Case report

Favism-induced severe hemolysis and methemoglobinemia in a patient with G6PD-deficiency: case report and literature review

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Abstract:

Acquired methemoglobinemia in favism is uncommon. We report a 4.5-year-old Thai boy presenting pallor and cyanosis after fava bean ingestion. Oxygen saturation by pulse oximeter was 64% while arterial blood gas showed normal partial oxygen pressure, and methemoglobin level was 18.6%. Glucose-6-phosphate dehydrogenase (G6PD) deficient status was diagnosed by pathognomonic blood smear in an acute hemolytic settings despite negative G6PD fluorescent spot test. Blood transfusion was administered without providing methylene blue. G6PD Songklanagarind (196T>A) variant was later confirmed with moderately deficient G6PD enzymatic activity.

Keywords : ● *Favism* ● *Methemoglobinemia* ● *G6PD deficiency*

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รายงานผู้ป่วย

ภาวะเม็ดเลือดแดงแตกรุนแรงและเมธฮีโมโกลบินนีเมียในผู้ป่วยโรคพร่องเอนไซม์ G6PD ที่รับประทานถั่วปากอ้า

สุรพงศ์ เลิศธรรมเกียรติ และ สโรชา อิทธิอมรกุลชัย

ภาควิชาโรงเรียนแพทย์รามาธิบดี สถาบันการแพทย์จักรีนฤบดินทร์ คณะแพทยศาสตร์โรงพยาบาลรามาธิบดี มหาวิทยาลัยมหิดล

บทคัดย่อ

ผู้ป่วยเด็กชายไทยอายุ 4 ปี 6 เดือนมาโรงพยาบาลด้วยอาการซีดหลังจากการรับประทานถั่วปากอ้า โดยออกซิเจนที่วัดได้จากเครื่อง pulse oximeter เท่ากับร้อยละ 64 ในขณะที่ระดับออกซิเจนในเลือดมีค่าปกติ ทำให้คิดถึงภาวะเมธฮีโมโกลบินนีเมียที่ยืนยันด้วยระดับเมธฮีโมโกลบินที่สูงถึงร้อยละ 18.6 การวินิจฉัยโรคพร่องเอนไซม์ G6PD ได้จากผลตรวจสเมียร์เลือดที่มีลักษณะเฉพาะในภาวะเม็ดเลือดแดงแตกเฉียบพลัน แม้การตรวจคัดกรองเอนไซม์ด้วย G6PD fluorescent spot test จะปกติ ทำให้ผู้ป่วยได้รับการรักษาที่เหมาะสมคือการรับเลือด โดยไม่ได้ให้ methylene blue ซึ่งผู้ป่วยรายนี้ได้รับการยืนยันการวินิจฉัยโรคพร่องเอนไซม์ G6PD โดยพบความผิดปกติของสารพันธุกรรมชนิด G6PD Songklanagarind (196T>A) และระดับการทำงานของเอนไซม์ G6PD ที่ต่ำกว่าปกติ

คำสำคัญ : ● *Favism* ● *Methemoglobinemia* ● *G6PD deficiency*

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2565;32:369-74.

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common red blood cell (RBC) enzymatic defect affecting more than 400 million individuals worldwide[1]. G6PD deficiency is an X-linked disorder. In Thailand, 11 G6PD variants were reported among 397 patients with G6PD-deficiency[2].

Favism is an acute hemolytic crisis among patients with G6PD-deficiency after ingesting fava beans. Divicine and isouramil, which are metabolites of vicine and convicine, produce reactive oxygen species causing severe oxidative damage in G6PD-deficient red cells[3]. Favism, reported in 3.6% of Thai children with G6PD-deficiency, occurring within 1 to 3 days after ingesting dried fava beans[4].

Methemoglobin (MetHb) is abnormal hemoglobin (Hb) where heme ferrous (Fe^{2+}) iron is oxidized to ferric (Fe^{3+}) iron. Clinical severity of methemoglobinemia depends on the percentage of MetHb. Low pulse oximeter reading, cyanosis and dark brown blood are the early signs in asymptomatic patients with methemoglobinemia[5].

Acquired methemoglobinemia from favism is an uncommon condition. There have been 11 case reports of favism-induced methemoglobinemia since 2009[6-14]. This study reported a 4.5-year-old vegan boy with methemoglobinemia after ingesting fava beans.

Case presentation

A previously healthy 4.5-year-old boy presented acute anemia for two days. One day after eating one pack (40 grams) of dried fava beans, he experienced a fever. He looked pale and his urine turned brown. He denied having any other symptoms, such as runny nose, cough, vomiting, diarrhea or rash. Acetaminophen was the only medication used to treat fever. His family members are all vegetarians. He used to eat one small piece of fava bean once, without any complications. Fortunately, he did not like it at that time. He had no history of jaundice requiring phototherapy during the neonatal period.

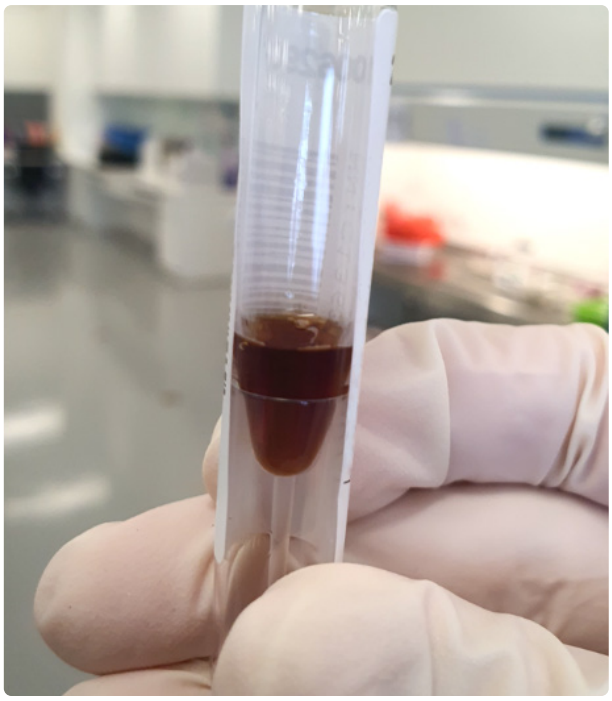

Figure 1 Patient's brown serum suggested methemoglobinemia

Physical examination revealed a body temperature 38.2°C, heart rate 160 bpm, respiration rate 28 times/min, blood pressure 102/66 mmHg and oxygen saturation 64% at room air. Marked pallor and mild jaundice were noted. Neither heart murmur nor respiratory distress were found.

Arterial blood gas at room air showed pH 7.38 and partial pressure of oxygen 97 mmHg despite low pulse oximetry reading. The color of his serum was brown (Figure 1), and co-oximetry confirmed a methemoglobin level of 18.6% (normal 0-1.5).

Laboratory results showed Hb 2.9 g/dL, Hct 10.2%, and reticulocyte count 9.3%. Serum lactate dehydrogenase level was 2,938 U/L and urinalysis showed blood 3+ without RBC. Serum creatinine was 0.35 mg/dL which was normal for age.

Ghost cells, hemoglobin leakage cells, irregular contracted red cells and blister cells were found in peripheral blood smear (Figure 2) which were consistent with acute intravascular hemolysis.

The G6PD enzyme was qualitatively measured using the fluorescent spot test but showed normal result, and Heinz body staining was negative. Despite the normal

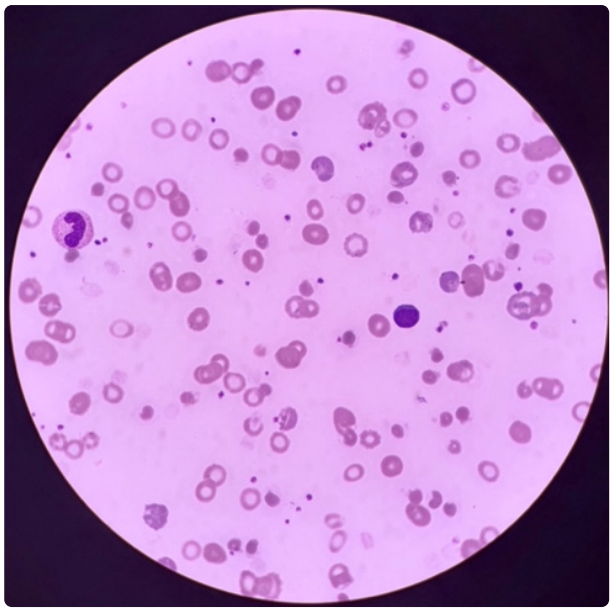

Figure 2 Peripheral blood smear revealed poikilocytosis 3+, anisocytosis 1+, microcytosis 1+, hypochromia 2+, ghost cells 2+, hemoglobin leakage cells 2+, irregular contracted red cell 2+ and blister cell 1+, which was consistent with acute intravascular hemolysis.

G6PD result from screening test, acute intravascular hemolysis from G6PD deficiency was still the most likely diagnosis due to the history of fava bean exposure and the pathognomonic blood smear finding.

Blood transfusion was given without administering methylene blue. Desaturation was rapidly resolved after RBC transfusion and MetHb level was gradually decreased to the normal level after the second unit of RBC transfusion, and Hb before discharge was 8.8 g/dL. No evidence of heart failure from severe anemia was observed, and good urine flow during admission was observed.

G6PD genotyping using multiplex amplification refractory mutation system-polymerase chain reaction (multiplex ARMS-PCR) for 10 G6PD variants was negative. Therefore, G6PD gene sequencing of 13 exons was requested and showed positive for G6PD Songklanagarind (196T>A) which is less common in the Thai population. The G6PD enzymatic activity was quantitatively measured five months later. The result showed 1.73 IU/g of Hb (Normal > 6.97) which was consistent with moderately deficient activity[15]. Repeated G6PD fluorescent spot test also showed G6PD enzyme deficiency.

Discussion

Altogether, 11 cases diagnosed as acquired methemoglobinemia from favism were reported (Table 1)[6-14]. To the best of our knowledge, this constitutes the first case report in a Southeast Asian population. The pathogenesis of methemoglobinemia in favism is caused by severe oxidative stress from the substances in fava beans leading to the overproduction of MetHb. Additionally, the depletion of many necessary enzymes counteracting the formation of MetHb, such as nicotinamide adenine dinucleotide phosphate (NADPH)-MetHb reductase, ascorbic acid and glutathione reductase results in under conversion of MetHb to Hb. Among patients with G6PD deficiency, the production of NADPH is decreased. Therefore, MetHb is increasingly formed[12-13].

Methylene blue is the primary treatment of methemoglobinemia by receiving an electron from NADPH to form leukomethylene blue; methylene blue can reduce ferric iron to ferrous iron in RBC. Due to insufficient NADPH among patients with G6PD deficiency, methylene blue may be ineffective with methemoglobinemia. Moreover, methylene blue can also induce hemolytic anemia and worsen methemoglobinemia[15].

The qualitative screening of the G6PD enzyme using a G6PD fluorescent spot test exhibits high sensitivity and high negative predictive value[16-17]. However, during acute hemolytic episodes, G6PD level can be falsely normal from a higher level of G6PD enzyme activity in reticulocytes rather than mature red cells[18]. The interpretation of G6PD result during acute hemolytic episode should be performed carefully.

A peripheral blood smear is necessary for making a diagnosis of G6PD deficiency in previously undiagnosed patients with G6PD deficiency and acute hemolysis because the decision of using methylene blue to treat methemoglobinemia is based on G6PD status[19].

G6PD genotyping using multiplex ARMS-PCR for 10 G6PD variants (Viangchan, Mahidol, Gaohe, Chinese 3, Chinese 4, Chinese 5, Canton, Kaiping, Union and Coimbra) in our institute covered most of the Thai

Table 1 Reported cases of methemoglobinemia from favism

Reference	Sex	Age	Origin	Lowest SpO2 (%)	% MetHb	Lowest Hb (g/dL)	G6PD activity	Reference value for G6PD activity
Schuurman M, et al. (2009)	Male	1 years	Afghan	70	6.2	6.3	0.6 IU/gHb	3.8-5.9
Odièvre MH, et al. (2011)	Male	6 years	Algerian	80	8.7	6.0	3.0 IU/gHb	8.0-22.0
Leunbach TL, et al. (2014)	Male	4 years	Iraqi	74	11.4	9.0	0.08 kU/mol	0.51-1.32
Leunbach TL, et al. (2014)	Male	6 years	Iraqi	78	14.9	6.8	< 0.10 kU/mol	0.51-1.32
Journal of Hospital Medicine (2015)	Male	43 years	Albanian	86	8.0	8.0	1.5 IU/gHb	8.0-13.0
Barent R, et al. (2015)	Male	9 months	Italian	80	7.6	5.5	1.2 IU/gHb	ND
Rehman A, et al. (2018)	Male	30 years	Nepalese	85	35.0	8.4	< 35 mU/10^9 RBC	245-500
Ata F, et al. (2020)	Male	43 years	Qatari	82	3.5	7.4	N/A	ND
Ata F, et al. (2021)	Male	56 years	Qatari	70	5.6	7.0	23 mU/10^9 RBC	224-517
Al-Dubai H, et al. (2021)	Male	47 years	N/A	88	3.6	12.0	24 mU/10^9 RBC	191-327
Pomoni A, et al. (2021)	Male	3 years	Serian	85	7.8	6.0	0.6 IU/gHb	ND
This study (2022)	Male	4.5 years	Thai	64	18.6	2.9	1.73 IU/gHb	≥ 6.97

G6PD, Glucose-6-phosphate dehydrogenase (G6PD); Hb, hemoglobin; ND, no data; RBC, red blood cell; SpO2, oxygen saturation by pulse oximetry

G6PD-deficient population[20-21]. Despite a negative multiplex ARMS-PCR result, our patient was highly suspicious of G6PD deficiency from the clinical presentation and his unique peripheral blood smear. As a result, mutation analysis by direct sequencing is required to confirm the diagnosis of G6PD deficiency[22].

According to the World Health Organization classification, residual G6PD enzymatic activity in our patient with the G6PD Songklanagarind (196T>A) variant was categorized as class III (moderately deficient)[23]. This differed from a related study reporting one patient with this variant presented much lower residual G6PD enzymatic activity defined as class II (severely deficient)[22]. Due to the rarity of cases, the amount of residual G6PD enzymatic activity in a population with this variant should be further collected. Nevertheless, acute intermittent hemolysis after oxidative stress can occur in both class II and III variants and this constitutes the first report of acquired methemoglobinemia from favism in this variant.

Conclusion

Severe hemolysis with methemoglobinemia from favism is uncommon. Methemoglobinemia should be suspected among patients with low pulse oximetry despite normal oxygen from arterial blood gas. A careful evaluation of blood smear during hemolytic episode guides the diagnosis of G6PD deficiency and the proper management of methemoglobinemia.

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