CASE REPORT

DENGUE COMPLICATED BY ACUTE HAEMOLYSIS, METHAEMOGLOBINEMIA, HEPATITIS AND RHABDOMYOLYSIS IN A PATIENT WITH G6PD DEFICIENCY

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Abstract

Glucose 6 phosphate dehydrogenase (G6PD) is a housekeeping enzyme critical in the redox metabolism. In red blood cells, it is the only source of nicotinamide adenine dinucleotide phosphate hydrogen(NADPH) that acts directly and, via glutathione, defends these cells against oxidative stress. Dengue infection,like other infections, can trigger intravascular haemolysis in G6PD deficiency patients. We have reported a 17 year old boy with G6PD deficiency who presented with dengue fever which was complicated by acute haemolysis, methaemoglobinemia, hepatitis and rhabdomyolysis.

Key words: Dengue infection, Haemolysis, Methaemoglobinemia, Hepatitis, Rhabdomyolysis, Glucose-6-Phosphate Dehydrogenase deficiency.

Introduction

Glucose 6 phosphate dehydrogenase (G6PD) is a housekeeping enzyme critical in the redox metabolism[1]. In red blood cells, it is the only source of NADPH that directly, and via glutathione, defends these cells against oxidative stress. In G6PD deficiency, haemolysis is usually triggered by exogenous agents. The G6PD gene is located in chromosome X and therefore its deficiency is more common in males than females[2]. Patients with G6PD deficiency can be clinically asymptomatic or present with neonatal jaundice or acute haemolytic anaemia[3]. Acute haemolytic anaemia can be triggered by Fava beans, infections and drugs[4,5]. Severe intravascular haemolysis in G6PD deficiency can lead to acute renal failure via a multitude of mechanisms including deposition of iron in the kidneys[6,7]. Although there is no clear association between G6PD deficiency and dengue severity or viral replication in general[8], dengue infection, like other infections, can trigger intravascular haemolysis in patients with G6PD deficiency. There are reported cases suggesting that G6PD deficient patients suffer more from Dengue Haemorrhagic Fever compared to normal G6PD subjects[9].

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Methaemoglobinaemia occurs when red blood cells contain methemoglobin at levels higher than 1% in which the heme iron is oxidized to the ferric state rather than the ferrous state. The cardinal feature of methaemoblobinaemia is cyanosis, mainly seen in the lips and nail beds, but patients also can present with lightheadedness, headache, tachycardia, fatigue, dyspnoea and lethargy. Severe haemolysis due to G6PD deficiency may manifest as methaemoglobinaemia[10], most probably due to the release of nitric oxide [11,12].

Case history

A 17-year-old Sri Lankan Tamil boy with G6PD deficiency was referred to the medical casualty on day two of a febrile illness with positive Nonstructural protein 1(NS1) antigen for dengue. He was diagnosed to have G6PD deficiency at the age of seven. His younger brother and his maternal uncle were also affected by this inherited condition. He had undergone a blood transfusion in the past following a febrile illness and the lowest Haemoglobin level recorded was 6.2g/dl. Otherwise he was leading a normal life with good school performance.

On admission, in addition to fever he had myalgia, arthralgia and severe nausea. On examination he was pale and mildly icteric. No lymphadenopathy or organomegaly were noted. His vital parameters were stable with an oxygen saturation of 99% on ambient air.

Initial investigations revealed a Haemoglobin of 8.9g/dl and the C-reactive Protein (CRP) was 27.6mg/l(Normal <5). On day 3 of the illness his Haemoglobin was 6.3g/dl and he was transfused two units of compatible blood. He also had blood transfusions on subsequent days to maintain his Haemoglobin more than 8.0g/dl. The patient then developed cyanosis of his nail beds with headache and oxygen saturation on ambient air was noted to be low (88%) without any lung signs., A possibility of methaemoglobinaemia was considered and spectroscopic examination of blood for methaemoglobin levels confirmed methaemoglobinaemia with a value of 9.5% (Normal<2%).

As the urine colour was persistently dark in the absence of significant haemolysis a Creatine Phospho Kinase (CPK) level was requested on day six of illness to exclude rhabdomyolysis and it was found to be 1677units. He also had a rise in serum creatinine levels on day 6 of illness and the presence of myoglobin in urine confirmed rhabdomyolysis. (See Table (1) for serial biochemical profile)

The liver enzymes continued to rise from day two to day seven in the absence of hypotension or organ hypoperfusion, which was compatible with primary dengue hepatitis. However, the disproportionate rise of AST compared to ALT, could also be explained by tissue hypoxia possibly due to methaemoglobinaemia. Even though he had ultrasonographic evidence of fluid leakage into the pleural space on day 4 of the illness his blood pressure, pulse pressure and urine output were well within normal range throughout the course of the illness. He was managed with minimal doses of antipyretics and meticulous fluid management and made an uneventful recovery with a hospital stay of 10 days. Renal and liver function returned to baseline on discharge.

The oxygen saturation returned to 99% indicating a reduction of metheamoglobineamia and it was confirmed by a repeat methaemoglobin level of 2%.

Table 1: Investigation profile

Test and normal range	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
WBC ($4-10x10^9$)	5.2	10.2	13.5	23.0	25.2	18.2	11.3	8.6	10.6	6.0
Haemoglobin (13-16g/dl)	8.9	6.3	7.3	8.0	8.0	9.0	8.4	8.6	8.6	8.1
Platelets ($150-410x10^9$)	145	49	50	71	90	80	70	60	110	120
ALT (16-63U/L)	44	42	631	1553	1489	1233	855	492	352	157
AST (15-37U/L)	304	471	2440	5128	4498	4107	1611	381	170	39
T.Bilirubin (0-17.1xμmol/L)		49.2			86.9	88.9	59	39.8	11.1	10
CRP (3.5-5.1mmol/L)	27.6	24.9		43.6	25.7	14.3	7.6	3.7	2.3	
S.Cr (71-115μmol/L)		93	103		210	303	387	385	341	254
LDH (100-190U/L)		4243				9996	7871	2635	1685	1253
PT (10-13sec)			15.5							12
APTT (21-39sec)			76.4							38
Methaemoglobin levels(%)			9.5							2

Table 2: Arterial blood gas analysis

Parameter	Value
PH	7.30
pCO_2	38 mmHg
pO_2	18 mmHg
Lactate	4.1 mmol/l
HCO_3^-	18.7 mmol/l
SpO_2	24%

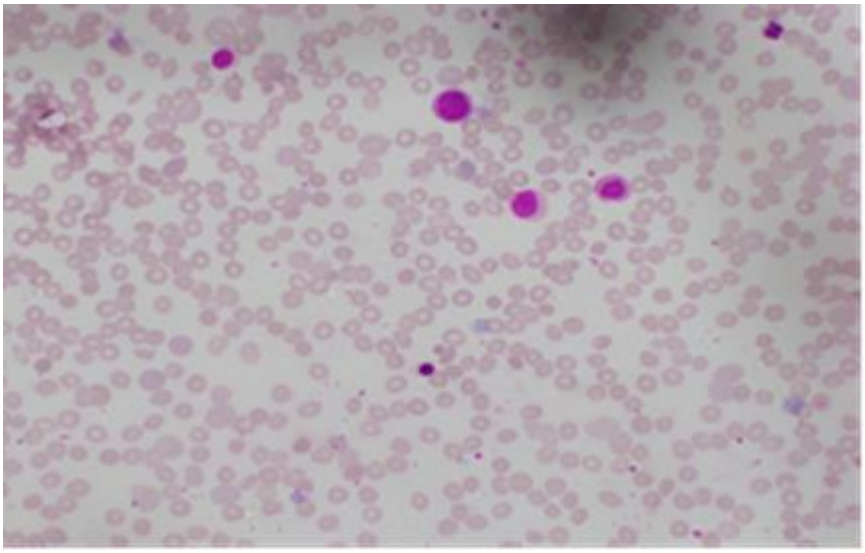

Figure 1: Blood film showing reticulocytes, nucleated red blood cells and bite cells which indicate active haemolysis

Discussion

G6PD deficiency is not a common inherited haemolytic anemia in Sri Lanka[13] and its prevalence has marked regional variation[14] . However dengue is endemic in the country[15]. In general there is no direct association between G6PD deficiency and dengue severity or viral replication[8] but there are some reported cases that altered redox state of dengue virus 2 infected monocytes from G6PD-deficient individuals appears to augment viral replication in these cells. Dengue virus 2 infected G6PD-deficient individuals may contain higher viral titers, which may be significant in enhanced virus transmission[16]. Furthermore, granulocyte dysfunction and higher viral loads in G6PD-deificient individuals may result in a severe form of dengue infection[16].

In this patient an elevated white blood cell count and CRP was noted. The elevated WBC count can be explained by hyperactive bone marrow due to ongoing active haemolysis. Modest elevation in CRP could be attributed to the inflammatory response of the rhabdomyolysis[17]. Elevated transaminases in the absence of hypotension or organ hypoperfusion are compatible with primary dengue hepatitis but it can also be explained by tissue hypoxia due to methaemoglobinaemia although there was no demonstrable evidence.

Clinical Management of dengue in a patient with G6PD deficiency is often challenging as it is complicated by acute haemolysis and its haemodynamic and biochemical sequalae. Elevated liver enzymes, dropping haemoglobin and reactive neutrophil leukocytosis would hinder the markers of dengue severity, bleeding, leakage etc. Methaemoglobinaemia with a false low reading of SpO_2 will further interfere with the monitoring of oxygenation in particular with the limitation of performing frequent arterial blood gases due to the risk of bleeding as a result of thrombocytopenia.

Drugs that are used to treat symptoms of a viral illness including pain relief, antiemetics, and medications to prevent upper gastro intestinal bleeding could not be used liberally as it might worsen the haemolysis due to oxidative stress in a patient with G6PD deficiency. Hence the only modality of treatment is an accurate and rational fluid management under close observation in a specialised unit, and appropriate blood transfusion as needed. This patient was managed according to the national dengue guidelines[18] and made an uneventful recovery.

Conclusion

Managing a dengue infected patient with G6PD deficiency is often challenging considering the influence of each condition on the other in several aspects including clinical monitoring, assessing severity and management. Meticulous management of fluid balance is the cornerstone in managing such complicated dengue patients under close observation by skilled health personal.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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