymal hemorrhage associated with HH.[6]

Around 10% of well-term infants encounter transitional hypoglycemia during the first 2 days of life.[7] Hypoglycemia in newborn infants is often asymptomatic, warranting a screening pathway for high-risk infants.[8] Neonatologists are challenged with the definition of hypoglycemia based on postnatal age. The Pediatric Endocrine Society (PES) and the American Academic of Pediatrics (AAP) has guidelines for screening neonates at risk of hypoglycemia.[9,10] PES guideline was expert opinion based on biological relevance, whereas AAP recommendation was expert opinion based on statistical observation. The recommended blood glucose thresholds for hypoglycemia by the AAP and PES were contrasting.[8]

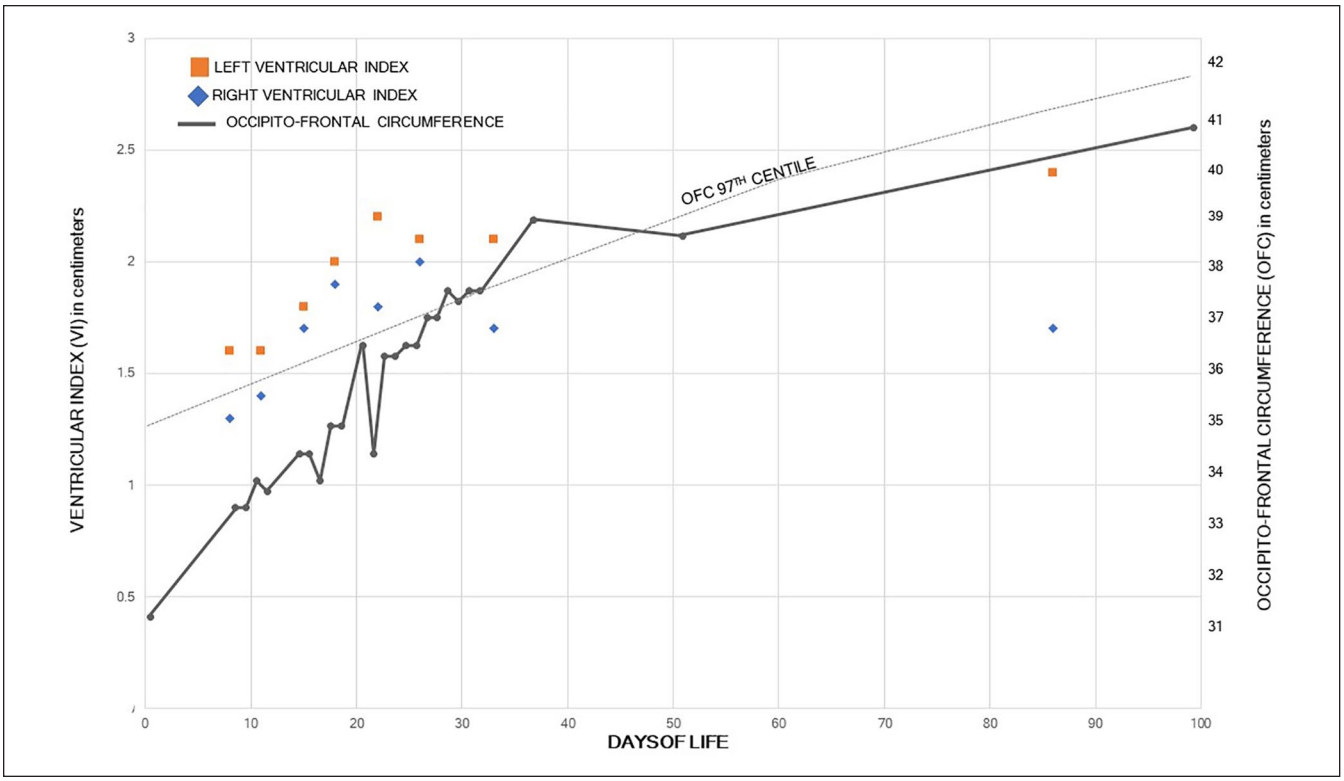

Figure 3. Record of VI and OFC of the infant. Both VI and OFC were above the 97th centile at term corrected gestation.
Abbreviations: VI, ventricular indices; OFC, occipitofrontal circumference.

Premature infants are at increased risk of hypoglycemia, and the cause is multifactorial. Preterm and SGA infants have lower glycogen stores and quickly deplete their energy reserves.[11] Other risk factors include the immaturity of enzymes required for glycogenolysis and gluconeogenesis. Hypoglycemia in SGA is attributed to perinatal stress hyperinsulinism (PSHI), which upscale the risk of prolonged hypoglycemia.[12] In our case, the critical risk factor for hypoglycemia was only prematurity as indicated by unremarkable fetal CTG with good Apgar scores and normal blood gas at 1 hour of age.

Hyperinsulinemic hypoglycemia is suspected in an infant with hypoglycemia needing a GIR of >10 mg/kg/min to maintain normoglycemia after 48 hours of life. In HH, critical blood samples show detectable insulin/C-peptide, low ketones, fatty acids, and appropriate cortisol and growth hormone response when hypoglycemic.[13] Two critical samples in our infant were diagnostic of HH.

The infant was transferred to our center on day 5 of life for further management. Diazoxide was initiated on day 9 of life, awaiting the septic workup results of a febrile episode. After sepsis was ruled out, diazoxide was initiated. Diazoxide is a K_{ATP} channel agonist inhibiting depolarization of the β-cell, preventing insulin release. Diazoxide responsiveness in an infant with HH confirms intact K_{ATP} channel. Inactivating mutations in the ABCC8 and KCNJ11 genes encoding SUR and Kir6.2 subunits, respectively, of the K_{ATP} channel account for 60% of all mutations identified, including 85% of diazoxide-unresponsive cases.[13]

In the present case, grade 4 IVH was detected on day 6 of admission. A febrile episode indicated a sepsis workup, and cranial USS was done as part of it. Severe IVH most commonly occurs in very preterm infants less than 28 weeks. In late preterm and term infants, IVH is rare, and its etiology and pathogenesis are also different. Reported causes include perinatal asphyxia, intracranial trauma following instrumental deliveries, hemorrhagic disease of the newborn, disseminated intravascular coagulation, coagulation disorders, hypernatremia, and sinovenous thrombotic events,[14] all of which were absent in our infant. The fragility of the germinal matrix vasculature and cerebral blood flow disturbances are the 2 key factors contributing to the genesis of IVH, especially in very low birth weight infants.[15] Levene et al[16] considered hypoglycemia as a key risk factor in the development of IVH in preterm infants of 30 to 34 weeks gestation. Mc Gowan[17] reported that IVH could occur with a moderate reduction in blood glucose levels in preterm infants following an increase in cerebral blood flow. Alderliesten et al monitored cerebral oxygen saturation ($rScO_2$) and cerebral fractional tissue oxygen extraction (cFTOE) and showed a relative cerebral hyperperfusion preceding IVH development in preterm infants using near-infrared spectroscopy. Authors concluded that

higher $rScO_2$ and lower cFTOE values indicate cerebral hyperperfusion before severe IVH.[18] Pryds et al[19] showed hemodynamic alteration with hypoglycemia in preterm infants (26-34 weeks). They reported a 37.5% increase in cerebral flow while hypoglycemic (CBG <1.7 mmol/L [30.6 mg/dL]), and the hyperperfusion lasted for more than 30 minutes after correction of hypoglycemia. Late preterm infants can increase cerebral blood flow by recruiting underperfused capillaries in response to hypoglycemia.[20] So, it is possible that cerebral hyperperfusion in preterm hypoglycemic infants can predispose them to IVH.

Brain injury following hypoglycemic episodes (≥1-episode, median PG of 1 mmol/L [18 mg/dL]) was reported by Burns et al[5] in 35 symptomatic newborn infants with a mean gestational age of 39.47 weeks. White matter and cortical abnormalities were noted in 94% and 51% of infants, respectively. Thirty percent of the infants in this cohort had white matter hemorrhages, highlighting the high incidence of cerebral hemorrhages with severe hypoglycemia. Neonatal hypoglycemia causes both white and gray matter injuries in the immature brain. The cerebral white matter has relatively low oxygen consumption; hence, it needs glucose supply to meet metabolic demands, elucidating the preponderance of white matter injury with hypoglycemic insult.[21]

Gu et al reported MRI brain abnormalities in 55% (36/66) of infants who had hypoglycemia. The authors concluded that abnormal MRI changes with an increasing number of days with hypoglycemia when compared to infants with normal MRI (mean day: 3.39 ± 4.20 vs 1.01 ± 0.80, $P < .001$).[22] These findings are similar to our case with recurrent hypoglycemic episodes of extremely low PG of <1.5 (27 mg/dL) in the first 5 days of life. Our case is an appropriate case for gestational age late preterm infant born by normal vaginal delivery with good Apgar scores and normal cerebral vascular anatomy demonstrated in MRA. And thus, by the process of exclusion of other etiological factors, the severe IVH in the reported case could be a consequence of recurrent/prolonged hypoglycemia.

A meta-analysis by Alkalay et al[23] indicated that PG concentrations <1.4 mmol/L (25.2 mg/dL) for several hours increased the relative risk for adverse neurodevelopmental outcome with a 21% incidence of significant neurological sequelae.

Earlier research by Koivisto et al[24] on symptomatic and asymptomatic hypoglycemic infants showed that brain injury is unlikely in the latter. Later, Koh et al[25] recorded abnormal evoked potentials in infants with asymptomatic hypoglycemia who had blood glucose levels below 2.6 mmol/L (46.8 mg/dL) and recommended maintaining glucose levels above 2.6 mmol/L. As noted in our asymptomatic infant, if there was no suspicion of sepsis, we would not have done brain imaging and could have missed the IVH.

Our infant is enrolled in the Early Intervention Programme for Infants and Children (EIPIC) of Singapore to minimize disabilities and increase the development growth potential.[26]

Recently, diazoxide-related adverse events are increasingly reported, including ≥ Bell stage 2 necrotizing enterocolitis, pulmonary hypertension, and pericardial effusion.[27] Diazoxide blocks the neuronal K_{ATP} channel causing hyperpolarization and thereby the potential to cause brain injury.[28] A normal hepatic and renal function tests and cardiac evaluation before diazoxide initiation are prerequisites to avoid complications.[29]

Regular follow-up appointments continue with neonatologist, endocrinologist, neurologist, and neurosurgeon. Diazoxide was allowed to self-wean with weight gain. He passed an 8-hour fasting study after 3 days of discontinuation of medication, confirming the resolution of HH at 4 months of age.

Conclusions

Our case underscores the importance of neuroimaging studies in high-risk late preterm and term infants who had prolonged or recurrent asymptomatic hypoglycemia and the need for long-term neurodevelopmental follow-up of such infants. Anticipation, prompt recognition, early diagnosis, and management of hypoglycemia are critical in preventing neuronal injury.

Consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or cases series.

Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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