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# Favism Induced Methemoglobinemia in G6DP Deficient Patients: Case Series and Review of Literature

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**Introduction:**

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a well-known cause of hemolysis. It has a notable prevalence in African, Asian, and Mediterranean countries. Favism is a common trigger of oxidative stress in G6PD deficient people, which can lead to hemolysis. Additionally, fava bean ingestion can cause methemoglobinemia (MethHgb), an abnormal variation in the Hgb in which the ferrous (Fe2+) iron in heme is oxidized to the ferric (Fe3+) state. It is rare to have both G6PD deficiency and MethHgb secondary to favism at the same time. The first-line treatment for MethHgb is methylene blue. However, in G6PD deficient patients, it can potentiate hemolysis.

**Methods:**

We reviewed the literature using PubMed and Google scholar and found 6 cases of MethHgb secondary to favism in patients with G6PD deficiency. We also analyzed two cases which are still unpublished, making a total of 8 cases.

**Results:**

All 8 cases were male with median age of 18 years (1 - 56). 1 patient had a prior diagnosis of G6PD deficiency while 7 were newly diagnosed. Median Hgb was 8.3gm/dL (4.6 - 12.5) and median MetHgb was 7.8 % (3.5 - 35). 1 patient received methylene blue, and 4 received Vitamin C. All of the patients recovered and were discharged [Table 1].

**Unpublished case 1:**

A 56-year-old male presented with MethHgb and hemolytic anemia, secondary to fava bean ingestion. Hgb on admission and lowest recorded were 9.9 and 6.5 gm/dL, respectively. He had an $SPO^2$ of 70% on room air and 101.2 % on ABG. Methylene blue administration worsened the hemolysis as he was G6PD deficient but not diagnosed before. He got better with discontinuation of methylene blue and Vitamin C and was discharged on day 5.

**Unpublished case 2:**

A 43-year-old male, known case of G6PD deficiency presented with MethHgb and hemolytic anemia, secondary to fava bean ingestion. Hgb on admission and lowest recorded were 12.5 and 7.4 gm/dL, respectively. He had an $SPO^2$ of 82% on room air and 100 % on ABG. He received IV vitamin C and recovered and was discharged on day 4.

**Discussion:**

Methemoglobinemia is usually acquired, secondary to oxidative stress in the body, but can rarely be congenital. Enzyme systems such as NADH methemoglobin reductase, NADPH methemoglobin reductase, ascorbic acid, and glutathione reductase systems keep a check on the accumulation of methemoglobin in the blood. However, these mechanisms can be insufficient to counter the conversion of Hgb to MethHgb, consequently promoting an oxidative state in the body. It can be due to the overproduction of methemoglobin (secondary to exposure to certain drugs, chemicals, or food items, but can sometimes be hereditary) or under conversion to Hgb due to unavailable enzyme mechanisms. One of the causes of the inability to counteract methemoglobin can be secondary to G6PD deficiency.

Patients with MetHgb have a low oxygen saturation ($SPO^2$) on pulse oximeters but a falsely high $SPO^2$ on arterial blood gasses (ABG). The treatment depends on symptoms and the level of MethHgb. The first step is to remove any possible precipitator if present. Symptomatic patients (and asymptomatic with a level of methemoglobin >30 %) are treated with methylene blue (1-2mg/kg), which is reduced to leuko-methylene blue via NADPH dependent methemoglobin reductase. This, in turn, reduces methemoglobin back to Hgb, correcting the abnormality [Figure 1].

Rarely, patients can present with co-occurrence of MethHgb and G6PD deficiency. In such cases, caution is required while giving methylene blue as they do not have sufficient levels of NADPH to reduce it. Otherwise, a cascade of oxidative hemolysis ensues secondary to underlying G6PD deficiency, resulting in a vicious cycle of further methemoglobinemia.

The most frequent cause of this co-occurrence is the ingestion of fava beans, which can simultaneously induce MethHgb and potentiate G6PD deficiency. One of our patients had a history of favism without developing any symptoms. Only this time, he ate fava beans in a larger amount, leading to hemolysis and MethHgb.

**Conclusion:**

Favism is a rare cause of the co-occurrence of methemoglobinemia and hemolysis in G6PD deficient individuals. It is vital to identify G6PD deficiency in patients presenting with MethHgb, as the initiation of methylene blue in such individuals can result in a cascade of oxidative hemolysis. A history of fava beans ingestion without any symptoms does not rule out G6PD deficiency, as it is proportional to the number of beans ingested.

| Author/ Journal | Patients' Age, Sex Nationality | G6PD deficiency | Type | Hgb (gm/dL) presentation / lowest | MetHgb | Methylene blue | Vit C | Outcome |
|---|---|---|---|---|---|---|---|---|
| Journal of hospital medicine | 43 years, Male Albanian | New diagnosis | NA | 8 / NA | 8 % | No | Yes | Discharged |
| Odievre MH et al. | 6 years, Male Algerian | New diagnosis | G6PD[Mediterranean] | 9.2 / 6 | 7.6 % | No | No | Discharged |
| Rehman A et al. | 30 years, Male Nepalese | New diagnosis | NA | 8.4 / 5.9 | 35 % | No | Yes | Discharged |
| Schuurman M et al. | 1 years, Male Afghan | New diagnosis | NA | 6.2 / 6.2 | 6.2 % | No | No | Discharged |
| Leunbach TL et al. case 1 | 1 year, Male Iraqi | New diagnosis | NA | 6.9 / NA | 11.4 % | No | No | Discharged |
| Leunbach TL et al. case 2 | 6 years, Male Iraqi | New diagnosis | NA | 4.6 / NA | 14.9 % | No | No | Discharged |
| Unpublished case 1 | 56 years, Male Qatari | New diagnosis | NA | 9.9 / 6.5 | 5.6 % | Yes | Yes | Discharged |
| Unpublished case 2 | 43 years, Male Qatari | Known case | NA | 12.5 / 7.4 | 3.5 % | Yes | Yes | Discharged |

**Table 1.** Reported cases of methemoglobinemia and G6PD deficiency secondary to favism (Hemoglobin: Hgb, Methemoglobin: MetHgb [normal 0 – 1.5%], Glucose-6-phosphate dehydrogenase: G6PD)

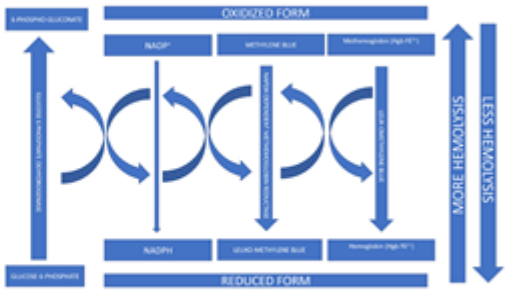


**Figure 1.** Mechanism of reduction of methemoglobin to hemoglobin by methylene blue; adapted from Schuurman et al. and Percy MJ et al.

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## Disclosures

No relevant conflicts of interest to declare.

# Author notes

* Asterisk with author names denotes non-ASH members.

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