TOPICAL SILVER SULFADIAZINE TRIGGER HEMOLYSIS IN A CHILD WITH BURN AND GLUCOSE 6 PHOSPHATE DEHYDROGENASE DEFICIENCY

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ABSTRACT Glucose 6 phosphate dehydrogenase deficiency (G6PD deficiency) is the commonest red blood cell enzyme disorder that affects hundreds of millions around the globe. The red cells deficient in the enzyme become vulnerable to oxidative stress after exposure to certain drugs, chemicals, or food leading to hemolysis. We present a five-year-old boy admitted to the Burn unit after scolding burn by boiling water. He was treated with an application of silver sulfadiazine cream to the burn sites, paracetamol, and intravenous fluids. The boy developed pallor and jaundice on the fifth day of admission with evidence of acute hemolysis and documented G6PD deficiency during the incidence. We hypothesize that sliver sulfadiazine could be absorbed through burn and trigger hemolysis in G6PD deficient individuals; therefore, replacing this antibiotic with a safe one is advised in these individuals, as well as introducing neonatal screening for G6PD deficiency in the high prevalent communities to avoid oxidative triggers and increase awareness in both health care workers as well as the general population.

KEYWORDS Acute hemolysis, G6PD deficiency, Burn

Introduction

Glucose 6 phosphate dehydrogenase enzyme (G6PD) is a housekeeping agent which helps to protect red blood cells from oxidative damage by the generation of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) from NADP, which in turn is the primary function of hexose monophosphate shunt [1]. The gene for G6PD is located on Xq28 that are cloned and sequenced [2].

Glucose 6 phosphate dehydrogenase (G6PD) deficiency is a group of hereditary abnormalities in which the activity of the G6PD enzyme is reduced, and the red blood cells become vulnerable to oxidative damage and hemolysis in the affected individuals [1,3]. The primary triggers are stress, infection and particularly after exposure to oxidizing drugs or contact with certain chemicals[2]. The effective management of G6PD deficient individuals includes educating patients, parents, care providers, and health care workers about the known triggers that may increase the risk of hemolysis. G6PD deficiency is inherited as an X-linked recessive trait. Therefore, male predominance is explained[1,2]. The older erythrocytes are affected most by hemolysis in such patients. This abnormality is most prevalent in African, Mediterranean, and Oriental ethnic groups[1]. Over 400 biochemical G6PD variants have been described with different clinical severity [4].

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Case report

A five-year Saudi Arabian boy sustained a scold burn with boiled water while playing in the family kitchen. Upon arrival to the emergency department, he was screaming from severe pain. He had a burn involving 15% of his body surface area (BSA). Burn over the abdomen was of first degree, while that over the chest and upper extremities was of second degree. Analgesia was administered in the form of intravenous paracetamol and intravenous fluids resuscitation.

He is the first child in non-consanguineous marriage. His past

Table 1 Patient laboratory data during admission.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 11
WBC (10^3)	17.5	17.1	15.	13.2	11	10.5	7.5
HB(gm/dl)	11.3	11.1	11	11	7.8	7.7	9
HCT (%)	35.3	35.1	35	35	20.4	20.1	26.7
MCV (fl)	79	79.1	80	81	84	85	88
RET (%)	1.1	1	NA	1	8.3	10	9.5
PLT (10^3)	236	240	250	266	265	301	295
ALT (U/L)	15	20	15	16	19	20	20
AST (U/L)	40	41	45	38	153	99	55
TB (mg/dl)	1.1	1.2	1.1	1.1	4.6	4.4	1.7
DB (mg/dl)	0.2	0.2	0.3	0.3	0.4	0.4	0.3

WBC: white blood cells; HB: hemoglobin; HCT: hematocrit; MCV: mean cellular volume; fl: femtolitre; RET: reticulocytes; PLT: platelets; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TB: total bilirubin; DB: direct bilirubin; U: unit; L: liter.

medical history was insignificant apart from neonatal jaundice treated with phototherapy.

Investigations requested after admission to burn unit include complete blood count (CBC), renal function test and electrolytes and liver function test, all of which were normal. He was kept on Nil Per Os (NPO) , intravenous fluids, analgesia, ranitidine, and prophylactic antibiotic (Cephradine). Silver sulfadiazine cream was applied locally to the burn sites twice a day. Next day he started oral feeding without adverse event. CBC, renal function and liver function tests (LFT) were monitored daily and they were normal. On day 5 CBC and liver function showed abnormal readings, low hemoglobin and high Aspartate aminotransferase which are presented on (table1). On the same day the patient developed orange discoloration of the urine with clinical evidence of pallor and jaundice on physical examination; this day on assessing Lactate dehydrogenase (LDH) level it was 631U/L and Coombs test was negative.G6PD activity and Heinz body preparation were requested. The results came back confirming significant presence of Heinz bodies and deficiency of G6PD enzyme. We suspected sulfadiazine cream as the precipitating cause of the hemolytic episode, so we held its application. The patient continued to improve both clinically and on laboratory levels, and he was discharged on 11th day with hemoglobin of 9 g/dl (table1).

Discussion

G6PD deficiency is highly prevalent in the Middle East and other countries [1,5,6]. It leads to various symptoms such as neonatal anaemia, neonatal hyperbilirubinemia, chronic non-spherocytic hemolytic anaemia (CNSHA), acute hemolytic episodes, and asymptomatic patients[1,5]. Acute neonatal bilirubin encephalopathy and gallstones are consequences of the hemolysis related to G6PD deficiency[1]. The clinical presentation, and the severity of hemolysis, however, are related to the level of enzyme deficiency and the intensity of the oxidative stressors affecting the erythrocytes such as drugs, chemicals, infection, diabetic ketoacidosis and food items with subsequent shutdown of production of NADPH making the older erythrocytes vulnerable to hemolysis [1,7,8,9]. In our patient thermal injury may be pointed as a cause of hemolysis. However, hemolysis, which is caused by a thermal injury, usually is acute and associated with peculiar morphological changes in erythrocytes in the peripheral blood smear (5), which were not identified in our patients. The hemolysis itself was not acute since it developed on the 5th day of burn (table1), plus the presence of Heinz bodies and low level of G6PD activity which conformed the state of glucose 6 phosphate dehydrogenase deficiency. Application of silver sulfadiazine cream to the burned skin caused vasodilatation and probably absorption of sulfadiazine, which led to oxidative stress and consequently hemolysis. Although SSD is a sulfa compound, it is not listed as the risk stressor for G6PD deficiency in recent references [8,9]. We have reviewed the literature for stressors in G6PD deficiency and found discrepancies in SSD listing some kept it as risk and unproven risk in recent references [3,4,6,7,8,9]. Topical application of silver sulfadiazine cream to burned skin was reported to cause hemolytic episodes in patients with G6PD deficiency and warned against by the united states food and drug administration (FDA) similar to our patient [10,11].

This advice us to explore this area that remained unstudied for over three decades as this disease affects millions of people worldwide. The causal relation of SSD application to the burn and hemolysis in the patient made us change the antiseptic cream to another antibiotic known to be safe in G6PD deficiency and list it with items causing acute hemolysis GDPD deficiency as suggested in (table 2). The introduction of an effective neonatal screening program for G6PD deficiency should be adopted in areas with high G6PD deficiency prevalence in order to prevent devastating severe hyperbilirubinemia and neurodevelopmental sequelae of this disease by either qualitative or quantitative methods with clear instructions for the parents or caregivers before discharging the babies after birth[12,13].

Conclusion

In areas where G6PD deficiency is prevalent or if G6PD status is unknown, careful choice of antibiotics to prevent hemolysis in such patients. Avoidance of SSD cream application in the burn is required until further studies explore its safety in G6PD deficient individuals. Neonatal screening for G6PD deficiency

Table 2 List of foods and chemicals which should be avoided, cautioned against or can be safely consumed by glucose-6-phosphate dehydrogenase (G6PD) deficient individuals.

Items that should be avoided by G6PD-deficient individuals	Items for which caution should be exercised during use	Items for which there is no evidence to contraindicate their use
• Fava beans • Primaquine • Methylene blue • Naphthalene • Aniline dyes • Henna dye • Ciprofloxacin • Moxifloxacin • Norfloxacin • Ofloxacin • Nalidixic Acid • Sulfasalazine • Nitrofurantoin • Silver sulfadiazine	• Food coloring agent 1-phenylazo-2-naphthol-6-sulphonic acid • Chloroquine • Quinine • Sulfasalazine	• Pumpkin • Unripe peaches • Vicia sativa • Fenugreek seeds • Flower pollen • Synthetic cannabinoids • Hoya carnosa • Menthol • Aluminum phosphide • Vicia faba

further adds to the preventive measures to avoid unnecessary morbidities.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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