Exercise-Induced Severe Rhabdomyolysis in G6PD Deficiency Presented with Heat Stroke: A Case Report

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ABSTRACT

BACKGROUND The prevalence of glucose-6-phosphate deficiency in Malaysian female population is 1.05%. Although triggers for haemolysis are well documented, exercised induced crises have been described. We report a 26-year-old female army officer who presented with loss of consciousness and severe dehydration after 4 consecutive days of the high-intensity sport. At presentation, she was hypotensive and had a high-grade fever. Blood investigations revealed acute kidney injury, elevated creatinine kinase of more than 100,000 U/L, anaemia, hyperbilirubinemia with raised lactate dehydrogenase suggestive of haemolysis. On further questioning, she had G6PD deficiency. Literature review on exercise-induced oxidative stress to the skeletal muscle is presented. Probable mechanisms of cellular injury in rhabdomyolysis related to G6PD deficiency are also discussed. Unrecognized G6PD deficiency among army personnel posed both health concerns to the patient and military service.

KEYWORDS Glucose-6-Phosphate Deficiency, Exercised Induced Crises, Army Officer, Rhabdomyolysis

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is most common enzymes deficiency in the world affecting almost half a billion population. It is a common inherited disorder affecting the Asian, Africans and Mediterranean populations. Although the mode of inheritance is x-linked, which cause by mutation of G6PD gene, female may also be affected. The prevalence of G6PD deficiency in Malaysia is 6.35% and of this, 1.05% are female. The highest prevalence is among the Orang Asli which account for 11% in male and 7% in female [1].

G6PD is used to catalyse the conversion of NADP to NADPH in a pentose phosphate pathway. G6PD deficiency will lead to haemolysis if exposed to oxidative stress. The red blood cell depends solely on this pathway for the generation of GSH since it lacks mitochondria. The most common manifestation of G6PD crisis is prolonged neonatal jaundice, acute and chronic haemolytic anaemia. However, haemolytic crisis together with severe rhabdomyolysis which occurs during exercise-induced heat stroke is rarely described.

We described a case of a 26-year-old lady officer who presented with severe rhabdomyolysis and hemolysis after she was involved in strenuous physical activities and developed heat stroke. We also discuss the possible related mechanisms involved and review cases of patients with G6PD deficient hemolysis and rhabdomyolysis.

CASE PRESENTATION

26-year-old Malay lady, an army officer from Royal Medical Corp with underlying G6PD deficiency, presented to the Emergency Department of 96 Armed Forces Hospital, Lumut with reduced conscious level, GCS 5/15, high-grade fever with a temperature of 40.7 degrees Celsius and hypotension. Prior to the presentation, she was involved in high-intensity sports for 4 consecutive days and took part in hiking competition at Bukit 300, a hill with 300m elevation above sea level, on the day of the presentation. She was well hydrated prior to the competition and wore appropriate sports gear.

At the Emergency Department, she was immediately resuscitated with 6 pints of intravenous fluid and vigorous tepid sponging. Her blood pressure picked up to 100/60mmHg with a pulse rate of 120 beats per minute and her GCS improved to 12/15. Her body temperature was later normalized. She was pale with no jaundice. Her lungs were clear with vesicular breath sound bilaterally and the cardiovascular system showed dual rhythms with no murmur. Her abdomen was soft with no evidence of hepatosplenomegaly. Her urine was dark coloured.

Laboratory findings showed mild normochromic normocytic anaemia with haemoglobin of 10.7g/dL, creatinine of 159umol/L, suggestive of acute kidney injury and uric acid level of 617umol/L. Her liver function test was normal and urine microscopy showed red blood cell (RBC) 5+.Initial creatinine kinase (CK) result showed 230U/L and lactate dehydrogenase (LDH) of 217U/L.

The patient regained full consciousness on day 2 of presentation and complained of pain at both the upper limbs and proximal part of the lower limbs. She was able to take orally well and her kidney function normalized with the hydration given. Unfortunately, the creatinine kinase level increased despite hydration and reached a peak level of 100,519 U/L five days after the initial presentation. Forced alkaline diuresis was then started. The force alkaline diuresis regime includes a 20mls of 8.4% Sodium Bicarbonate in each pint of normal saline and intravenous Frusemide to induce diuresis. The haemoglobin level was also noted to be on the decreasing trend, from 10.7g/dL to 9.0g/dL with raised LDH (1190U/L) and bilirubin level (27.2umol/L) suggestive of acute haemolysis. The full blood picture, however, did not show bites/fragmented red blood cells

or Heinz bodies. The urine myoglobin was also negative but there was evidence of RBC in the urine.

The creatinine kinase level decreased after the initiation of forced alkaline diuresis and the episode of mild haemolysis was halted as the haemoglobin stabilized and returned to baseline after 10 days from the initial presentation. On further questioning, she admitted to the fact that she was G6PD deficient. However, she never had any episode of dark-coloured urine on strenuous activities prior to this episode. The patient was finally discharged after 2 weeks of hospitalisation and was given follow up at the Medical Outpatient Clinic for further assessment on her medical fitness status.

DISCUSSION

Our patient had a severe case of rhabdomyolysis with haemolysis after bouts of high-intensity physical activities that can be considered as an oxidative stress to the patient with G6PD deficiency. She also complained of myalgia of both her upper and lower limbs and dark coloured urine even after an adequate hydration.

Heavy exercise is well known to accelerate the production of reactive oxygen species (ROS) which can exceed the capacity of antioxidant defence and causes oxidative stress. During the exercise where the production of ROS increases, erythrocytes are at increased risk of oxidative damage. These oxo-radicals are also responsible for myofibre disruption and loss of intracellular proteins, which cause post-exercise soreness [2]. Both erythrocytes and myocytes contain an antioxidant defence system in order to combat the formation of ROS.

However, several studies have shown that G6PD deficient individuals exhibit increase oxidative stress in several other tissues, including myocytes. In one study, Jamurta [3] compared the effect of moderate strength exercise to the oxidative stress among a group of normal individuals and G6PD deficient individuals, they found that the oxidative stress markers remained unaffected in both groups. Moderate strength exercise in this study is defined as exercise up to 75% of their maximum target heart rate for 45 minutes. The negative findings in this study could be explained by the fact that muscle, unlike erythrocytes has an alternative pathway to generate glutathione (GSH).

In our patient, however, she was involved in high intensity (defined as an exercise where subject achieved more than 80% of maximum target heart rate). This can generate an overwhelming ROS which could not be compensated by the alternative pathway and hence causing extensive rhabdomyolysis and haemolysis.

Meister [4] demonstrated that marked glutathione (GSH) depletion induced skeletal muscle degeneration was associated with mitochondrial damage. Since G6PD plays a key role in the production of NADPH utilized by the glutathione reductase to maintain GSH in the reduced form, one may deduce that, in G6PD deficient muscle, a lower level of NADPH leads to a decrease of intracellular GSH, which in turn increases the cell vulnerability to the reactive oxygen compounds and free radicals formed in the aerobic metabolism. With reference to this, it should be emphasized that heart and skeletal muscle have low levels of catalase and superoxide dismutase as compared with other tissues and therefore might be expected to be dependent on GSH linked reactions, for detoxication of reactive oxygen species [5].

On the contrary, a study by Theodorou [6] has shown that muscle function and redox status of G6PD deficient individuals are very similar to those of controls. Their study has shown that G6PD is not a critical component in a cellular antioxidant both for the erythrocytes and myocytes. They suggested that the free radicals generated after an exercise as the major contributor for the red cell and muscle damage and hence it opposed the concern that G6PD deficient individuals are less capable of performing high intensity, muscle-damaging physical activities.

In another study by Ninfali et al [7], it has been shown that there is a statistically significant correlation between erythrocytes and myocytes G6PD activity. In a patient who has hemolysis after an oxidative stress together with symptoms of myalgia, raised CK level and myoglobinuria, we can clinically speculate the role of G6PD in muscle metabolism which predisposed myocytes injury. The speculative interpretation of the proportionality of the two tissue comes from the fact that they arise from a common mesodermal origin. Hence, both tissues are vulnerable to the same oxidative stress.

Furthermore, this study also shows that the different type of G6PD deficient variant may react differently to oxidative stress whereby an A variant is associated with less pronounce enzyme defect at the muscle cells compared to the Mediterranean and Seattle-like.

CONCLUSION

Due to the relationship between the role of the G6PD enzyme in both erythrocyte and myocyte, we postulate that G6PD deficiency as the most probable cause which contributes to our patient's symptoms and clinical signs. In our opinion, G6PD deficient patient should avoid high-intensity physical exercises, since the high amount of oxygen radicals produced by aerobic muscle metabolism may induce skeletal muscle degeneration and myoglobinuria, namely rhabdomyolysis. Hence, to mitigate the risk of developing severe rhabdomyolysis in G6PD deficient personnel, we should address the exercise intensity, adequacy of hydration and controlled heat exposure on military personnel involved in exercise and training.

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