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Hypoglycemia in a term newborn small for gestational age with early onset sepsis - literature review and case report

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ABSTRACT

Neonatal hypoglycemia presents significant challenges in the management of small for gestational age (SGA) infants with early onset sepsis. This literature review and case report examine the clinical implications and therapeutic strategies in such cases. The study underscores the importance of timely recognition and intervention to mitigate the risks associated with hypoglycemia and sepsis in term newborns, emphasizing early glucose management and appropriate antibiotic therapy for optimal outcomes.

Keywords: neonatal hypoglycemia, small for gestational age, sepsis, glucose management, antibiotic therapy

INTRODUCTION

Neonatal hypoglycemia during the transition from intrauterine to extrauterine life is one of the most common conditions encountered in the neonatology wards. After birth, the plasmatic glucose concentration physiologically falls below the level that was reached in fetal life among healthy newborns [1]. Hypoglycemia, on the other hand, represents disequilibrium between glucose supply and utilization [2]. Among healthy full term and late preterm (34 to 37 weeks) formula-fed infants a plasma glucose value of 30-36 mg/dl or higher during first 24 hours of age it is acceptable according to the study of Cornblath, but the acceptable cut-off will be increased from 45 to 50 mg/dl if the infant is sick, low birth weight or experience early onset sepsis, perinatal hypoxia, or had other major systemic illness [2]. Small for gestational age newborns (SGA) have an excess utilization of glucose for several reasons: hyperinsulinism [3], increased calories expenditure for thermoregulation, excess of glucose dependent tissue (liver: brain high ratio); the improper production of glucose is also encountered among SGA: inadequate feeding, delayed feeding, and suppression of the gluconeogenesis [4]. The clinical signs of hypoglycemia are not specific and include a wide spectrum of local and systemic physical abnormalities which may also be attributable to other common neonatal conditions [5]. The association between hypoglycemia and early onset sepsis (EOS) is another important aspect; specifically, in a recent study published in The Journal of Pediatric Infectious Diseases Society, the authors demonstrate hypoglycemia to be an early predictor of EOS caused by gram-negative pathogens [6]. EOS is another important illness responsible for 10% of deaths under 1 month of age worldwide [7]. The signs and symptoms of the EOS are unspecific and one of the greatest risk factors is prematurity [8,9]. Group B streptococcus (GBS) is the most common etiologic agent, while *Escherichia coli* is the most common cause of mortality [10,11].

The aim of this article is to highlight the fact that hypoglycemia detected by point-of-care among at

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risk infants for hypoglycemia had corresponding implications for appropriate initial antibiotic therapy during early transitional neonatal time. Written informed consent was obtained from the newborn mother for the publication of this case report.

CASE REPORT

Presenting concerns

The patient mother was a 22-year-old women (gravida 1, para 1) with no significant past medical history, who didn't receive prenatal care in our hospital, and was admitted in our department with painful, regular uterine contraction at 39 weeks gestational age. Her first ultrasonographic antenatal examination was performed in the first trimester of gestation and was unremarkable. The perinatal screening tests were negative for group B Streptococcus at 35 weeks of gestation. Personal pathological antecedents: The mother did not know if she had any abnormalities of the blood glucose level before or during pregnancy and she doesn't recall any urinary tract infection (UTI) symptoms. Membrane rupture occurred at the 39 weeks of gestation and 20 hours before vaginal delivery (latency interval is the time between membrane rupture and birth).

A term, small for gestational age (SGA) male infant weighing 2560 grams soon after birth was placed on radiant warmer, and his clinical examination was unremarkable. The length and head circumference are at the 50th percentile on the postnatal growth charts. His physical features were normal. His Apgar score was 8, 9 and 9 at 1, 5, and 10 minutes respectively. Shortly after birth the mother and the baby were transferred to the nursery room. On admission to the nursery at 60 minutes of age the infant had a point-of-care blood glucose level measurement, and it was 45 mg/dl. The infant appears to be well enough to be breastfed and the recommendation was to be feed again and also to supplement the infant with 30 ml of formula and re-check the blood glucose level again after one hour to make sure the baby is no longer hypoglycemic. At 3 hours of age, after the feeding, which was described to be a "sluggish" feed, the baby had slight tremors and apparent limpness, and his point-of-care blood glucose level was 40 mg/dl one hour after formula feeding. The newborn was transferred to the Neonatal Intensive Care Unit (NICU) and followed further. As per our unit protocol any infants receiving care in NICU are serially screened for sepsis at 12, 24 and 48-hours age with C-reactive protein (CRP) and Complete blood count (CBC) according to the Guidelines of National Institute for Health and Clinical Experience (NICE) [12].

Clinical findings

On physical examination the baby is pink and active; his vital signs are normal except for mild respiratory effort and a respiratory rate of 75 breaths per minute, nasal flaring, good bilateral air entry and subcostal retraction. SpO2 was 98% without oxygen supplementation. At this point the patient was considered still on physiologic transition from intrauterine to extrauterine life and the mild respiratory symptoms were not remarkable under the first 6 hours of age. The early onset of respiratory progressive condition on an SGA infant born at 38 weeks of gestation after prolonged membrane ruptures and despite the absent signs of maternal chorioamnionitis would be highly suggestive for EOS. After another 2 hours an apneic episode was observed with skin color changes which resolved spontaneously without any respiratory support. The cool extremities were observed soon after and capillary refill time (CRT) was measured higher than 4 seconds. His tone is decreased compared with 2 hours earlier and his mean arterial blood pressure fell from 45 mmHg to 34 mmHg. The heart sounds were rhythmic, heart rate was 150 beats/minute, and a systolic murmur was detected on left parasternal border, the peripheral saturations were 97% pre-ductal and 97% post-ductal.

Clinical management

A peripheral infusion of glucose 10% was initiated (6 mg/kg/minute, this was equivalent to 90 ml/kg/day) after an immediate bolus of 2 mg/kg over 1-2 minutes. Plasma glucose level was measured again after 30 minutes and was 95 mg/dl, and maintained at this level at the second and third measurements which was done at 2 and 4 hours respectively. A saline bolus of 10 ml/kilogram was administered at the time when arterial blood pressure was found to be lower than the 10th percentile and after the administration rise to the 50th centile for gestational and chronological age. A blood culture was drawn and antibiotic therapy was without any further delay. At 6 hours of age the antibiotic treatment was started.

Laboratory tests

The blood gases showed pH=7.24, pCO2=48 mmHg, HCO3=20 mmol/L, Lactate=7.4 mmol/L, the urinary output was normal. The baby is now 6 hours old and has received one dose of ampicillin and one dose of gentamicin. The combination of ampicillin and aminoglycoside (Gentamicin) is appropriate for empiric coverage for a newborn with mild symptoms which covers 94% of EOS pathogens [13]. The CRP at 24, 48 and 72-hours age was 29, 18, and 15 mg/dl. The immature to total (I:T) neutrophil ratio

was higher than 0.25, on the first and the second measurement. The laboratory results at admission are presented in Table 1.

TABLE 1. Laboratory data

Variable	Reference newborns	On NICU admission
Hemoglobin (g/dl)	14.5-19.5	15.6
Hematocrit (%)	45-60	44.1
Platelet count (per microL)	150,000-450,000	320,000
Reticulocytes (%)	2.5-4.5	7
White cell count (per microL)	9400-34000	13 800
Sodium (mmol/liter)	135-145	133
Potassium (mmol/liter)	3.5-5.0	3.6
Urea nitrogen (mg/dl)	5-20	34.2
Creatinine (mg/dl)	0.3-1.00	1.06
Calcium (mg/dl)	8.5-10.5	6.3
Uric acid (mg/dl)	2.3-6.6	3.2
Lactate dehydrogenase (U/liter)	110-210	1023
Alanine aminotransferase (U/liter)	7-33	12
Aspartate aminotransferase (U/liter)	45-150	96
Carbon dioxide (mmoli/liter)	22-27	48
Chloride (mmoli/liter)	98-106	109

Radiology aspects

Chest X ray obtained at 5 hours of life showed 8 to 9 rib expansion, the lungs were clear, no pleural effusions were present, and cardio thoracic index was lower than 50%. No other abnormalities were detected (Figure 1).

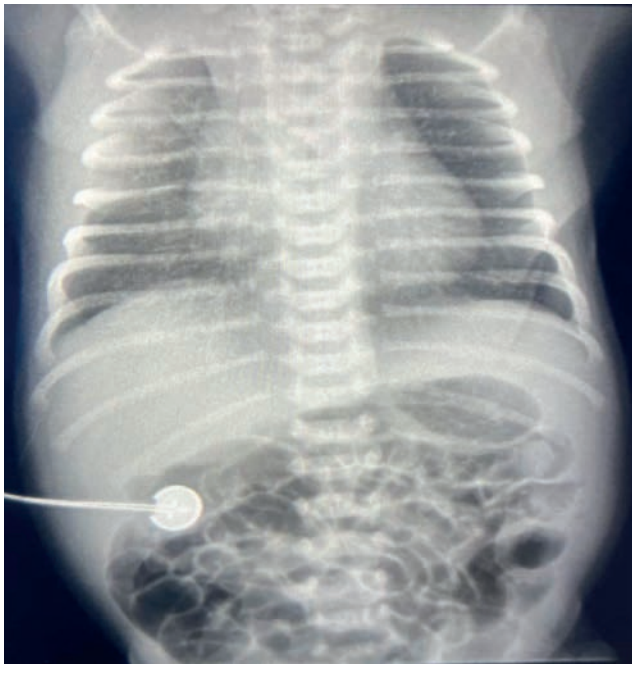

FIGURE 1. Antero-posterior chest X-Ray of a newborn term SGA with respiratory difficulties at 6 hours of life

Ultrasound findings

The cranial and abdominal ultrasound point-of-care examination was performed and was unremarkable. Initial echocardiography performed at 12 hours of age was notable for pulmonary pressure and was estimated at 55 mmHg according to the tricuspid regurgitation jet, (Figure 3) left ventricle impaired diastolic function (E/A=0.7), and normal tricuspid annular plane systolic excursion (TAPSE=9 mm). Left ventricular output (LVO) was decreased to 140 ml/kg/min, and right ventricular output (RVO) was normal at 220 ml/kilograms/min. Low velocity bidirectional shunt was detected across patent ductus arteriosus (Figures 4, 5) and left to right shunt at the level of the atrial wall (PFO). (Figure 6)

The recommended intensive care management focus was on maintaining arterial blood pressure and ventricular filling in order to normalize the systolic function administering the normal saline boluses, optimizing sedation and maintaining peripheral oxygenation with non-invasive expiratory continuous positive pressure (CPAP).

Follow up and monitoring

With this treatment in place, the newborn experienced stabilization, his mean arterial blood pressure had risen from 35 mmHg to 45 mmHg. Clinical improvement was observed after 12 hours after the antibiotic treatment was initiated, the urinary output was improved, and the lactate level was reduced. Oxygen requirement was decreased 8 hours after from FiO2 40% to FiO2 21%. A second echocardiography performed after 12 hours revealed improved left ventricular systolic function (Mitral E/A ratio = 0.8) and improved LVO = 190 ml/kg/minute, small PDA with left-to-right high velocity shunt, and a small left-to-right shunt at the level of PFO.

The blood culture was positive at 72 hours of age for *Escherichia Coli,* and the antibiotic treatment was changed to Ampicillin (150 mg/kg/dose) and Cefotaxime (75 mg/kg/dose) both given every 12 hours and maintained for 7 days, this association is recommended also for the proven cover and good penetration into the central nervous system. However, this association should not be chosen for the first line treatment in suspected newborns with EOS due to potential later complication from multidrug resistant organism infections [14].

DISCUSSIONS

EOS among term infants is difficult to detect because the signs and clinical symptoms are subtle and usually overlap many other medical conditions such as abnormal transition, transient tachypnea, or hypoglycemia. In a large multicenter European study, and in a recent US study, the incidence of EOS

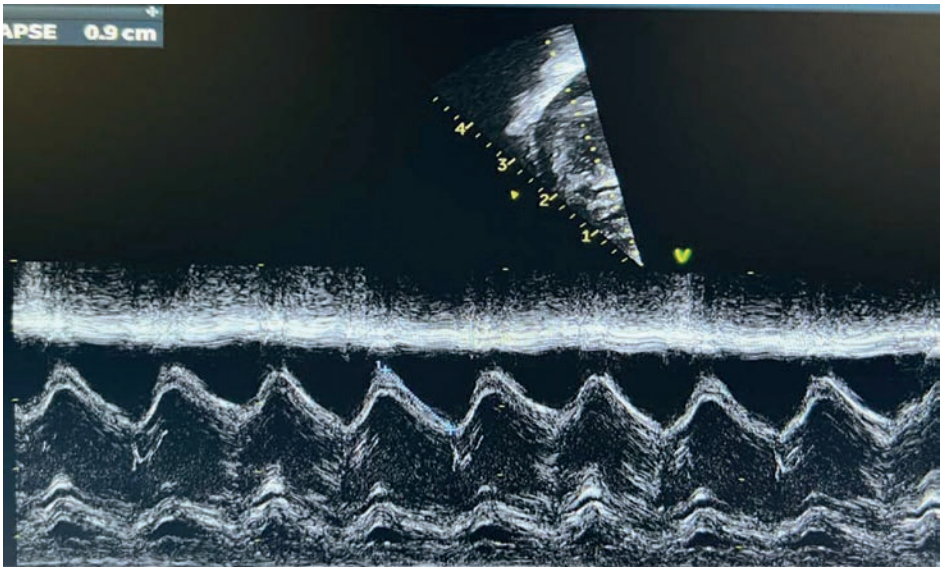

FIGURE 2. Tricuspid annular planar systolic excursion

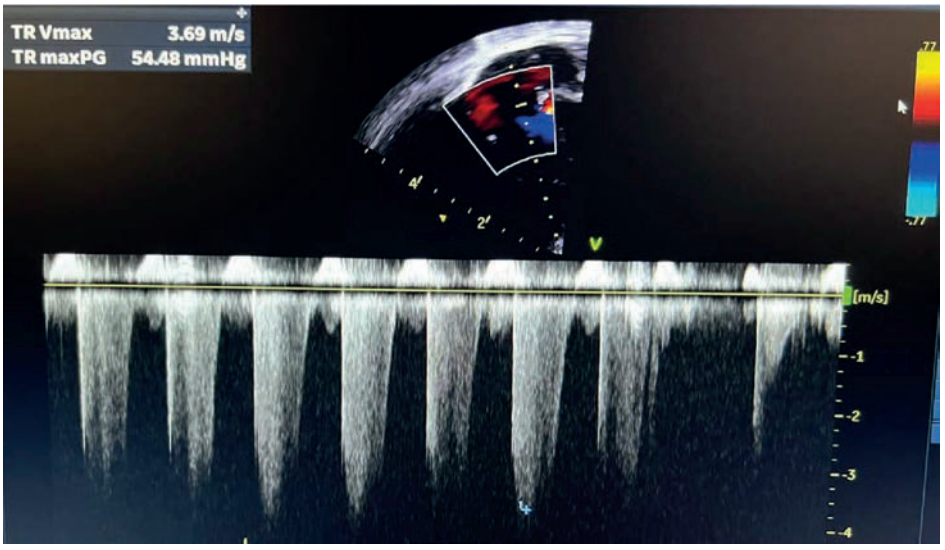

FIGURE 3. Tricuspid regurgitation jet

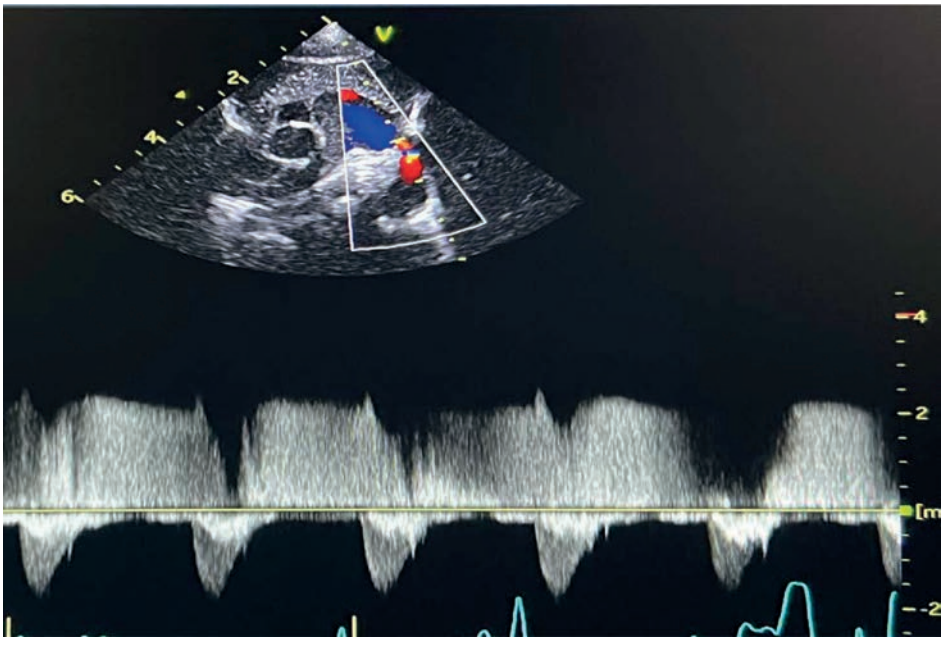

FIGURE 4. Patent ductus arteriosus bidirectional shunt

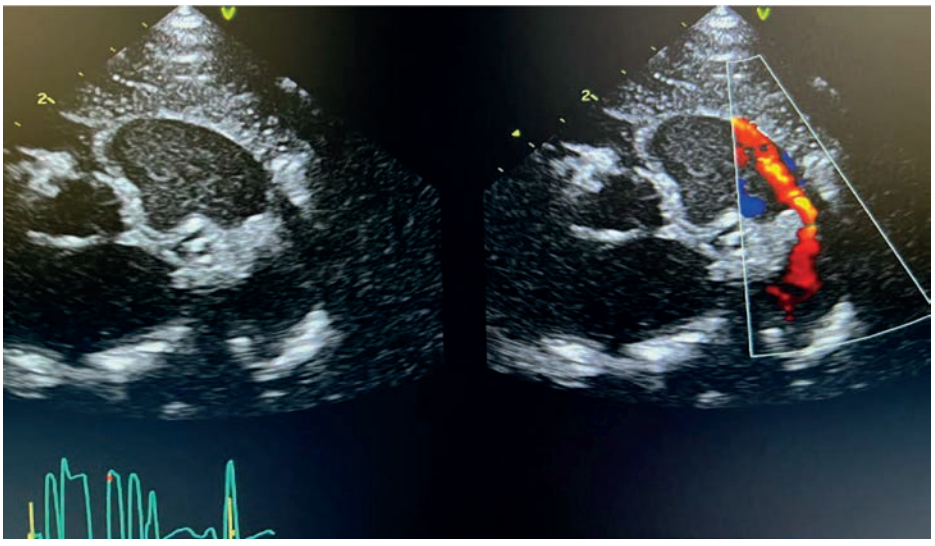

FIGURE 5. Patent ductus arteriosus bidirectional shunt-high parasternal view

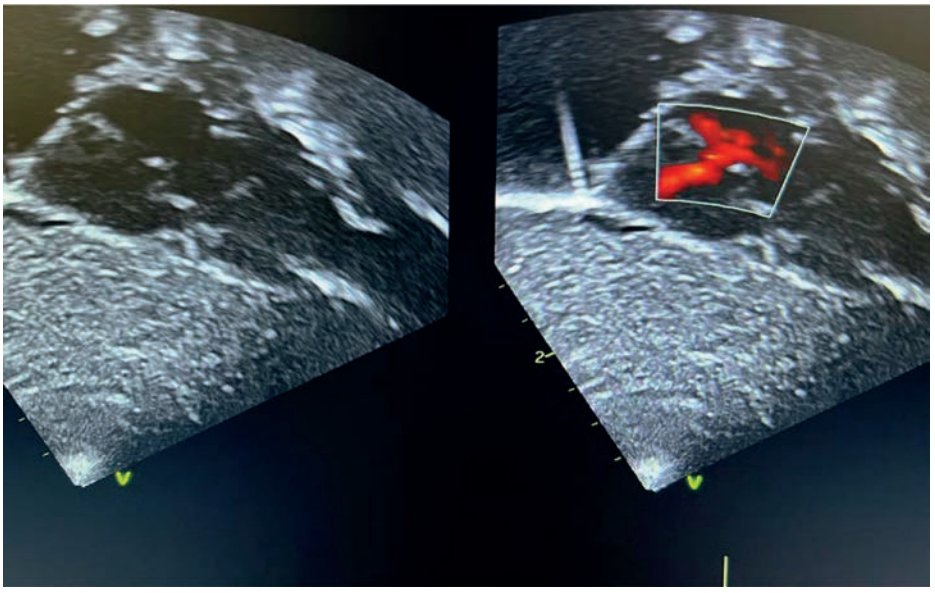

FIGURE 6. Interatrial shunt-subcostal view

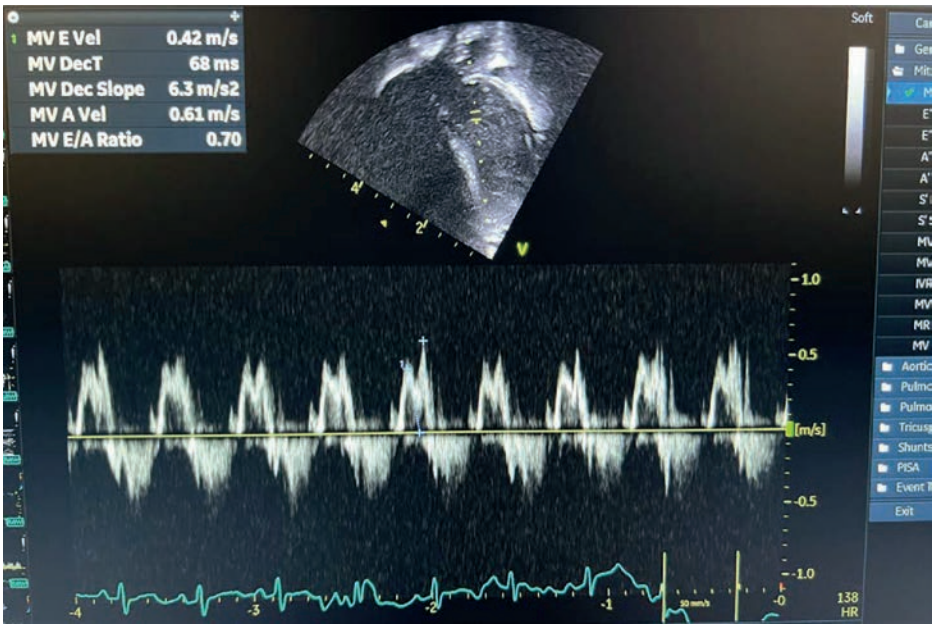

FIGURE 7. Apical 4 Ch view trans-mitral flow

among term infants were 0.6-0.8/1000 term newborn cases [15,16], and the authors conclude that a large proportion of infants without infection were treated with antibiotics during early transitional time based on clinical suspicion. The clinical signs of EOS in this case were subtle features of respiratory distress (intermittent tachypnea, moderate retractions, rales) otherwise the baby's breath was comfortable in the first 6 hours of life. Also, the retraction and tachypnea are considered common during first few hours of life in the context of physiologic transition from intrauterine to extrauterine life. Early suspicion and closely monitoring during fist 72 hours of life are important for a favorable outcome among symptomatic newborns with risk factors for EOS.

The management of symptomatic newborns with hypoglycemia hinges on the level of the plasmatic glycemic level. It's standard clinical practice to treat any term newborn with plasma glucose less than 40 mg/dl. The incidence of hypoglycemia in term infants is less than 2% except for those infants who are at risk immediately after birth (i.e. SGA) such as the baby in the case. The signs of hypoglycemia in the case were nonspecific (poor feeding, tremors, and limpness).

In this presentation authors aimed to highlight the importance of the early monitoring of the clinical signs and biochemical surveillance of a symptomatic term newborn with low maternal risk factors detected with EOS with positive blood culture. This result is in line with different studies, showed a positivity rate of 63% depending on the time of sampling, extent of bacteremia, and prior antibiotic treatment [19,20].

In this case the I/T ratio was 0.25, which is in accordance with previous published studies conducted by others [22,23]. I/T ratio higher than 0.2 with high specificity and positive predictive rate but low specificity [21] was an important diagnostic tool for detecting EOS in our case.

Sepsis evaluation and treatment is usually straightforward in case of symptomatic preterm infants or among those term symptomatic infants with maternal risk factors [chorioamnionitis and Group B Streptococcus (GBS)]. For this newborn with mild symptoms in the absence of maternal risk factors that don't point to an obvious management, the presence of hypoglycemia was considered to be a strong indicator for EOS. In our case, the association between hypoglycemia and neonatal sepsis is comparable with studies conducted by authors who demonstrated increased metabolic rate and peripheral utilization of glucose and bacterial endotoxin mediated metabolic effects among infected newborns during the early neonatal period [24,25]. In contrast to our appropriate for gestational age case, in a recent study the authors highlight the association between small for gestational age term newborns and GBS related EOS, and also demonstrate the higher risk for morbidity in the presence of a longer latency interval and the need of vasopressor treatment [17].

In line with our case, other authors demonstrate hypoglycemia to be a strong indicator for EOS with gram negative pathogens in a large cohort of preterm infants during a long study period performed across North-American NICU's [6].

CONCLUSIONS

Early onset sepsis with Escherichia Coli is a rare condition among term infants. Early identification of EOS is difficult because of the nonspecific clinical signs, and often neonatal EOS develops in the absence of detectable maternal risk factors. The delayed treatment initiation may cause important morbidity and mortality. Lack of specific signs and symptoms of EOS among term newborns needs a high index of suspicion, is associated with antibiotic overuse, and increased healthcare resource utilization.

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