Received: 28 March 2024 | Accepted: 2 April 2024

DOI: 10.1002/ajh.27324

MORPHOLOGY UPDATE

Beware of methylene blue in possible G6PD deficiency

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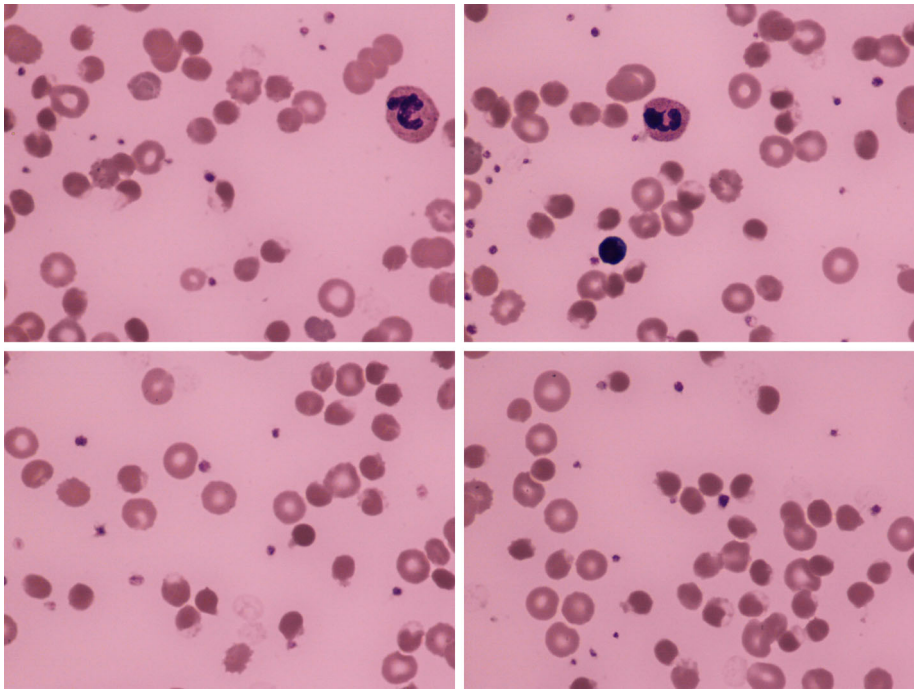

A seven-year-old, previously fit and well, Northern European boy presented with fever, shortness of breath, pallor, jaundice, and left upper quadrant pain. His family reported a two-day history of upper respiratory tract infection and fever. He was found to have tachycardia, tachypnea, and low oxygen saturation of 85% on room air. He was commenced on oxygen supplementation. Despite this, the oxygen saturations remained low. Venous blood gas analysis showed a pH of 7.43, lactate 1.4 mmol/L, and hemoglobin concentration (Hb) of 53 g/L with a high methemoglobin percentage of 11.1%. His blood count confirmed the Hb and showed a reticulocyte count of 114×10^9/L, platelet count of 376×10^9/L, and white cell count of 16.1×10^9/L. The child was in respiratory distress and appeared gravely ill. There was nothing in the history to suggest a diagnosis of glucose-6-phosphate dehydrogenase (G6PD) deficiency and a decision was therefore made to administer methylene blue. An infusion with a dose of 1 mg/kg was prescribed. Within a few minutes of the start of the infusion, the oxygen saturation fell from mid 80s to low 70s with the lowest reading of 68%, leading to stopping the infusion. The total administered dose of methylene blue was approximately 0.35 mg/kg. The oxygen saturation returned to 85% within 10 min of stopping the infusion. The child was admitted to the intensive care unit for respiratory support and blood transfusion, leading to clinical

improvement. After cessation of the infusion results of blood film examination became available. This revealed numerous irregularly contracted cells and hemighosts (top left and right, all images ×100 objective). There were red cell inclusions suggestive of Heinz bodies, protruding from erythrocytes and within hemighost cells (bottom left and right). Polychromatic macrocytes were present. The blood film was strongly suggestive of severe oxidant-induced hemolytic anemia, raising the possibility of G6PD deficiency. An assay showed low G6PD activity of 2.4 u/gHb (normal range 6.3–11.2 u/gHb). Renal function was normal, bilirubin was 128 μmol/L and lactate dehydrogenase was greatly raised at 1903 units/L. A chest X-ray did not identify any lung pathology and hypoxia was attributed to methemoglobinemia. Subsequently further clinical details were obtained and revealed a history of transient neonatal jaundice and consumption of fava bean prior to the acute deterioration. The boy was commenced on folic acid supplementation. He was discharged from hospital with an Hb of 77 g/L. Repeat blood tests showed complete recovery of hemoglobin to 128 g/L 3 weeks from discharge. A subsequent G6PD assay showed G6PD activity of 0.7 u/gHb. DNA analysis showed a hemizygous mutation of *G6PD*, c. 653C>T; p. (Ser218Phe), also known as G6PD Mediterranean.

Methemoglobinemia is an uncommon feature of oxidant exposure in G6PD deficiency, resulting from inhibition of NADPH reductase. It can be induced, together with acute hemolysis, by broad bean consumption.[1] It is sometimes the presenting feature. Methylene blue can be indicated for the treatment of severe methemoglobinemia, which can be a life-threatening condition. However in G6PD deficiency, it is specifically contraindicated since it can add to oxidant stress and increase methemoglobin concentration. G6PD deficiency was not strongly suspected in this boy since no previous relevant history was known and both parents identified their ethnicity as White British. Only a single maternal great-grandmother was not of Northern European origin.

If a blood film during acute hemolysis suggests severe oxidant damage in the absence of any known history of oxidant exposure, G6PD deficiency should be suspected, even when the ethnic origin and previous history are not suggestive. In the absence of a clear diagnosis, transfusion including exchange transfusion, is a therapeutic option.

The value of performing a G6PD assay during an acute hemolytic episode is questioned since a raised reticulocyte count can lead to a falsely normal result. If the level is reduced, the information is valuable but if the result is normal it is important to retain this as a diagnostic possibility and perform a follow-up assay after full recovery from the hemolytic episode.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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How to cite this article: Tatarinova O, Lund K, Bain BJ. Beware of methylene blue in possible G6PD deficiency. *Am J Hematol*. 2024;99(10):2016-2017. doi:10.1002/ajh.27324