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Acute encephalopathy bilirubin in the first week of life: A case of G6PD-deficient neonate

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ABSTRACT

Background. Acute bilirubin encephalopathy is an acute neurological manifestation due to indirect bilirubin deposits in the basal ganglia and brainstem nuclei. In several developed countries, the incidence reaches 0.6-2.5 cases/100,000 births, while a recent study in 8 hospitals in Indonesia showed an incidence rate of 2%. In this paper, we describe an acute bilirubin encephalopathy in a neonate with G6PD deficiency.

Case Presentation. A 5-day-old male neonate was admitted to the ER with recurrent generalized tonic seizures which started 6 hours prior to admission. Post seizure, the neonate cried then fell asleep. He had seemed less active and did not want to breastfeed for the last 12 hours. The neonate was born at full term (3160 grams) by a spontaneous vaginal delivery in the hospital, APGAR score 7/9, mother blood type AB+. He was exclusively breastfed with adequate intake. Physically examined, the neonate was lethargic with flat anterior fontanelle, Kramer V jaundice, fever, hypertonia, decreased sucking reflex, physiologic reflexes +2/+2, Babinski +/+, without cranial nerve paresis. Laboratory results of total bilirubin 44.79 mg/dL (indirect 43.04 mg/dL; direct 1.75 mg/dL), Hb 14.2 g/dL, WBC 15,000/µL, reticulocytes 124,500/µL, negative Coombs's test, blood type A+, peripheral blood morphology within normal limits. The neonate was planned for exchange transfusion, intensive (triple) phototherapy was performed while waiting for the exchange transfusion. Bilirubin levels fell significantly within 12 hours after phototherapy initiation. Phototherapy was continued, the neonate was discharged on the seventh day of hospitalization in good condition. During treatment, etiology tracking was performed towards G6PD (G6PD level: 6.6 U/dL).

Conclusion. Acute bilirubin encephalopathy is a rare morbidity found in newborns. ABE that occurs in the first week of life, prompt further investigations other than physiologic jaundice. Most frequent etiologies are ABO incompatibility, G6PD deficiency, sepsis and hereditary spherocytosis. In this case, we found G6PD as the cause of acute bilirubin encephalopathy in the first week of life.

Keywords: bilirubin encephalopathy, G6PD deficiency, hyperbilirubinemia

INTRODUCTION

Hyperbilirubinemia occurs in 60-80% of neonates and generally has a good outcome; however, extreme increases in total serum bilirubin levels can lead to bilirubin encephalopathy or kernicterus [1-5]. It is estimated that approximately 480,000 neonates experience severe hyperbilirubinemia (TSB levels >25-30 mg/dl) annually worldwide, with 63,000 experiencing kernicterus [4,6]. In Indonesia, hyperbilirubinemia is the number 5 cause of neonatal morbidity, with a prevalence of 5.6% [7].

Acute bilirubin encephalopathy is an acute neurological manifestation caused by indirect bilirubin deposition in the basal ganglia and brainstem nuclei [1,8,9]. In several developed countries, the incidence ranges from 0.6 to 2.5 cases in 100,000 births, whereas a recent study in eight hospitals in Indonesia showed an incidence rate of 2%. Risk factors for bilirubin neurotoxicity include ABO & Rhesus incompatibility, hemolysis (G6PD deficiency, hereditary spherocytosis), prematurity, asphyxia (first-minute APGAR score <5), acidosis (cord pH <7.0), sepsis, and hypoalbuminemia (< 3.0 mg/dL) [1,2,7]. In conditions with associated risk factors, a lower threshold value of bilirubin is used to initiate phototherapy and exchange transfusion [2,7].

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency, which affects ± 400 million people worldwide with a global prevalence of 4.9%, is a recessive X-linked enzymatic disorder that reduces protection against oxidative stress and is currently recognized as one of the most important causes of hyperbilirubinemia, which causes kernicterus worldwide [2,6,10,11].

PATIENT PRESENTATION

A 5-day-old male neonate was admitted to the emergency unit of Ulin General Hospital with a chief complaint of recurrent seizures. Generalized tonic seizures, 1-2 minutes in duration, recurred every 20 to 30 min with a frequency of more than 10 times in the past 6 h prior to admission. The neonate developed fever 8 h before admission. The neonate tended to sleep at all times and had not been breastfed for 12 h before admission. At the age of 24 h, the parents noticed that the neonate began to appear yellow on the head, which worsened and reached the ends of the extremities the next day. The mother tried to sunbathe her baby in the morning, but the jaundice was only getting worsened.

The neonate was born at 40 weeks' gestational age to a gravida 3, para 2 mother with blood type AB (+) via spontaneous vaginal delivery in a hospital without any pregnancy-associated complications or any significant medical history. The birth weight was 3160 g, length was 50 cm, and APGAR scores were 7 and 9 at 1 and 5 min, respectively. The neonate was discharged after 24 hours. During home care, the neonate was exclusively breastfed with an adequate intake.

The frequency of bowel movements is 3-4 times a day, greenish in color, and urination is 6 times a day with dark, tea-like colored urine. There was no history of consanguineous marriage between the parents or jaundice between his parents and his two older sisters.

On emergency admission, the neonate experienced tonic, generalized convulsions for 30 seconds. When the seizure ended, the neonate cried and fell asleep. Except for a subfebrile temperature of 37.8°, other vital signs were within normal ranges. Marked

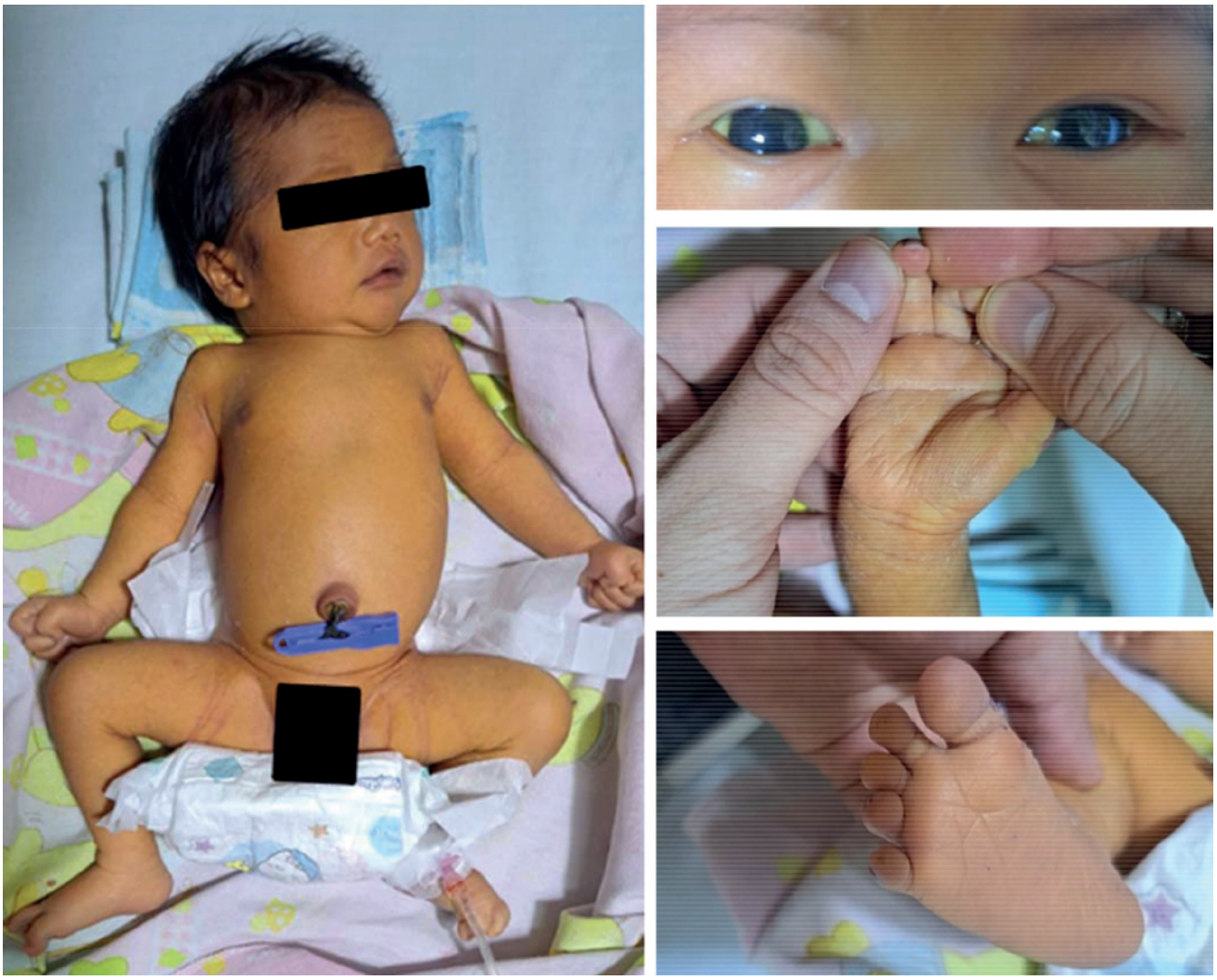


FIGURE 1. Clinical appearance of the baby on emergency admission

physical examination included a lethargic neonate with a weak cry, inability to feed, hypertonia; accompanied by a decreased sucking reflex, and Kramer V jaundiced skin. Laboratory test results showed total serum bilirubin of 44.79 mg/dL (indirect 43.04 mg/dL; direct 1.75 mg/dL), reticulocytes 124,500/µL, and albumin level of 3.2 mg/dL (Table 1).

According to anamnesis, physical examination, and laboratory results, the neonate was diagnosed with acute encephalopathy bilirubin in the advanced phase due to G6PD deficiency, with a differential diagnosis of late-onset neonatal sepsis. He was immediately transferred to the NICU and received intensive (triple) phototherapy while preparing for an exchange transfusion. Other treatments included thermoregulation, total parenteral nutrition with a total fluid requirement of 150 mL/kgBW/day + 20% consisting of 10% dextrose and electrolytes (sodium, calcium, and potassium), phenobarbital loading 20 mg/kgBW (continued with maintenance), ampicillin 50 mg/kgBW/dose every 12 h, and gentamycin 5 mg/kgBW/dose every 36 h. The Coombs test result was negative, the neonate's blood type was A (+), and the peripheral blood morphology was within normal limits. A significant decrease (30.9%) in bilirubin level was observed in 12 hours after initiation of intensive phototherapy, with total bilirubin 30.95 mg/dL (indirect 29.57 mg/dL, direct 1.38 mg/dL) (Figure 3).

Intensive phototherapy was continued. The neonate was discharged on the seventh day of treatment in a good condition, and was no longer icteric. During hospitalization, etiology tracking was performed for G6PD (G6PD level: 6.6 U/dL).

The neonatal head ultrasound results were within the normal limits (Figure 2). Ten days after discharge, follow-up was carried out at the neonatology outpatient clinic. No neurological complaints or sequelae were noted. Otoacoustic emissions (OAE) examination was performed when the baby was 6 weeks old, resulting in Pass for both ears (Figure 4), and a repeated OAE was scheduled for the next 6 months.

DISCUSSION

The greatest risk associated with hyperbilirubinemia is the development of bilirubin-induced neurological dysfunction, which typically occurs with high indirect bilirubin levels [7,8]. Acute bilirubin encephalopathy (ABE) is a rare but preventable neurological complication of untreated, severe hyperbilirubinemia. The main clinical symptoms are abnormalities in the level of consciousness, tone and movement, and brainstem function, which are particularly related to feeding and crying [1,8]. The severity of abnormalities appears to correlate with both the severity and duration of hyperbilirubinemia [1,8]. In this case, the patient was a term neonate (40 weeks) who had jaundice starting 24 hours after birth and gradually progressed throughout the entire body, observed as Kramer 5 on emergency admission.

TABLE 1. Laboratory results of the patient

Laboratory parameters	On admission (0 h)	12 h post admission	36 h post admission	60 h post admission
Hb (g/dL)	14,2	12,7	12,5	17,4
Ht (%)	41,9	37,5	35,9	50,5
Leukocyte (/µL)	15.000	15.700	12.500	12.300
Thrombocyte (/µL)	360.000	373.000	362.000	346.000
Netrophil (/µL)	9.100	8.870	6.730	12.300
Netrophil (%)	60,8	56,7	49,2	100
Lymphocyte (/µL)	3.300	3.290	4.440	0
Lymphocyte (%)	22,0	21,0	32,4	0
Reticulocyte (/µL)	-	-	124.500	-
Reticulocyte (%)	-	-	3,4	-
Blood glucose (mg/dL)	68	-	-	-
Total bilirubin (mg/dL)	44,79	30,95	18,95	10,32
Direct bilirubin (mg/dL)	1,75	1,38	0,77	0,48
Indirect bilirubin (mg/dL)	43,04	29,57	18,18	9,84
Albumin	-	3,2	-	3,4
CRP (mg/L)	6,2	-	-	-
I/T ratio	0,12	-	-	-
Direct Coombs' Test	-	Negative	-	-
Blood type/Rhesus	-	A / (+)	-	-
G6PD (U/dL)	-	-	-	6,6
Peripheral blood smear	-	-	Normal	-

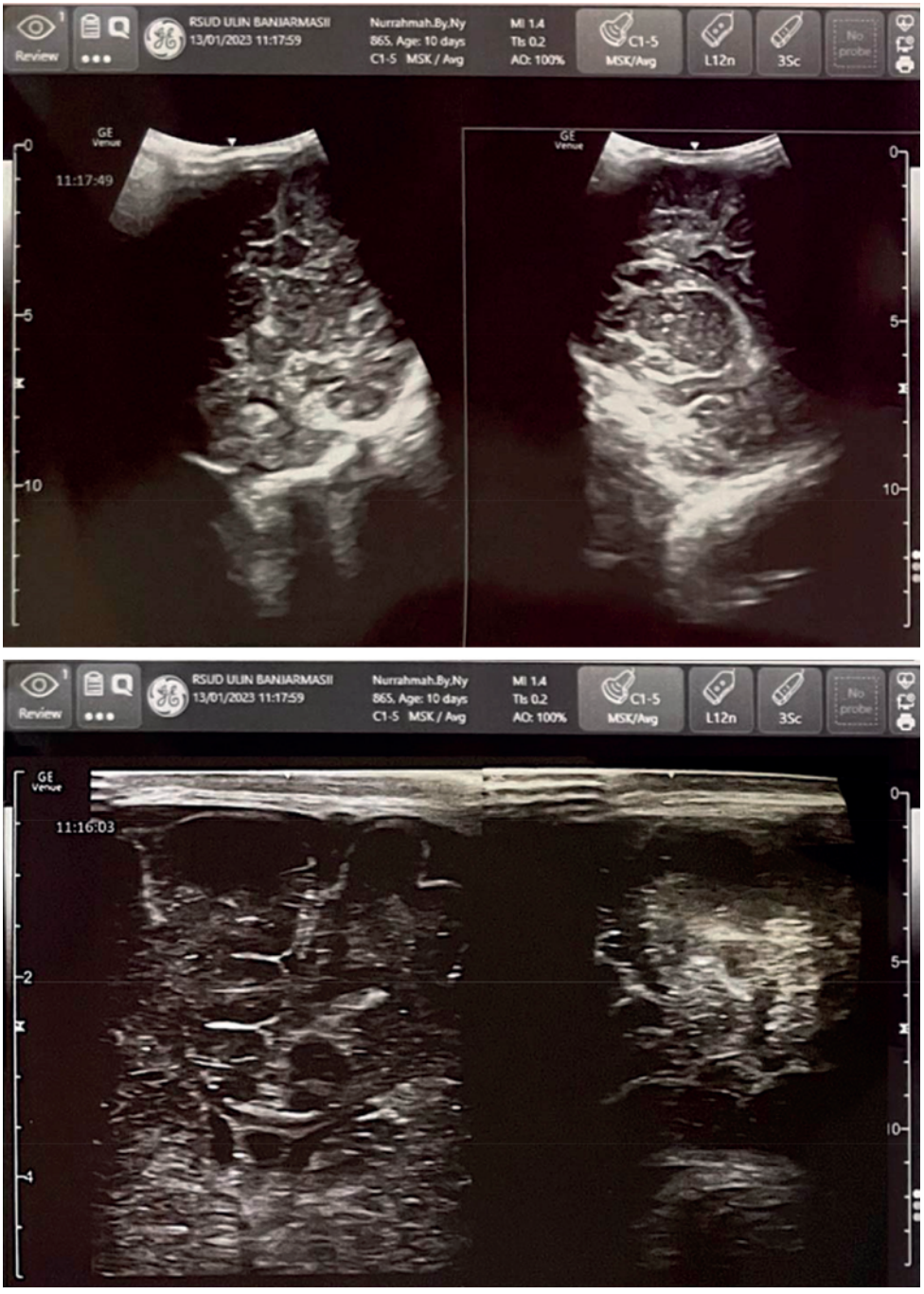


FIGURE 2. Neonatal cranial ultrasonography result was within normal limits

ABE typically progresses in 3 clinical phases over several days [1,8]. Symptoms in the initial phase are rather nonspecific, such as lethargy, hypotonia, decreased movement, and poor sucking. Upon entering the intermediate phase, the neonate showed cardinal signs of moderate stupor, irritability, and increased tone. Retrocollis, opisthotonos and also fever have been reported to occur during this phase of the syndrome [1,5,8]. The advanced phase is characterized by deep stupor or coma, increased tone or hypertonia, inability to feed, high-pitched cry, and often seizures [1,5,8]. The patient showed rapid progressive jaundice that started at 24 hours of age. Clinical signs and symptoms of bilirubin toxicity were observed gradually, including decreased sucking reflex, hypotonia, lethargy, fever, recurrent seizures, and hypertonus. Based on the course of the disease, the ABE in our patient fits the description of the advanced phase [2,7,10]. This phase is the most ominous stage of ABE because of the possibility of irreversible central nervous system damage and can later develop into chronic bilirubin encephalopathy [1,2,10].

Potentially preventable causes of bilirubin encephalopathy include (1) early discharge (<48 h) with no early follow-up (within 48 h of discharge); this problem is particularly important in near-term neonates (35-37 week of gestation); (2) failure to

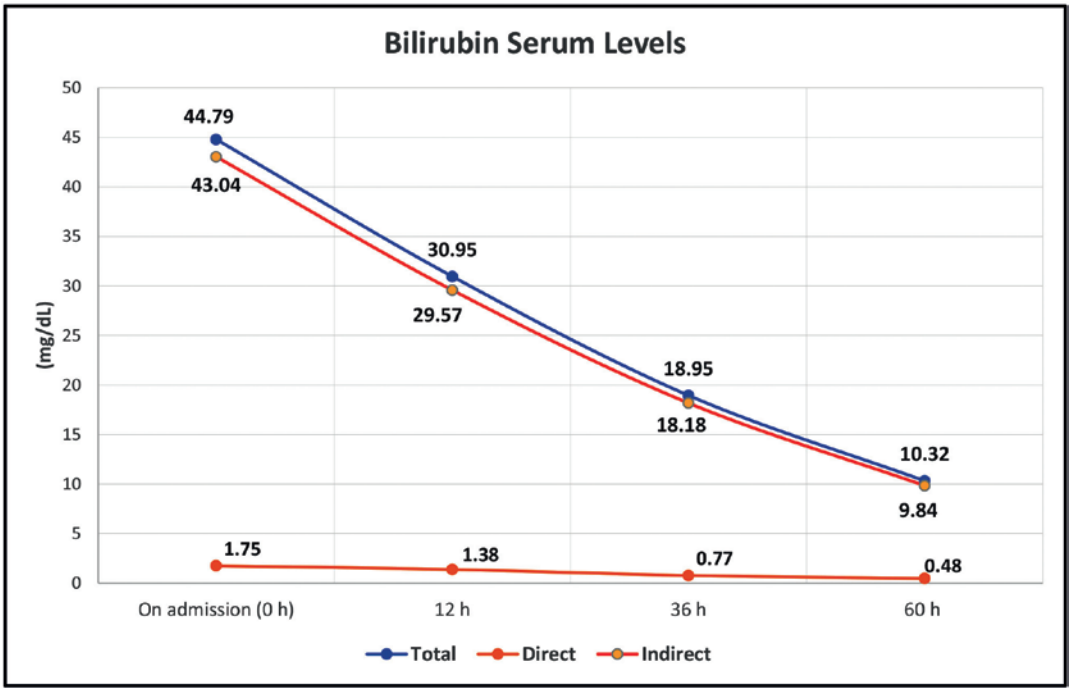
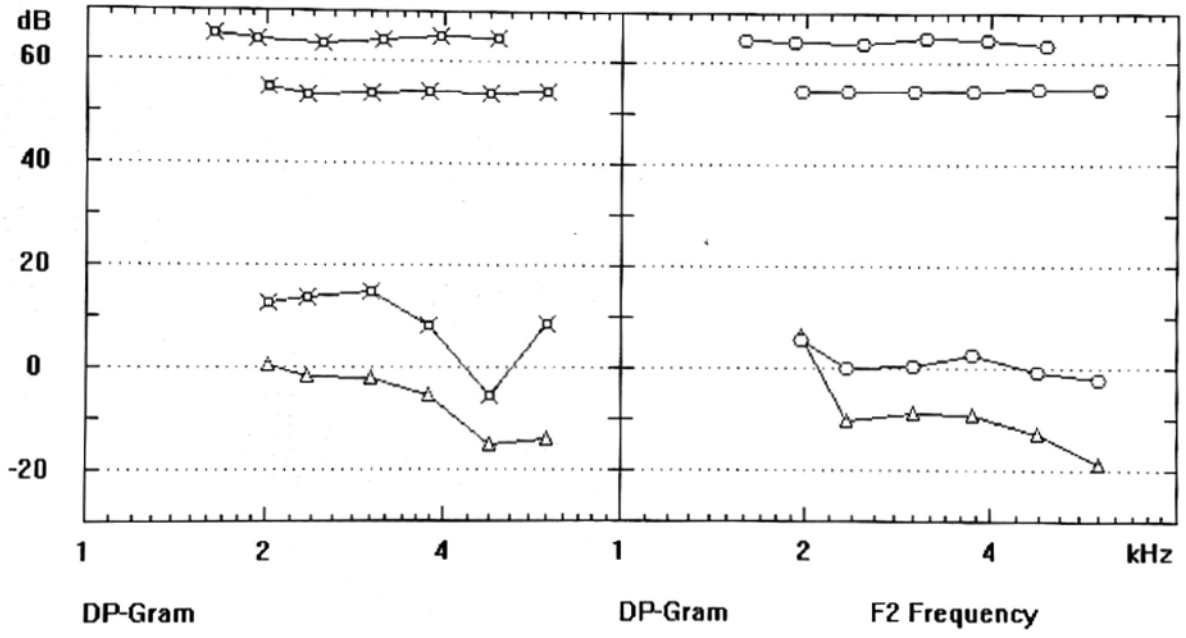


FIGURE 3. Bilirubin serum levels during hospitalization



Result: PASS Ear: Left Date: 15/02/2023

Protocol: 2-6 kHz Screen, 4/6 for Pass
Time: 2:36:33

L1 (dB)	L2 (dB)	F1 (Hz)	F2 (Hz)	GM (Hz)	DP (dB)	NF (dB)	DP-NF (dB)	Result
64.6	54.3	4922	6000	5434	8.3	-14.1	22.4	Pass
64.8	54.0	3938	4781	4339	-5.7	-15.3	9.6	Pass
64.3	54.3	3141	3750	3432	8.2	-5.7	13.9	Pass
63.4	53.8	2484	3000	2730	14.8	-2.4	17.2	Pass
64.2	53.5	1922	2344	2122	13.7	-2.0	15.7	Pass
65.2	55.1	1641	2016	1818	12.4	0.2	12.2	Pass

Result: PASS Ear: Right Date: 15/02/2023

Protocol: 2-6 kHz Screen, 4/6 for Pass
Time: 2:57:35

L1 (dB)	L2 (dB)	F1 (Hz)	F2 (Hz)	GM (Hz)	DP (dB)	NF (dB)	DP-NF (dB)	Result
63.5	54.9	4922	6000	5434	-2.3	-19.1	16.8	Pass
64.7	55.1	3938	4781	4339	-1.0	-13.1	12.1	Pass
64.9	54.6	3141	3750	3432	2.6	-9.3	11.9	Pass
64.0	54.7	2484	3000	2730	0.2	-9.1	9.3	Pass
64.3	54.5	1922	2344	2122	0.1	-10.4	10.5	Pass
64.5	54.4	1594	1969	1771	5.5	6.1	-0.6	Refer

FIGURE 3. Bilirubin serum levels during hospitalization

check the bilirubin level in a neonate noted to be jaundice in the first 24 h; (3) failure to recognize the presence of risk factors for hyperbilirubinemia; (4) underestimation of the severity of jaundice by clinical (visual) assessment; (5) lack of concern regarding the presence of jaundice; (6) delayed measurement of the serum bilirubin level despite marked jaundice or delay in initiating phototherapy in the presence of elevated bilirubin levels; and (7) failure to respond to parental concern regarding jaundice, poor feeding, or lethargy [8].

A recent epidemiological case-control study was conducted by Wang, et al. in The First Affiliated Hospital of Zhengzhou University between January 2015 and July 2018, with a total of 669 neonates (bilirubin encephalopathy = 153, non-bilirubin encephalopathy = 516). The study found a positive correlation between bilirubin-albumin (B/A) ratio level and bilirubin encephalopathy; B/A ratio could be a potential predictor of bilirubin encephalopathy in neonates (odds ratio (OR) = 1.67), and a higher total bilirubin-albumin ratio increased the risk of bilirubin encephalopathy by 23% (OR = 1.23) [12]. In our case, the neonate's total serum bilirubin level on admission was 44.79 mg/dL, accompanied by a B/A ratio of 9.6, which was an indication for exchange transfusion.

G6PD deficiency, an inherited X-linked disorder, is estimated to affect 400 million people worldwide [2,11,13]. This is caused by one or more mutations in the G6PD gene. Currently, 230 known G6PD variants are known to result from different mutations. G6PD, a cytoplasmic enzyme, is an oxidoreductase that catalyzes the oxidation of glucose-6-phosphate to 6-phosphoglucono-lactone coupled with the reduction of NAD phosphate (NADP) to reduce NADP (NADPH). It is often referred to as the first enzyme of the pentose phosphate pathway. NADPH is an electron donor in reactions required for the biosynthesis of deoxyribonucleotides, fatty acids, and steroids. It is also the coenzyme of cytochrome P450, which is central to the metabolism of many drugs and other xenobiotics. The reducing power of NADPH is required for the defense against oxidative stress. Erythrocytes are extremely vulnerable to oxidative damage because they have no alternative NADPH-producing pathway [14].

The earlier classification of G6PD variants observed in hemizygous-mutated males was proposed by Yoshida et al. in 1971, and consists of five classes: I – severe enzyme deficiency, with chronic non-spherocytic anemia; II – severe enzyme deficiency (<10% residual activity); III – moderate-to-mild G6PD activity (10-60% residual activity); IV – very mild-to-no deficiency (60-100% residual activity); and V – increased G6PD activity (more than 200% residual activity) [13]. Since G6PD deficiency is an X-linked disorder, males have only one G6PD allele, whereas females have two alleles. Thus, males have two different G6PD genotypes (wild and hemizygous), whereas females have three genotypes (wild, homozygous, and heterozygous). Based on the WHO classification, the five genotypes in males and females resulted in three phenotypes: G6PD normal (>80% enzyme activity), G6PD deficient (<10% enzyme activity in males and <30% enzyme activity in females), and G6PD intermediate (30 – 80% normal enzyme activity) in heterozygous females only [13]. In this case, our patient was a male neonate, in accordance with G6PD, which affects more males than females, with a G6PD level of 6.6 U/dL.

The majority of G6PD deficient individuals are asymptomatic [13,15,16]. Exposure to several drugs, certain chemicals, infectious agents, and hypoxia can cause oxidative stress and induce hemolysis in G6PD-deficient individuals, including 8-aminoquinoline agents, dapsone, ciprofloxacin, henna, and fava beans. Symptoms are induced when erythrocytes are exposed to exogenous oxidative stress, such as certain drugs or infectious agents (hydrogen peroxide is generated by activated polymorphonuclear neutrophils). Clinically, it may manifest as neonatal jaundice, acute hemolytic anemia and drug-induced hemolysis [11,14,16]. Explaining the chronological events in this case, the peak incidence of G6PD-induced hyperbilirubinemia occurs from day 2 to day 3 after birth [14], which is important because the mother and baby may have already been discharged; therefore, there may be delay or even failure of a diagnosis that requires urgent management.

In this patient, the total serum bilirubin level measured was 44.79 mg/dL (indirect 43.04 mg/dL; direct 1.75 mg/dL) on admission, with B/A ratio of 9.6. Thus, it can be concluded that our patient has risk factors for developing neurological sequelae in the future. The neonate is scheduled for periodic follow-up to monitor any long-term outcome and sequelae signs, including choreoathetoid cerebral palsy, kernicteric facies (setting-sun sign/upward gaze paresis with eyelid retraction), primary tooth enamel dysplasia, and sensorineural deafness [5,8].

CONCLUSION

Acute bilirubin encephalopathy is a rare morbidity in newborns. Occurring in the first week of life, it should be evaluated for causes other than physiological jaundice, namely ABO incompatibility, G6PD deficiency, sepsis, and hereditary spherocytosis. Failure to administer intensive phototherapy and occasional delays in providing exchange transfusions may have influenced the outcomes of bilirubin encephalopathy. Periodic follow-up is necessary to monitor long-term outcomes and signs of sequelae after bilirubin encephalopathy. A prospective cohort study is needed to determine the long-term

clinical outcomes in neonates with bilirubin encephalopathy.

Ethical Statement

This case report follows the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Informed Consent

The patient's guardian agreed to participate and signed an informed consent form for having their data published in a journal article.

Author Contributions

DRKH wrote the manuscript and provided data, PGH conducted the patient interviews. AY and PA revised and corrected the manuscript. All authors reviewed the final manuscript.

Conflict of Interest

The authors declare no financial or personal relationships that might bias the content of this work.

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