Association Between Glucose 6-Phosphate Dehydrogenase (G6PD) Deficiency And Fatal Outcome Of Hepatitis E Infection In Middle-aged Men

Dear Sir,

Due to contaminated food sources from China, hepatitis E virus (HEV) has become the leading cause of acute oral-faecal transmitted hepatitis in Hong Kong. Notification of incidence is required by law. From 2001 to 2010, a total of 525 cases were reported to the Department of Health. Of these, 352 were men and 173 were women, with a male to female ratio of 2:1. The median age of the patients was 51 (range 2–89) years. The severity ranged from asymptomatic enzyme derangement to hepatic failure, and 12 patients had since died (ten men and two women with a median age of 67 [range 53–82] years). Among them was one of our patients, a 54-year-old man with glucose 6-phosphate dehydrogenase (G6PD) deficiency, who died of haemolysis and methaemoglobinaemia after consuming undercooked porcine liver.[1] Intriguingly, a retrospective review of the other 11 death records showed two other G6PD-deficient men. In the other nine cases (seven men, two women), the G6PD status was either not tested or not recorded.

The first case of G6PD-deficiency was a 53-year-old man who presented with right upper quadrant pain. Over four days, he developed progressive jaundice, anaemia (haemoglobin [Hb] from 11.6 g/dL to 7.9 g/dL) and acute renal failure (creatinine from 68 IU/mL to 622 IU/mL). There was no history of recent travel. Orthotopic liver transplantation was contemplated. The workup showed absent haptoglobin, reticulocytosis and circulating hemighost cells, and G6PD deficiency was confirmed. Despite haemodialysis and transfusion support, the patient developed recurrent seizure and sepsis, and died 58 days after initial presentation.

The second case was a 54-year-old man who developed flu-like symptoms and epigastric pain. He had just returned to Hong Kong after consuming seafood in Shenzhen, China. This was followed by jaundice and tea-colored urine. Three days after admission, he developed anuria, hyperkalaemia and experienced a rapid fall in Hb levels (from 12 g/dL to 8.3g/dL) with haemoglobinuria. Biochemical screening revealed G6PD deficiency. Despite haemodialysis, the patient died of hepatic and renal failure two days later.

This is the first attempt at a comprehensive estimation of risk factors for HEV-related mortality. Since HEV case reporting is difficult to enforce, its registration may be incomplete and biased toward severe cases. However, despite the inherent limitations, there is an important signal associating fatal outcome with middle-aged G6PD-deficient men. Fatality rates are higher in males than females (2.8% vs. 1.2%), but this was not statistically significant. On the other hand, all deaths occurred among patients aged over 50 years ($n = 301$) and none among the younger patients ($n = 224$) (relative risk [RR] = 10.9, $p < 0.001$, Fisher's exact test). Most importantly, three of the ten male deaths occurred in G6PD-deficient patients. Clinically and statistically, this is unlikely to be a chance occurrence. The recurrent pattern of death, severe intravascular haemolysis followed by acute renal failure, was uniform in all three cases. Such a course of events is well-recognised for G6PD deficiency complicating viral hepatitis.[2] The local incidence of G6PD deficiency for males ($n = 223,696$) and females ($n = 208,457$) was 4.47% and 0.27%, respectively.[3] Even assuming that all the other seven male fatalities had normal G6PD levels, this represents a 6.8 times deviation from the expected incidences ($p = 0.008$, Fisher's exact test). An alternative explanation would be that G6PD deficiency per se contributes to either HEV susceptibility and/or symptoms, rendering the G6PD-deficient proportion of non-fatal cases higher than the expected background population percentages.

The obvious absence of universal G6PD screening in all reported HEV patients makes verification of such a hypothesis impossible. Nevertheless, our simple observation of risk association between HEV and G6PD still holds. Furthermore, it has important implications. With decades of universal birth screening, many middle-aged members of the public are aware of their G6PD status. Avoidance of relevant drugs and food items has largely eliminated G6PD-related deaths. Proper food preparation should be added to the list, with undercooked seafood and porcine meat and liver being the most common sources of HEV infection.[4] Hence, thorough cooking of such food items would be prudent.[5] At the same time, G6PD status should be screened in all HEV patients. In addition, rapid deterioration may ensue for middle-aged male patients with G6PD deficiency; thus, early consideration should be made for exchange transfusion and renal support.

Although now well-recognised in Hong Kong, such awareness should be extended to all other areas where G6PD deficiency is prevalent. Two separate studies from Singapore reported incidences of G6PD deficiency at 1.62% for Chinese, 1.80% for Malays, 0.76% for Indians among army recruits,[4] and 3.2% in newborn males.[6] In many Asian countries, consumption of uncooked, undercooked or contaminated food is commonplace.[7] Hopefully, with increased awareness, unnecessary cases of death in otherwise healthy individuals can be prevented.

Yours sincerely,

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