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A typical pattern, really?

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Title figure:
Zebra skin (source: ohneski, Photocase)

INTRODUCTION

Hypoglycemia is a commonly encountered problem in neonatology. Newborns often have low blood glucose levels within the first few hours of life, usually without symptoms and without long-term consequences. However, infants with very low blood glucose concentrations, infants with prolonged hypoglycemia, and infants with recurrently low blood glucose concentrations are at risk of neurodevelopmental sequelae. Therefore, timely diagnosis and appropriate therapy are important to prevent brain injury that could lead to neurodevelopmental delay, learning difficulties and seizures (1).

We report the case of a female neonate, who was born by normal spontaneous vaginal delivery in a peripheral hospital at 39 1/7 weeks of gestation. The infant adapted well with Apgar scores 9, 10 and 10 at 1, 5 and 10 minutes, respectively. Her birth weight was 2900 g (P 28), birth length 50 cm (P 56) and head circumference 35 cm (P 71).

On day of life 3, the infant was noted to be weak, displaying feeding difficulties for more than 12 hours. Hypoglycemia was suspected and confirmed by bed-side blood glucose measurement with a concentration of 0.6 mmol/l. In addition, the infant was hypothermic (34.6° C). Antibiotic therapy was started for suspected sepsis.

The infant was transferred to the Neonatal intensive Care Unit at the University Children's Hospital of Basel for further evaluation and therapy. The infant was transported on CPAP due to apnea. The referring team felt these apneas could be a manifestation of seizures due to prolonged hypoglycemia.

On admission, laboratory examinations showed a negative CRP (0.9 mg/l) and a normal full blood count except for mild thrombocytopenia (88 G/l). Lactate concentration was slightly elevated (3.5 mmol/l). Despite the negative CRP, empiric antibiotic therapy was continued. Apneas resolved shortly after transfer, and the infant was taken off CPAP.

However, the patient experienced recurrent hypoglycemic episodes after admission. Glucose infusion had to be increased to a maximum glucose administration rate of 10.7 mg/kg/min. Underlying causes of hypoglycemia such as inborn errors of metabolism or hormone deficiencies were excluded by analyses of blood and CSF samples.

On admission, the infant had unilateral right-sided neonatal focal seizures, which ceased within 12 hours after initiation of phenobarbital therapy. Cerebral hemorrhage was ruled out by cranial ultrasound. The EEG revealed abnormal and discontinuous background activity. MRI of the brain was performed (image acquisition after feeding and in snug tucking, no anesthesia) and showed typical occipital and parietal signal changes of neonatal hypoglycemia in the acute stage as described by different authors (Fig. 1, 2) (2).

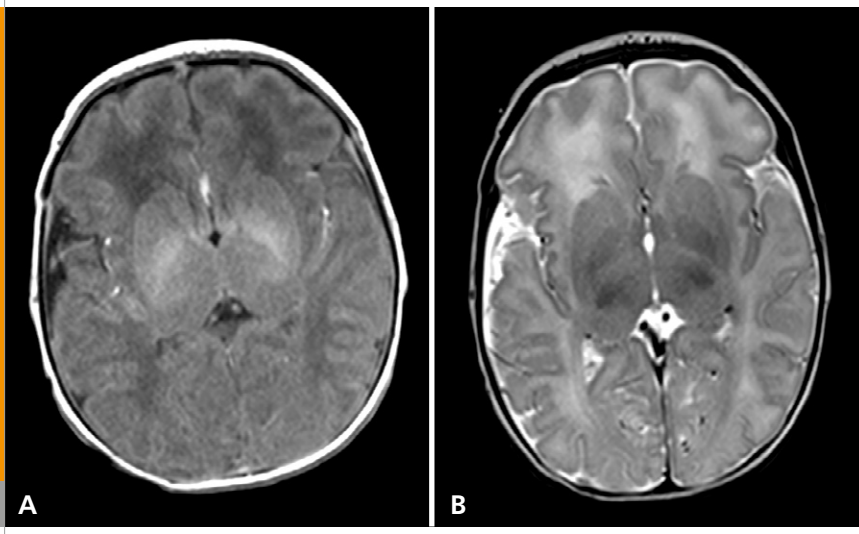

Fig. 1

Magnetic resonance imaging (MRI): corresponding T1w flash (A) and T2w spin echo (B) images showing loss of gray – white matter differentiation in the occipital areas. Basal ganglia, thalami, hippocampi and brainstem are not involved. Myelination is appropriate for gestational age. No signs of hemorrhage, necrosis or atrophy.

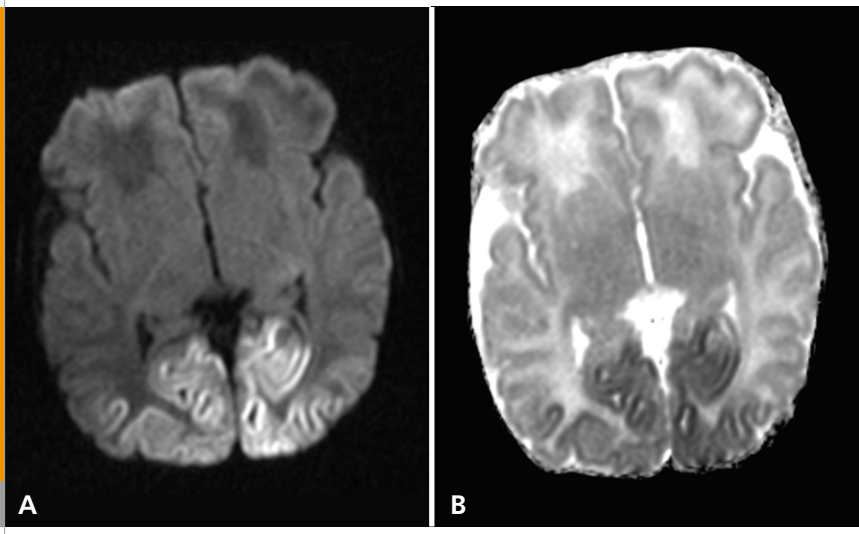

Fig. 2

Magnetic resonance imaging (MRI): corresponding diffusion-weighted imaging (DWI) (A) and apparent diffusion coefficient (ADC) map (B) showing bilateral occipital (shown here) and parietal (not shown here) diffusion restriction involving both cortex and underlying white matter.

Subsequently, the glucose infusion rate was reduced stepwise without the reoccurrence of hypoglycemia. The remainder of the hospitalization was unremarkable, and the infant was discharged on DOL 19. A first neuro-developmental follow-up is scheduled at the age of three months.

DISCUSSION

The present case highlights the importance of a thorough assessment of infants at risk of hypoglycemia after birth. We will first discuss the pathophysiologic background of hypoglycemia in newborn infants and will then focus on the new Swiss national guidelines on the prevention and treatment of hypoglycemia in near- and full-term infants. Finally, we will briefly discuss cerebral injury patterns seen on imaging studies after neonatal hypoglycemia.

Hypoglycemia can lead to neurologic injuries and abnormal neurodevelopmental outcome (3). Two main factors put the newborn term infant at risk of hypoglycemia. First, continuous transplacental glucose supply is interrupted at the time of cord clamping. As a result, plasma glucose concentrations in healthy newborn infants decrease during the first two hours after delivery. Subsequently, glucose concentrations increase over the next 18 hours and stabilize between 2.5 – 4.4 mmol/l over the first 48 hours of life (4). Second, the large brain and the increased ratio of brain to body mass lead to an increased demand for glucose in newborn infants compared with older children (3).

Various metabolic adjustments facilitate the transition from placental glucose supply and fetal glycogen synthesis to independent glucose production and glucose homeostasis in the newborn. Nevertheless, transient low blood glucose levels are common

during metabolic transition to extrauterine life among infants born at term (5). Up to one third of healthy term infants experience at least one episode of hypoglycemia below 2.6 mmol/l during the first 12 hours after birth (6).

Infants at increased risk for hypoglycemia are a) small for gestational age (SGA) infants, b) large for gestational age (LGA) infants, c) infants born preterm, d) infants of diabetic mothers and e) infants who have experienced perinatal stress. Moreover, screening should be extended to newborns with clinical signs and symptoms compatible with low blood glucose levels (7). These include jitteriness, cyanosis, apnea, hypothermia, poor muscle tone, poor feeding, lethargy and seizures. However, none of these symptoms are specific. In contrast, infants without obvious risk factors (such as the presented patient) do not primarily qualify for screening but can still experience severe and prolonged hypoglycemia (3, 6).

The new Swiss guidelines for the prevention and treatment of hypoglycemia in neonates with a gestational age > 35 0/7 weeks in maternity wards were published in September 2020. Two important changes from the previous version should be emphasized. First, a new threshold level of < 2.6 mmol/l is used to define neonatal hypoglycemia, independent of the method used to determine (plasma, full blood) glucose concentrations (7). Second, the administration of a 40%

dextrose gel in addition to oral nutrition is recommended to prevent hypoglycemia in infants at risk or to treat hypoglycemia when first diagnosed (7).

McKinley et al. highlighted the importance to prevent recurrent hypoglycemia, severe hypoglycemia < 2.0 mmo/l and prolonged hypoglycemia (8). As outlined above, all three conditions are associated with an increased risk of neurological impairment.

Several small cohort studies had shown a strong association between hypoglycemia and parietal and occipital brain injury including the primary visual cortices and extrastriate visual areas. More recently, a larger study reported more widespread and more variable patterns of cerebral injuries associated with neonatal hypoglycemia. White matter injury was not confined to the posterior regions; hemorrhage, middle cerebral artery infarction, and basal ganglia/thalamic abnormalities were seen, and cortical involvement was common. Early MRI findings were more instructive than the severity or duration of hypoglycemia for predicting neurodevelopmental outcomes (5).

Cerebral cell damage is thought to be occur by apoptosis caused by mitochondrial free radicals (9) and neurotoxins, which are active at N-methyl-D-aspartate receptors (10). Consistent with the findings of the study by Burns et al. mentioned above (5),

the parietal/occipital areas are not known to be more vulnerable to these mechanisms, which might explain the findings reported in their study.

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