Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2018/68

Case Report

Methemoglobinemia in a Child with Glucose-6-phosphate Dehydrogenase Deficiency - A Case Report

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Abstract

Methemoglobin is the reduced form of hemoglobin which is normally found in blood in levels <1%. Methemoglobinemia (MHb) is a disorder which is characterized by methemoglobin levels >1% in blood. Spontaneous formation of methemoglobin is normally counteracted by protective enzyme systems, for example, nicotinamide adenine dinucleotide phosphate methemoglobin reductase. A 2-year-old male child presented with lethargy, oliguria, hemoglobinuria, and icterus. Child had been treated with ofloxacin for urinary tract infection 2 days before presentation. Child had low saturation even with high flow oxygen. Hence, a clinical diagnosis of methemoglobinemia was made. On evaluation, the child was found to have severe hemolysis with low glucose-6-phosphate dehydrogenase (G6PD) activity. Methylene blue, the treatment of choice for MHb, is contraindicated in the presence of G6PD deficiency. Child improved with packed cell transfusion and supplemental oxygen. This case illustrates the potential for severe hemolysis with the use of methylene blue in a case of MHb presenting with G6PD deficiency. Hence, it is advisable to check G6PD activity before administering methylene blue.

Key words: Cyanosis, Glucose-6-phosphate dehydrogenase deficiency, Methemoglobinemia, Methylene blue

INTRODUCTION

Methemoglobinemia (MHb) may arise from a variety of etiologies including genetic, idiopathic, and toxicological sources.[1] Symptoms may vary from mild headache to coma/death and may not correlate with measured MHb concentrations. The diagnosis may be complicated by the effect of MHb on arterial blood gas and pulse oximeter oxygen saturation results. Treatment with methylene blue can be complicated by the presence of underlying enzyme deficiencies including glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD deficiency is the most common red cell enzymopathy in humans and has an X-linked inheritance. It has been reported from India more than 30 years ago and the prevalence varies from 0 to 27% in different caste, ethnic and linguistic groups.[2] The major clinical manifestations are drug-induced hemolytic anemia, neonatal jaundice, and chronic non-spherocytic hemolytic anemia.[3]

Methemoglobin which is normally produced in blood is neutralized by nicotinamide adenine dinucleotide phosphate (NADPH) methemoglobin reductase. Methylene blue provides artificial electron acceptor for NADPH methemoglobin reductase. In a suspected or proven case of G6PD deficiency, methylene blue is contraindicated because G6PD is the key enzyme for production of NADPH through pentose phosphate pathway. G6PD-deficient individuals generate insufficient NADPH to efficiently reduce methylene blue to leukomethylene blue, which is necessary for the activation of NADPH-dependent methemoglobin reductase system[1].

Access this article online

www.ijss-sn.com

Month of Submission : 12-2017
Month of Peer Review : 01-2018
Month of Acceptance : 01-2018
Month of Publishing : 02-2018

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CASE REPORT

A 2-year-old male child second order born out of non-consanguineous marriage presented to emergency with complaints of letharginess for the past 1 week and oliguria and hematuria for past 2 days. 2 days earlier to presentation, the child was prescribed ofloxacin for urinary tract infection, following which pallor and yellowish discoloration of eyes were noted by parents. No significant past medical history or family history noted.

Clinical examination revealed severe pallor and icterus with no cyanosis. Tachycardia, HR-184/min with SpO_2 of 60%, was observed (without O_2 therapy). The child was initially started on high flow oxygen support. In view of persistent desaturation, the child was intubated and ventilated. Saturation did not pick up even after mechanical ventilatory support. Hence, ABG was done which showed pH of 7.24, pCO_2 = 36.0 mm Hg, pO_2 = 216 mm Hg, and O_2 saturation = 99.6%. The presence of chocolate brown discoloration of blood along with the saturation gap (SpO2 -60% and ABG SaO2 -99% and pO2-216 mm of Hg) was suggestive of MHb. Methemoglobin (metHb) levels by spectrophotometry were 32.6% (normal- 0–2%).

Hematologic examination showed severe anemia with hemolytic picture. Bedside analysis of whole blood in a test tube showed chocolate brown color. Most notable finding on peripheral smear was the presence of blister cell, which leads to suspicion of G6PD enzyme deficiency. Supravital staining showed Heinz bodies. Sickle test and indirect and direct coombs test were negative, hemoglobin electrophoresis showed normal pattern and normal osmotic fragility test. Qualitative analysis showed low G6PD activity (HEMOPAK-visual dye decolorization method).

In a male child with a background history of ofloxacin intake, hemoglobinuria, indirect hyperbilirubinemia, high lactate dehydrogenase, high reticulocyte count, and blister cells on peripheral smear with low G6PD enzyme activity, the diagnosis of G6PD hemolytic anemia was made.

Although IV methylene blue is treatment of choice, it is contraindicated in the presence of G6PD deficiency, the other modalities of therapy were blood transfusion or exchange transfusion.[4] Hence, packed red blood cell transfusion was done and the child's saturation improved along with improving general condition. The child was discharged with a list of drugs to be avoided, which may induce hemolysis.

On follow-up 3 months later, his Hb was 11.7 g% and metHb level was 8.6%, and he was clinically well.

DISCUSSION

G6PD deficiency anemia is an X-linked recessive hereditary disease. It is the most common human enzyme defect, being present in more than 400 million people worldwide.[5] G6PD is a metabolic enzyme involved in the pentose phosphate pathway, especially important in red blood cell metabolism. Individuals with the disease may exhibit non-immune hemolytic anemia in response to a number of causes, most commonly infection or exposure to certain medications or chemicals (oxidants). G6PD is the rate-limiting enzyme of this metabolic pathway that supplies reducing energy to cells by maintaining the level of the coenzyme NADPH. The NADPH in turn maintains the supply of reduced glutathione in the cells that is used to mop up free radicals that cause oxidative damage. The G6PD/NADPH pathway is the only source of reduced glutathione in red blood cells [Figure 1]. The role of red cells as oxygen carriers puts them at a substantial risk of damage from oxidizing free radicals except for the protective effect of G6PD/NADPH/glutathione. People with G6PD deficiency are therefore at risk for hemolytic anemia in states of oxidative stress.

MHb is a disorder characterized by the presence of >1% metHb in the blood.[6] metHb, an oxidized form of hemoglobin (contains Fe^{3+} in place of Fe^{2+} in Hb),[4] has slightly greater affinity for oxygen due to its chemical structure, thus shifting the oxygen dissociation curve to the left, resulting in decreased release of oxygen in tissues. Spontaneous formation of metHb is normally counteracted by protective enzyme systems, for example, NADH metHb reductase (cytochrome-b5 reductase) (major pathway), NADPH metHb reductase (minor pathway),[7] and to a lesser extent the ascorbic acid and glutathione enzyme systems [Figure 2]. MHb can be treated with supplemental oxygen and methylene blue, which acts by providing an artificial electron acceptor for NADPH metHb reductase.

However, known or suspected G6PD deficiency is a relative contraindication to the use of methylene. G6PD-deficient individuals generate insufficient NADPH to efficiently

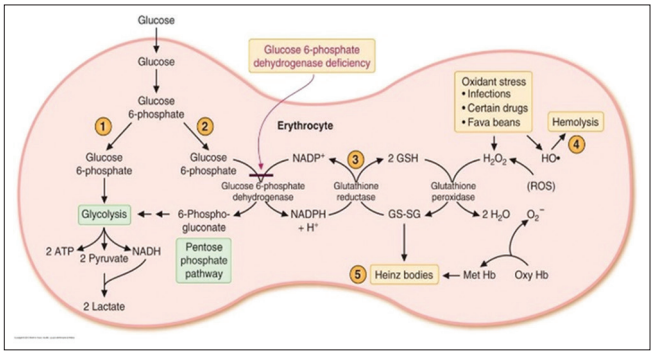

Figure 1: NADPH/ G6PD pathway

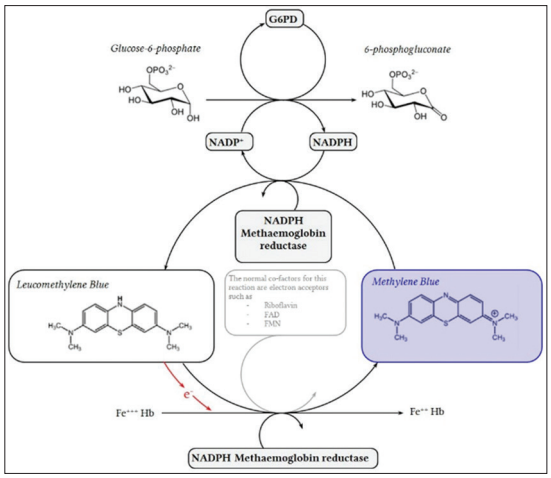

Figure 2: Methemoglobin reduction pathway

reduce methylene blue to leukomethylene blue, which is necessary for the activation of the NADPH-dependent metHb reductase system. G6PD-deficient individuals are also prone to methylene blue-induced hemolysis. Methylene blue may also add to oxidative hemolysis. Moreover, in the presence of hemolysis, high-dose methylene blue can itself initiate metHb formation.[8,9]

TREAMENT OF METHEMOGLOBINEMIA

Hereditary methemoglobinemia is treated with ascorbic acid, 300 to 600 mg orally daily divided into 3 or 4 doses.[10]

The first-line therapy for drug-induced methemoglobinemia is IV methylene blue (1–2 mg/kg). Treatment should be considered when the metHb is 30% in an asymptomatic patient and 20% in a symptomatic patientafter exposure to oxidizing drugs.[11] Exchange transfusion is reserved for patients in whom methylene blue therapy is ineffective.

CONCLUSION

Methylene blue (BLUE) cures cyanosis (BLUE) of MHb, but we should be cautious about the presence of accompanying G6PD deficiency or else, it can be potentially hazardous to the condition of patient causing excessive hemolysis, and sometimes, even leading to fatality. Therefore, in any patient presenting with MHb associated with severe hemolytic anemia, it is desirable to check G6PD activity before administering methylene blue.

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How to cite this article: Ragupathi S, Priya A, Kannan, Kumar S, Muralidharan U. Methemoglobinemia in a Child with Glucose-6-phosphate Dehydrogenase Deficiency - A Case Report. Int J Sci Stud 2018;5(11):182-184.

Source of Support: Nil, Conflict of Interest: None declared.