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Case Report Open Access

Hemolytic Anemia Due to Glucose-6-Phospate Dehydrogenase Deficiency in Neonate

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme in erythrocytes that functions to maintain glycolysis, form an erythrocyte membrane, and protect hemoglobin from oxidative denaturation. Clinical manifestations of anemia and severe jaundice are risk factors for acute hyperbilirubinemia encephalopathy, which can progress to kernicterus. G6PD deficiency is X-linked. The incidence is most common in males with an incidence in Indonesia of 1-14%.

A 3-day-old male baby appeared yellowish and had a history of being pale since 1 day of age. There was a history of phototherapy and packed red blood cell transfusion from a previous hospital. The baby was born via caesarean section, term baby, with a birth weight of 2700 grams. The Physical examination revealed Kramer V, tachypnea, but no hepatosplenomegaly. A previous laboratory examination at AM Hospital showed total bilirubin of 23.3 mg/dL, indirect bilirubin 23 mg/dL, and pre-transfusion hemoglobin 9.8 g/dL. Chest X-rays revealed grade I–II hyaline membrane disease. Meanwhile, the laboratory test results at the Dr Wahidin Sudirohusodo Hospital showed a total bilirubin of 38.5 mg/dL, indirect bilirubin 37.17 mg/dL, reticulocytes 9.95%, hemoglobin 11.8 g/dL, CRP 5.2 mg/L, Procalcitonin 0.5 ng/mL, and a negative Coombs test. The peripheral blood smear showed fragmented cells of erythrocytes. The G6PD level was 17.2 U/dL (reference value >20.5 U/dL). The patient received low-flow oxygenation, antibiotics, and 72 hours of intensive phototherapy. On the 7th day of treatment, the condition improved, and the baby was discharged. Therefore, Rapid diagnosis and treatment of G6PD deficiency are important to prevent other potential complication such as acute hyperbilirubinemia encephalopathy.

Keywords: Hemolytic anemia; glucose-6-Phosphate dehydrogenase; neonates

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Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is one of enzymes in erythrocytes that maintains glycolysis, shape and flexibility of erythrocyte membrane, and protects hemoglobin from oxidative denaturation. The most common clinical manifestations are hemolysis and indirect hyperbilirubinemia. Bilirubin is a primary breakdown product of red blood cells by the reticuloendothelial system. Bilirubin concentrations > 5 mg/dL bilirubin will appear clinically in the form of yellow staining of the skin and mucous membranes called jaundice. [1,2]

It is estimated that around ± 400 million people worldwide suffer from G6PD enzyme disorder/deficiency. This is spread across Africa (7.5%), the Middle East (6%), Asia (4.7%), Europe (3.9%), and the America (3.4%). The highest frequency is found in the tropical area, such as Southeast Asia, with the most common causes were jaundice and acute hemolytic anemia. In Indonesia, the incidence was estimated at 1-14%.[1,3]

In many countries, G6PD screening is conducted as part of the national newborn screening program, but Indonesia has not yet implemented it. G6PD deficiency has been identified as a major risk factor in severe neonatal hyperbilirubinemia which can lead to the complication of acute encephalopathy hyperbilirubinemia which could lead to kernicterus and causes permanent neurological damage if left untreated.[1,2,4]

Case

A 3-day-old male baby appeared yellowish and had been pale since the first day of life. He received phototherapy and packed red blood cell transfusion from a previous hospital. He had shortness of breath since birth. The baby was born via caesarean section due to previous section history during first pregnancy (this was the 2nd pregnancy), 37 weeks gestation, and weight 2700 grams. There was no history of antepartum hemorrhage or birth trauma in delivery. The mother has blood type O Rhesus +, and the father has blood type B Rhesus +, while the baby's blood type is B Rhesus +. During the time of treatment at Dr. Wahidin Sudirohusodo Hospital, a negative Coombs test was obtained, and we ruled out the possibility of ABO incompatibility.

The physical examination revealed Kramer V (figure 1), tachypnea, but no hepatosplenomegaly. A previous laboratory examination at AM Hospital (when the baby was aged 1 day) showed a total bilirubin of 23.3 mg/dL, indirect bilirubin 23 mg/dL, and hemoglobin 9.8 g/dL pre-transfusion (> 13 g/dL), leucocyte 6.350/uL (3.100/uL - 21.600/uL), platelet 338.000/uL (150.000/uL – 450.000/uL). Chest X-ray revealed grade I-II hyaline membrane disease. After packed red cell transfusion (when the baby was 2 days old) hemoglobin 14.5 g/dL (> 13 g/dL), leucocyte 17.500/uL (3.100/uL - 21.600/uL), platelet

306.000/uL (150.000/uL – 450.000/uL).

Figure 1. Baby when admitted to Dr. Wahidin Sudirohusodo Hospital.

The laboratory test results at the Dr Wahidin Sudirohusodo Hospital, complete blood count, peripheral blood smear, septic workup, bilirubin, albumin, SGOT, SGPT, Coombs test, and G6PD enzyme examination were performed. Septic workup was done because of respiratory distress. Laboratory results showed high reticulocytes (9.95%), HB 11.6, MCV 107 fl, MCH 36 pg, total bilirubin 38.5 mg/dl, direct bilirubin 1.33 mg/dl, albumin 3.5 mg/dL, procalcitonin 0.5 ng/mL, CRP 5.2 mg/L, SGOT and SGPT within normal limits, a negative Coombs test, and G6PD enzyme 17.2 U/dL (reference value >20 U/dL). Blood culture showed no bacterial growth. Peripheral blood examination showed normochromic normocytic erythrocytes, anisopoikilocytosis, positive ovalocytes, positive spherocytes, positive fragmented cells, positive normoblasts and no toxic granulation or vacuolization in leukocytes. These results indicate non-autoimmune hemolytic anemia due to G6PD deficiency, which is accompanied by indirect hyperbilirubinemia.

The patient was diagnosed with respiratory distress of the newborn, hemolytic anemia, indirect hyperbilirubinemia, and G6PD deficiency. The patient received low-flow oxygenation (0.5 liter/minute), antibiotics (ampicillin 125 mg/12 hours/intravenously and gentamicin 13 mg/24 hours/intravenously) for five days, and 72 hours of intensive phototherapy (after 48 hours after phototherapy, bilirubin total 16.87 mg/dL, bilirubin direct 0.8 mg/dL, and phototherapy continued). On the 7th day of treatment, the condition improved (figure 2), the baby was discharged, and the family was educated on how to prevent things that can trigger G6PD deficiency.

Figure 2. Baby after intensive phototherapy

Discussion

Anemia in the neonatal period (0-28 days) at gestational age > 34 weeks is defined as hemoglobin (HB) in central venous < 13 g/dL or capillary blood < 14.5 g/dL. The incidence of anemia in neonates is the most frequent blood abnormality. Normal reticulocytes in neonates are 3-5%. The average MCV value in neonates is 107 fL. In preterm infants, HB is slightly lower, MCV and reticulocytes have higher values. HB levels do not change until the 3rd week of life and then decrease to 11 g/dL.[2,5]

The etiology of anemia in neonates comes from 3 processes:[2] 1) Erythrocyte loss or bleeding such as placenta previa, placental abruption, caesarean section, birth trauma, cephalhematoma, caput succedaneum, intracranial hemorrhagic, 2) Increased erythrocyte destruction or hemolytic (most common) such as autoimmune (Rh and ABO incompatibility, autoimmune hemolytic anemia), nonimmune (sepsis, TORCH), Congenital erythrocyte defects (G6PD deficiency, Thalassemia, hereditary spherocytosis), 3) Low erythrocyte production or hypoplastic anemia such as sideroblastic anemia, congenital leukemia.

In this case, the patient was pale and jaundiced at 1 day of age. The causes of anemia followed by jaundice on the first day of life are ABO and Rhesus incompatibility, as well as G6PD deficiency. Other risk factors that could cause anemia in this case included cesarean section surgery and respiratory distress (sepsis risk).

ABO and rhesus incompatibility is an isoimmune hemolytic anemia caused by blood group differences between the mother and infant. Infants with blood type A or B are typically incompatible with mother with blood type O. This is because in the mother's blood type O, the dominant isoantibody is 7S-IgG and can cross the placenta, whereas in blood types A or B, the dominant isoantibody is 19S-IgM so that it cannot cross the placenta. The clinical manifestations are hemolytic anemia and early onset unconjugated hyperbilirubinemia.[2]

G6PD deficiency is the most prevalent human enzyme deficiency, with an estimated global frequency of 4.9% and approximately 400 million people affected worldwide. In Indonesia, the incidence is estimated at 1-14%. A study by Soemantri stated that the G6PD deficiency prevalence in Central Java was 15%. Suhartati et al study in small isolated islands in Eastern Indonesia (Babar, Tanimbar, Kur and Romang Islands in Maluku Province) reported that the incidence of G6PD deficiency was 1.6-6.7%.[1,3,6,7]

G6PD deficiency affects one-third of male infants with neonatal jaundice, while the frequency in female infants is lower. Jaundice usually appears at 1-4 days of age, similar to physiological jaundice. If kernicterus occurs, it can cause permanent nerve damage if not treated immediately. Premature infants with G6PD deficiency have more severe neonatal jaundice. If G6PD deficiency is not routinely screened, more comprehensive screening should be done in newborns who have hyperbilirubinemia >150 mmol/L

(> 9 mg/dL) in the first 24 hours or have relatives with a history of neonatal jaundice, and in Asian males.[4,6,8] In this case, the bilirubin on the first day of life was 23.3 mg/dL.

G6PD deficiency is an x-linked defect. The basic biochemical abnormalities of G6PD deficiency are due to mutations in the G6PD gene. Women have two X-chromosomes, therefore they can be homozygous normal, homozygous G6PD deficient, and heterozygous G6PD deficient. Males have only one X-chromosome, therefore males are at greater risk than females. In this case, G6PD occurred in a male baby. The WHO categorizes G6PD deficiency into several classes (Table 1)[1,6,8]

Table 1. Classification of G6PD deficiency [7,8]

Class	Variant	Enzyme Activity	Symptoms	Prevalence
I	Mediterranean type	<1%	Chronic non-spherocytic anemia	Uncommon across population
II	A^-/Med	1 – 10%	Intermittent acute hemolysis	More common in Asian and Mediterranean populations
III	A^-/Med	10 – 60%	Intermittent acute hemolysis	US black males
IV	A^+/Med	60 – 150%	No clinical symptoms	Rare
V	A^+/Med	>150%	No clinical symptoms	Rare

Acute hemolysis can also occur in G6PD-deficient infants and cause hemolysis crises in children and adults when consuming drugs or fava beans, or exposure from the environment. Mothballs is an example of a widespread and inexpensive household item used as an insecticide in the clothes closet of Asian, Latin American, and African populations. Mothballs contain naphthalene, a polycyclic aromatic hydrocarbon that causes oxidative stress in G6PD-deficient RBCs.[9] A more toxic naphthalene-derived metabolite, alpha-naphthol, could cause hemolysis, severe anemia, and the production of Heinz bodies after accidental intake. In addition, severe jaundice and kernicterus was experienced by a 4-day-old Panamanian baby boy with G6PD deficiency after direct contact or inhaling vapors from naphthalene-containing clothing.[10] Some medications that should be avoided can be seen in table 2.[6]

Table 2. Drugs to avoid in patients with G6PD deficiency [11]

Unsafe for Class I, II, and III	Safe for Class II and III
Acetanilid	Acetaminophen
Dapsone	Aminopyrine
Furazolidone	Ascorbic acid
Methylene blue	Aspirin
Nalidixic acid	Chloramphenicol
Naphthalene	Chloroquine

Niridazole	Colchicine
Nitrofurantoin	Diphenhydramine
Phenazopyridine	Isoniazid
Phenylhydrazine	L-DOPA
Primaquine	Menadione
Sulfacetamide	Paraaminobenzoic acid
Sulfamethoxazole	Phenacetin
Sulfanilamide	Phenytoin
Sulphapyridine	Probenecid
Thiazosulfone	Procainamide
Toluidine blue	Pyrimethamine
Trinitrotoluene	Quinidine
Vitamin K	Quinine
	Sulphamethoxpyridazine
Anesthetic Agents	Streptomycin
Diazepam	Sulfisoxazole
Isoflurane	Tripelennamine
Sevoflurane	Trimethoprim
	Anesthetic Agents
	Halothane
	Prilocaine
	Ketamine
	Fentanyl
	Propofol
	Benzodiazepines (except Diazepam)

In this report, the physical and laboratory examination results support non-autoimmune hemolytic anemia due to G6PD deficiency followed by induced hyperbilirubinemia. The principal treatment for G6PD deficiency is to avoid oxidative stress-causing agents such as medications, certain foods, and infections. However, the anemia may be severe enough to require blood transfusions. Neonates with G6PD deficiency may also develop chronic hemolysis leading to hyperbilirubinemia with a more gradual increase in total bilirubin. Phototherapy is required if bilirubin levels meet the criteria for phototherapy. Phototherapy is still the first choice therapy and exchange transfusion is done for patients who are not responsive to phototherapy.[2,8,12,13]

In our case, the patient received packed red cell transfusion from the previous hospital, and received intensive phototherapy. In Dr. Wahidin Sudirohusodo Hospital, the patient underwent intensive phototherapy again for approximately 72 hours because the baby still appeared yellow throughout the body (Kramer V jaundice), with a total bilirubin level of 38.5 mg/dL, direct bilirubin 1.33 mg/dL. The patient also received antibiotics for the management of respiratory distress for five days. On the 7th treatment, the patient's condition improved and the patient was discharged.

The American Academy of Pediatric guidelines recommend an exchange transfusion when the patient's total serum bilirubin (TSB) level continues to rise and is still higher than the exchange transfusion

threshold after 4-6 hours of intensive phototherapy. Furthermore, exchange transfusion is recommended when there are clinical signs of acute bilirubin encephalopathy.[14] In his study, Zhang M et al reported that intensive phototherapy is an effective and secure treatment for severe hyperbilirubinemia. Indications for exchange transfusion for patients with hyperbilirubinemia can be more stringent. However, emergency exchange transfusion should be planned as soon as intensive phototherapy begins, especially for newborns with risk factors. If intensive phototherapy can be guaranteed and proven effective, exchange transfusion should be avoided wherever possible.[15] In this case the bilirubin level was improved with intensive phototherapy.

Conclusion

A 3-day-old male baby with hyperbilirubinemia and anemia due to hemolytic anemia due to G6PD deficiency had been reported. Physicians should focus on early recognition to decrease the morbidity of the patient. Rapid diagnosis and treatment are important to prevent other potential complications such as acute hyperbilirubinemia encephalopathy.

Conflicts of Interest

There is no conflict of interest

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