CASE REPORT

Acute haemolytic anaemia and myolysis due to G6PD deficiency

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SUMMARY

A 2-year-old African-American male patient with sickle cell trait developed cough, red coloured urine, pallor and fatigue. The patient was hospitalised. Diagnostic workup showed that he was glucose 6 phosphate dehydrogenase (G6PD) deficient in erythrocytes. He also had chest X-ray findings of pneumonia. His urine examination showed the presence of haemoglobin and myoglobin. On repeated questioning it was found that he had a moth ball in his mouth a few days prior to this medical episode. This case illustrates a rarely described complication of myolysis in G6PD deficient persons on exposure to a strong oxidant. A review of the literature showed that most people with G6PD deficiency tolerate exercise well without untoward effect in muscles. However, assay of myoglobin in urine has not been routinely performed in these patients during acute haemolytic episode, and thus it is uncertain how frequent myoglobulinaemia occurs in a similar stress situation.

BACKGROUND

Glucose 6 phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect, caused by mutations in the X-chromosome G6PD gene. More than 400 million people worldwide are affected by this enzyme deficiency.¹ The total global prevalence of G6PD deficiency was estimated to be 7.1%.² It is expressed in all tissues, where it catalyses the first step in the pentose monophosphate pathway converting glucose-6 phosphate to 6 phosphogluconate with production of reduced nicotinamide adenine dinucleotide phosphate (NADPH). NADPH is used to convert GSSG (oxidised glutathione) to GSH (reduced glutathione). GSH then reduces peroxides to prevent oxidative damage of cell membrane and other cell constituents. Unlike other tissues, erythrocytes depend solely on this pathway for generation of GSH since it lacks mitochondria.¹ Thus erythrocytes are most severely affected by this enzyme deficiency. Chronic non-spherocytic haemolytic anaemia, acute haemolytic crisis and the neonatal jaundice are the most commonly known manifestations of individuals with G6PD deficiency.^{1 3} Manifestations of G6PD deficiency of the muscles such as myalgia, cramping and myoglobi-nuria in association with haemolytic crisis have rarely been reported. In fact two representative review articles^{1 3} of G6PD deficiency fail to mention this complication.

We describe a 2-year-old male patient with sickle cell trait and G6PD deficiency, who was admitted

with acute haemolytic episode together with evidence of myolysis. We will also review past reports of patients who developed rhabdomyolysis during acute haemolytic crisis due to G6PD deficiency.

CASE PRESENTATION

A 2-year-old African-American male patient with sickle cell trait was admitted with cough, increasing pallor and red coloured urine. The patient or parents did not specifically mention of any pain of legs or difficulty in walking. Besides having sickle cell trait and mild reactive airway disease, he had been a healthy child. He had no significant neonatal jaundice. A younger brother has sickle cell disease and both parents have sickle cell trait. No history of G6PD deficiency in the family was reported. At the time of admission, the parents denied ingestion of any toxin, drugs or fava beans.

At the time of hospital admission, he had heart rate of 135/min, respiratory rate of 41/min. and his oxygen saturation by a pulse oxymetre reading was 90% with a half litre of oxygen supplement through a nasal cannula (normal above 93 without supplemental oxygen). Pallor and scleral icterus were also noted. Bibasilar decreased air entry along with rales in the right lower lungs were appreciated on the auscultation. Spleen was palpable about 1 cm below the left costal margin. Wet diaper had crimson red colour.

The initial complete blood count showed the following: haemoglobin, 6.6 gm/dL, white cell count (WBC), 13 000/ μ L, platelet, 383 000/ μ L, absolute reticulocyte count, 0.38 million/ μ L (14.3%). Blood smear showed five nucleated red blood cells (RBCs)/100 WBCs and many schistocytes and microspherocytes. Direct antiglobulin test was negative. Other laboratory tests showed: lactate dehydrogenase (LDH), 2947 (100–225 U/L), creatine kinase, 2155 (26–174 U/L), serum ferritin, 4708 ng/mL (22–322) and methaemoglobin, 4.7% (0.4–1.5%). Myoglobin/haemoglobin was detected in the patient's urine by Hemastix (Siemens Health Care Diagnostics Inc, Tarrytown, New York, USA). The urine then was ultrafiltered using centrifree ultrafiltration devices (Merck Millipore Ltd. Tullagreen, Carrigtwohill, Co. Cork, IRL; pore size 30 000 MW) (myoglobin has approximate molecular size of 16 700, while haemoglobin's molecular size is 65 000–68 000, and thus haemoglobin is retained in the filter). The filtrate was again positive, when tested with Hemastix indicating that the urine contained myoglobin. RBC G6PD assay showed a very low level of 4.1 U (7.0–20.5 U/g of

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haemoglobin) in the presence of marked reticulocytosis. Chest X-ray showed lower lobe infiltrates.

On learning the low G6PD enzyme level, we revisited the history with the parents. It revealed that 3 days prior to admission, he was found a moth ball in his mouth at home. Mother retrieved the whole moth ball from his mouth and he later developed cough. Myoglobin in urine and increased creatine kinase are indicative of rhabdomyolysis. The patient recovered successfully with respiratory support and supportive management.

TREATMENT

Supportive care only.

OUTCOME AND FOLLOW-UP

The patient completely recovered from acute haemolytic episode and pneumonia.

DISCUSSION

Our patient showed clear signs of acute haemolysis, but also evidence of myolysis consisting of high LDH, elevated creatine kinase in blood and myoglobin in urine. G6PD activity in the erythrocytes was very low in spite of the significant reticulocytosis, but not absent, suggesting most likely A- variety. Though he had pneumonia that occurred later, the most likely triggering event was ingestion of moth ball (naphthalene). In our region (Flint, Michigan, USA) we believe that this is the most common offending agent for acute haemolytic crisis in the G6PD deficient children. It is unclear whether the sickle cell trait played any role in his myoglobinuria. Kimmick and Owen⁴ reported a 36-year-old man with G6PD deficiency and sickle cell trait developing acute haemolysis and rhabdomyolysis (myoglobinuria, myalgias and malaise) following 'vigorous exercise'. Since myoglobinuria appears to be rare in G6PD deficient participants, and our patient and this patient had sickle cell trait, sickle cell trait may have contributed to myolysis. It remains to be seen, however, how rare myoglobinuria is in association with haemolytic crisis in G6PD deficient individuals, since it is not routinely looked for.

G6PD activity of the muscle cells correlates well with that of erythrocytes.⁵ Thus one may expect that in G6PD deficient individuals there may be symptoms due to oxidative damage of myocytes. However, such reports have been rare. Two of four cases reported by Bresolin *et al*⁶ had muscular symptoms (myalgia, weakness and muscle fatigability). Another patient in the same report, a pentathlon-trained athlete, collapsed and became unconscious while competitively running,⁶ but the fourth patient in the same report was asymptomatic. A patient described by Ninfali *et al*⁷ developed myalgia and dark urine without anaemia. Ninfali *et al* in 1995⁵ reported a study of G6PD activity of quadriceps muscle biopsy specimens, and concluded that in all three subsets of deficiency (A-, Mediterranean and Seattle-like), the activity was between 1.4% to 18.8% of controls. All patients studied reported symptoms of cramps, myalgia and fatigability. However, this is most likely due to selection bias of the participants. In fact, in most cases patients remain asymptomatic with exercise. For example, an elite long distance runner was fortuitously discovered to have G6PD deficiency without any symptoms in his long competitive sports life.⁸

A few studies were carried out to demonstrate whether G6PD deficient patients who exercised under controlled conditions showed evidence of excess oxidation damage compared with non-deficient individuals. One study with nine male G6PD

deficient and control participants, performing eccentric muscle damaging exercise protocol, showed 'the same time course and magnitude of the changes of the selected muscle performance, redox status and haemolysis measured' between these two groups of participants.⁹ In another study, nine G6PD deficient volunteers and nine non-deficient controls ran at 75% of their maximum heart rate for 45 min. There was no increase in blood oxidative biomarkers (reduced glutathione, oxidised glutathione, lipid hydroperoxides, etc.) after exercise in either group of individuals.¹⁰ This may be partly due to the fact that muscles unlike erythrocytes have alternative way to generate GSH. NADP+ (oxidised form of NADP) can be generated by NAD+ kinase, then reduced to NADPH by the action of malic enzyme or/and NADP+ dependent isocitrate dehydrogenase.⁹ This alternate pathway may also apply to the oxidative stress situation such as in our patient, but in this instance reactive oxygen radicals may have been too overwhelming for the alternative pathway to compensate totally.

Pneumonia this patient had may be related to naphthalene inhalation. We think that inhalation was a more likely route than ingestion for this toddler who could have kept moth ball in his mouth and later was discovered by the parent. In a murine model, inhalation or intraperitoneum injection of naphthalene causes acute injury to Clara cells (non-ciliated bronchial epithelial cells).¹¹ The toxicity seems to be related to metabolic products of naphthalene catalysed by P450 mono-oxygenase, an enzyme located in Clara cells.¹² Though we were unable to find any case of human pneumonia due to naphthalene inhalation in the literature, variability in activities of this enzyme due to polymorphism may account for the respiratory symptoms and severity of toxicity, though this is speculative.

In conclusion we described a 2-year-old African-American male patient who developed rhabdomyolysis, together with acute haemolytic crisis on exposure to a moth ball. The current literature indicates that severe manifestations related to muscle damage in G6PD deficient individuals are rare. Experimental reports indicate that exercise does not cause any measurable oxidative damage to muscle tissues in deficient individuals.

Learning points

- ▶ In sickle cell trait acute drop in haemoglobin could be due to associated enzyme defect.
- ▶ Acute haemolysis in glucose 6 phosphate dehydrogenase deficient participants may develop significant myoglobinuria, which may jeopardise renal function, if not treated.
- ▶ Red colour of the urine is not always due to haemoglobinuria, but it could be myoglobinuria.

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Competing interests None.

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