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Acute glomerulonephritis secondary to G6PD deficiency with secondary Methemoglobinemia

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Abstract
Introduction: G6pd deficiency is a X linked chromosomal disorder affecting males and females are carriers. It presents with haemolytic anaemia and intravascular hemolysis. The enzyme deficiency causes decreased production of NADPH in the erythrocytes which keeps glutathione in reduced form preventing oxidative stress in cells. Secondary meth-haemoglobinaemia occurs in susceptible individuals, due to decreased active form of haemoglobin available for caring oxygen to cells.
A 2 years old male child presented in the hospital emergency with complaints of cough, cold and fever for 3days and increased work of breathing with scanty brown coloured urine since 24hours. On examination there was severe pallor, mild perioral cyanosis and icterus. He had respiratory distress with bilateral crepitation, on auscultation the heart sounds are normal with S3 gallop rhythm. Child was managed in PICU by the standard protocols. Investigations revealed g6pd deficiency, meth-haemoglobinaemia, slight increase in bilirubin levels, normal complement levels. Uri analysis had protein 2+, blood 3+, raised urine: creatinine ratio and on microscopy 10-12RBCS. The child was managed conservatively and gradually improved with high concentration oxygen therapy and blood transfusion.
Discussion: the hemolysis was triggered by oxidative stress on the erythrocytes by acute infection and use of anti-pyretic drug. The child clinically improved with conservative treatment and was discharged.

Keywords: Acute glomerulonephritis secondary, g6pd deficiency, secondary Methemoglobinemia

Introduction
G6PD deficiency affects around 400 million people worldwide and is characterized by considerable biochemical and molecular heterogeneity [8]. The prevalence of G6PD deficiency varied from 2.3 to 27.0 per cent with an overall prevalence of 7.7 per cent. Frequency of G6PD deficiency was observed in the *Gamits* (31.4%), *Dhankas* (20.4%), *Warlis* (19.6%), *Dhodias* (17.8%), *Bhils* (16.3%) and *Garasiyas* (15.2%). *Bhils* from Nasik district of Maharashtra have a very low frequency (1.4%). A complete absence of Gd^- gene was observed among the *Mahadev Kolis* from Ahmednagar district of Maharashtra [9].
G6PD deficiency is an X linked chromosomal disorder, which affects males and females are carriers. Glucose- 6 -phosphodiesterase is an important enzyme for maintenance of red blood cell energy production, it catalyses the first step of the hexose monophosphate shunt and gives one molecule of NADPH, which maintains the glutathione in reduced functional state, thus preventing oxidative stress. The most common manifestation is the episodic haemolytic anaemia caused by triggers (infection, use of drugs) and chronic non-spherocytic haemolytic anaemia.
Methemoglobinemia is a clinical syndrome caused by increased levels of methaemoglobin in serum as a result of congenital changes in the haemoglobin synthesis or metabolism leading to imbalance in reduction and oxidation of haemoglobin.

Case summary
A 2years male child presented in the hospital emergency with complaints cough, cold and fever since 3days with increased work of breathing and passage of scanty dark brown urine.
On examination, the child was conscious and irritable. On general examination the child had severe pallor, mild perioral cyanosis, mild icterus. The pulse rate was 150/min, on auscultation normal heart sounds were heard with S3 gallop rhythm; Respiratory rate: 70/min with signs of respiratory distress and bilateral crepitation; blood pressure 90/50mmhg;

oxygen saturation 68-70% off O2, peripheral pulses were well felt and capillary refill time <3sec., no oedema, and lymphadenopathy. On per abdominal examination the liver was soft, palpable 3cm below the costal margin in the mid clavicular plane. The urine output was low (0.3-0.5ml/kg/hr).

The patient was immediately shifted to paediatric intensive care unit and airway, breathing and circulation was stabilized. Child was not maintaining oxygen saturation was put on mechanical ventilatory support and vitals stabilized. Necessary treatment was started as per the standard protocols. The arterial blood gas analysis demonstrated: ph: 7.46, PaCO2: 26mmhg, PaO2: 98mmhg, HCO3 13.3mmol/l. The investigation demonstrated the following results: haemogram - Hb: 5.4gm/dl, Haematocrit:13.8%, Mean corpuscular volume: 79.7%, Mean corpuscular haemoglobin concentration: 36.8g/dl, Peripheral blood smear: normocytic normochromic red blood cells, Anisopoikilocytosis, polychromasia +, occasional bite cells, Reticulocyte count: 1%, White blood cell: 21000/mm3, Platelet count 2.80lakh/mm3. The liver function test showed total bilirubin: 1.8mg%, direct bilirubin: 0.2mg%, indirect bilirubin 1.6mg% S. Lactate dehydrogenase: 430IU/l, SGPT: 20IU/L, SGOT 127IU/L, S. ALP 48IU/l.G6pd levels: 1.5 (>0.5U/gm. hb), sickling test: negative and direct coombs test: negative. The renal parameters viz. S. creatinine: 0.5mg% and blood urea: 37mg/dl with electrolytes and serum proteins within the normal range. Urinalysis revealed specific gravity: 1.010, pH- 6.5, raised red blood cells in urine 10-12/hpf, urine protein 2+, blood 4+, urine changed colour on standing to dark brown. Spot urine protein level 625.0mg/dl, Urine protein: creatinine ratio 13.92. S. C3 Complement levels: 1.27gm/l normal. The chest x-ray was within normal limits and the 2DECHO was also normal.

The patient was transfused with one unit of packed cell volume. The patient was maintaining a Spo2 of 80-85% on Fio2 of 100% on mechanical ventilation. The colour of the blood drawn was also dark brown on blotting paper and this raised the suspicion of meth-haemoglobinaemia. The meth-haemoglobin levels were 29.57%. The urine continued to be dark brown in colour for 3days and The renal function test was within normal limits.

The patient was given 2nd PCV transfusion. The urine output gradually improved from day 3 of illness. In view of the above clinical picture and laboratory findings a diagnosis of acute glomerulonephritis due to G6pd deficiency induced hemolysis with meth-haemoglobinaemia. The patient improved clinically and was discharged.

Discussion

G6pd deficiency occurs most commonly in the tropical and subtropical zones of eastern hemisphere in India the prevalence is of 3% [2]. This was the first episode of haemolysis in this child, triggered by use of antipyretic drug for fever leading to oxidative stress on the red blood cells.

Methaemoglobin is the oxidised form of haemoglobin, which does not bind to oxygen and increases affinity of O2 for the partially oxidised portion of haemoglobin and shifts the oxygen dissociation curve to the left [3]. The predominant pathway for methb reduction is NADPH dependent reaction catalysed by cytochrome b5, it utilises the NADPH produced by G6PD in hexose monophosphate pathway. The diagnosis depends on high degree of suspicion. These patients will not be maintaining the saturation in spite of normal pao2 and without significant cardiopulmonary insufficiency. Anaemia makes the patient more suasceptible to Met-Haemoglobinemia by reducing the functional stores of Hb. Meth-haemoglobin levels above 10-15% change colour of the blood to brown and the child develops central cyanosis which is not responsive to O2 therapy [5]. Cardiovascular symptoms of anxiety, dysponea and cyanosis are common between 20-30% which the patient had.

Treatment of Methemoglobinemia primarily depends on the severity of the disorder. Once the causative agent is removed the patient improves within a span of 36hours. Supportive therapy with supplemental oxygen increases plasma levels of dissolved oxygen. Methylene blue, an oxidising agent which is used in reduction of the meth-Hb levels but in g6pd deficiency the red blood cells do not produce enough NADPH to reduce the methylene blue to methylene leucolblue [8]. This patient responded to high concentration oxygen administration, two units of packed cell tranfusion and supportive treatment.

In a case report by Marijin Schurman *et al.* noted the rare occurrence of Methemoglobinemia with g6pd deficiency after the boy ingested fava beans. The presentation was with anaemia and cyanosis and due to intravascular hemolysis developed acute renal failure,

In the a study done by Sarkar *et al.* [7] in children with intravascular haemolysis secondary to hemolysis due to G6pd deficiency found azotaemia in 20 patients. Those without oliguria were treated with supportive care and those with oliguria and acute renal failure were treated by dialysis.

The principle intervention for reducing hemolysis in individuals with G6PD deficiency is avoiding exposure to drugs known to trigger hemolysis. In a 2016 systematic review of published reports, revealed no evidence of harm for vitamin C, vitamin E, vitamin K, ginkgo biloba, or alpha-lipoic acid when used in g6pd patients as supportive therapy [3].

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