

Case report

Successful treatment of methemoglobinemia in two boys with G6PD deficiency and favism following ascorbic acid therapy

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Abstract:

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common X-linked hematologic disorder that predisposes individuals to acute hemolysis under oxidative stress. A rare complication is the co-occurrence of favism and methemoglobinemia, a condition where hemoglobin is oxidized to the ferric (Fe^{3+}) state, impairing oxygen transport. Management is complicated because methylene blue, the first-line treatment for methemoglobinemia, is contraindicated in G6PD deficiency. **Case Report:** This report describes two Thai boys (aged 2.8 and 3.2 years) who presented with respiratory distress, low oxygen saturation (SpO_2 83-89%), unresponsive to oxygen therapy, and dark urine following fava bean ingestion. Laboratory findings revealed acute intravascular hemolysis with the presence of ghost and blister cells on peripheral blood smears, alongside elevated methemoglobin levels (3.3 and 8.0%). Both patients were newly diagnosed with G6PD deficiency, with case 1 confirmed as the G6PD Mahidol mutation (487G>A) and case 2 confirmed as the G6PD Viangchan mutation (871G>A). Due to the contraindication of methylene blue, both patients were treated with ascorbic acid (intravenous in case 1; oral in case 2) and blood transfusions. The oxygen saturation normalized within 2 and 5 hours after ascorbic acid administration, respectively. **Conclusion:** The co-occurrence of favism and methemoglobinemia is rarely reported, with only 16 previous cases. These cases highlight the importance of recognizing methemoglobinemia among patients with G6PD deficiency presenting with desaturation and demonstrate that ascorbic acid is a safe, effective alternative to treat methemoglobinemia. However, careful consideration of ascorbic acid dosage is essential to avoid potential pro-oxidant effects.

Keywords : ● G6PD deficiency ● Methemoglobinemia ● Favism ● Ascorbic acid

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รายงานผู้ป่วย

การใช้วิตามินซีในการรักษาภาวะเมธฮีโมโกลบินนีเมียในผู้ป่วยโรคพร่องเอนไซม์ G6PD ที่รับประทานถั่วปากอ้า

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บทคัดย่อ

ที่มาและความสำคัญ โรคพร่องเอนไซม์ glucose-6-phosphate dehydrogenase (G6PD) เป็นความผิดปกติทางโลหิตวิทยาแบบ X-linked ที่พบได้บ่อย ทำให้ผู้ป่วยเสี่ยงต่อการเกิดภาวะเม็ดเลือดแดงแตกเฉียบพลันเมื่อได้รับ oxidative stress บางอย่าง ภาวะแทรกซ้อนที่พบได้น้อย คือ ภาวะเม็ดเลือดแดงแตกจากการกินถั่วปากอ้าร่วมกับภาวะเมธฮีโมโกลบินนีเมีย โดยเป็นภาวะที่ฮีโมโกลบินถูก oxidize เป็น ferric state (Fe^{3+}) ทำให้การขนส่งออกซิเจนบกพร่อง การรักษาภาวะนี้มีผลข้างเคียงเนื่องจาก methylene blue ซึ่งเป็นการรักษาหลักสำหรับภาวะเมธฮีโมโกลบินนีเมียมีข้อห้ามใช้ chez ผู้ป่วยโรคพร่องเอนไซม์ G6PD **รายงานผู้ป่วย** ผู้ป่วยเด็กชายชาวไทย 2 ราย (อายุ 2.8 และ 3.2 ปี) มาด้วยอาการหอบเหนื่อย ค่าความอิ่มตัวของออกซิเจนในเลือดต่ำ (SpO_2 83-89%) ซึ่งไม่ตอบสนองต่อการให้ออกซิเจน และมีปัสสาวะสีเข้มภายหลังรับประทานถั่วปากอ้า ผลตรวจทางห้องปฏิบัติการพบภาวะเม็ดเลือดแดงแตกในหลอดเลือดเฉียบพลัน และสเมียร์เลือดพบ ghost cells และ blister cells ร่วมกับระดับเมธฮีโมโกลบินที่สูงขึ้น (3.3% และ 8.0%) ผู้ป่วยทั้งสองรายได้รับการวินิจฉัยว่าเป็นโรคพร่องเอนไซม์ G6PD โดย ผู้ป่วยลำดับที่ 1 ยีนแฝดเป็น G6PD Mahidol mutation (487G>A) และ ผู้ป่วยลำดับที่ 2 เป็น G6PD Viangchan mutation (871G>A) เนื่องจากมีข้อห้ามใช้ methylene blue ผู้ป่วยจึงได้รับการรักษาด้วยวิตามินซีทางหลอดเลือดดำในผู้ป่วยลำดับที่ 1 และทางการกินในผู้ป่วยลำดับที่ 2 ร่วมกับการให้เลือด ค่าความอิ่มตัวของออกซิเจนในเลือดกลับมาเป็นปกติภายใน 2 และ 5 ชั่วโมงหลังได้รับวิตามินซีตามลำดับ **สรุป** ภาวะเม็ดเลือดแดงแตกเฉียบพลันหลังกินถั่วปากอ้าร่วมกับภาวะเมธฮีโมโกลบินนีเมียพบไม่บ่อย การศึกษาก่อนหน้านี้มีรายงานผู้ป่วยเพียง 16 ราย รายงานนี้ชี้ให้เห็นถึงความสำคัญในการวินิจฉัยภาวะเมธฮีโมโกลบินนีเมียในผู้ป่วยโรคพร่องเอนไซม์ G6PD ที่มาด้วยภาวะออกซิเจนในเลือดต่ำ โดยมีวิตามินซีเป็นทางเลือกที่ปลอดภัยและมีประสิทธิภาพในการรักษาภาวะเมธฮีโมโกลบินนีเมีย อย่างไรก็ตามควรพิจารณาขนาดวิตามินซีอย่างระมัดระวังเพื่อหลีกเลี่ยงผลข้างเคียงอันไม่พึงประสงค์

คำสำคัญ : ● ภาวะเมธฮีโมโกลบินนีเมีย ● โรคพร่องเอนไซม์ G6PD ● วิตามินซี

● ภาวะเม็ดเลือดแดงแตกจากการกินถั่วปากอ้า

วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2569;36:307-14.

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common X-linked red blood cell enzymopathy worldwide, affecting over 500 million people, with the highest prevalence in Asian and African populations. This genetic defect impairs the red blood cell's ability to withstand oxidative stress, leading to a spectrum of clinical manifestations ranging from acute hemolytic crisis to asymptomatic carrier states. However, upon exposure to specific triggers - such as infection, oxidative drugs or the ingestion of fava beans - patients can develop life-threatening acute hemolytic anemia.¹ Favism, the specific hemolytic response following fava bean consumption, is observed in approximately 3.6% of Thai children with G6PD deficiency and is classically characterized by pallor, jaundice and hemoglobinuria.²

A particularly rare complication is the co-occurrence of favism with methemoglobinemia, a condition in which ferrous (Fe^{2+}) hemoglobin (Hb) is oxidized to the ferric state (Fe^{3+}), significantly impairing oxygen-binding capacity.³ The management of this dual pathology presents a profound therapeutic dilemma: methylene blue is the standard first-line treatment for methemoglobinemia, but is strictly contraindicated among individuals with G6PD deficiency as it can precipitate massive, fatal hemolysis. Consequently, ascorbic acid has emerged as a vital alternative reducing agent, though its use in this specific context is infrequently documented.⁴ With only 16 cases of concurrent favism and methemoglobinemia reported in the literature to date, clinical experience remains limited.⁵⁻¹⁷ This report contributes to the existing body of knowledge by describing two cases of Thai boys with G6PD deficiency who presented this rare dual complication and were successfully managed using ascorbic acid.

Case report

Case 1

A previously healthy 2.8-year-old Thai male presented low-grade fever, cough and rhinorrhea for two

days. He had a recent history of fava bean ingestion. After that, his urine turned dark brown. He had mild respiratory distress with oxygen saturation (SpO_2) of 89 to 91% at room air despite oxygen supplementation. Physical examination revealed anicteric sclerae, no pale conjunctivae, no abnormal lung signs, and no hepatosplenomegaly. Arterial blood gas (ABG) analysis showed a partial pressure of oxygen (PaO_2) of 186 mmHg despite low pulse oximetry readings. This discrepancy prompted further testing, which detected a methemoglobin (MetHb) level of 3.3%. Laboratory findings revealed a Hb level of 9.1 g/dL, elevated lactate dehydrogenase (LDH), reticulocytosis and urine blood 3+ without red blood cells, supporting the evidence of hemolysis and hemoglobinuria. Peripheral blood smear (PBS) demonstrated blister cells, Hb leakage cells, and bite cells, supporting a diagnosis of acute hemolysis secondary to G6PD deficiency (Figure 1A). One gram of intravenous (IV) ascorbic acid every 4 hours for 8 doses was administered following by a red cell transfusion. His oxygen saturation was normalized within 2 hours after ascorbic acid administration while waiting for a blood transfusion. No adverse reaction to ascorbic acid was observed. Three months after the event, G6PD deficiency was confirmed by G6PD enzymatic activity of 1.35 U/gHb (Normal > 6.7).¹⁸ G6PD genotyping using multiplex amplification refractory mutation system-polymerase chain reaction (multiplex ARMS-PCR) for common G6PD variants later revealed a G6PD Mahidol mutation (487G>A).

Case 2

A 3.2-year-old Thai boy presented with fever, diarrhea and abdominal pain for three hours. He consumed an uncertain number of fava beans the day before. He exhibited mild respiratory distress and SpO_2 of 83% at room air, which was not corrected by oxygen therapy. No abnormalities of the lungs were observed. Physical examination showed moderately pale conjunctivae, anicteric sclera, no abnormal lung signs and no hepatosplenomegaly. ABG analysis revealed PaO_2 of 284 mmHg, where MetHb level was 8%. Laboratory findings

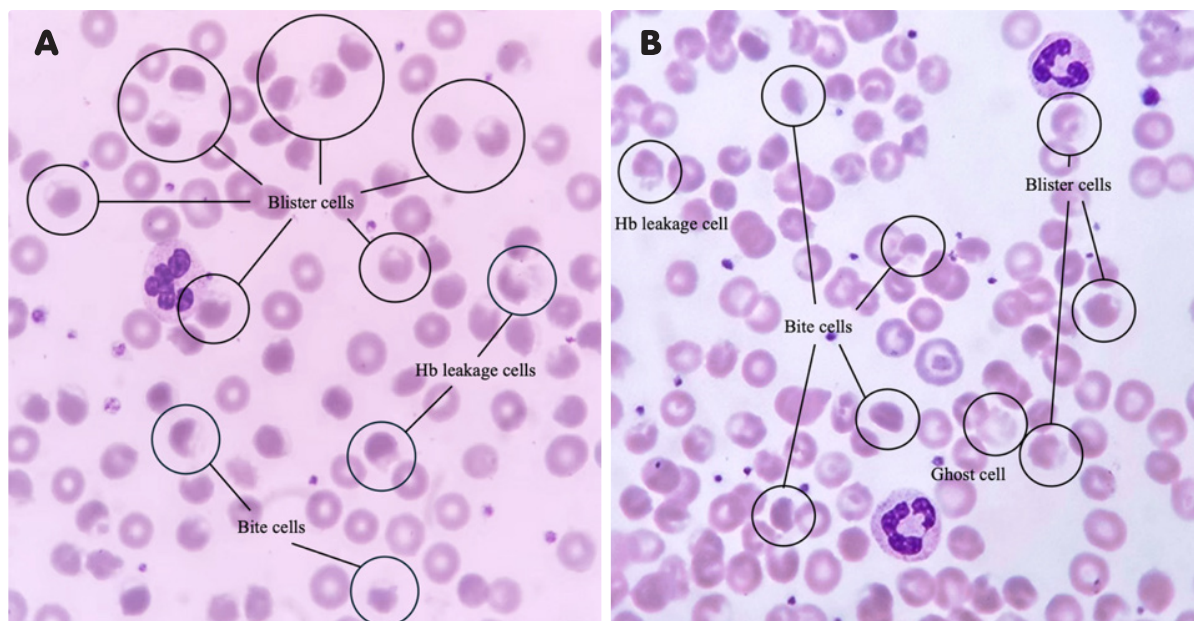


Figure 1 Peripheral blood smear from case 1 (A) and case 2 (B) showed the unique characteristics of acute hemolysis from G6PD deficiency, demonstrated by the presence of blister cells, Hb leakage cells, bite cells and ghost cells.

revealed Hb of 6.1 g/dL, elevated LDH and the presence of hemoglobinuria. PBS also showed blister cells, Hb leakage cells, bite cells and ghost cells, compatible with acute hemolysis from G6PD deficiency (Figure 1B). Oral 100-mg ascorbic acid was administered three times daily for 12 doses together with a blood transfusion. SpO₂ was returned to normal after five hours of ascorbic acid administration without any adverse reaction to the treatment. G6PD deficiency was diagnosed three months thereafter with a G6PD activity at 1.09 U/gHb (Normal > 6.7)¹⁸, compatible with class B variant. Multiplex ARMS-PCR for common G6PD variants was later confirmed for G6PD Viangchan mutation (871G>A).

Discussion

This study reported two cases of favism with methemoglobinemia, a rare concurrent condition.⁵⁻¹⁷ A diagnosis of methemoglobinemia is confirmed when MetHb levels exceed the normal physiological range of 1 to 2%. This often manifests as low pulse oximetry readings despite exhibiting a normal PaO₂. Most reported cases of concurrent favism and methemoglobinemia including our two reported cases remained asymptomatic, presenting

only low pulse oximetry because MetHb levels were not sufficiently high to impair oxygen delivery.¹⁹ One exception involved a case with a MetHb level of 35% where the patient presented headache and tachypnea.⁹

Under physiological conditions, the accumulation of MetHb is primarily prevented by the nicotinamide adenine dinucleotide (NADH)-dependent cytochrome b5 methemoglobin reductase pathway, removing 95 to 99% of endogenous MetHb, where another pathway, nicotinamide adenine dinucleotide phosphate (NADPH)-MetHb reductase, removes the remaining MetHb. Although the latter pathway normally plays a minor role, it serves as the mechanism for methylene blue, the mainstay pharmacologic treatment, to convert MetHb to Hb. Alternatively, ascorbic acid is used to treat methemoglobinemia by reducing oxidant substances, resulting in decreased MetHb production.²⁰

While methylene blue is the first-line treatment for most patients with methemoglobinemia, it is strictly contraindicated in the G6PD-deficient population. Because these individuals lack sufficient NADPH, methylene blue remains unreduced and can exacerbate both hemolysis and methemoglobinemia.^{21, 22} For these high-risk patients,

management shifts to alternative strategies including high-dose ascorbic acid, supplemental oxygen and blood transfusion. In life-threatening or refractory cases, exchange transfusion is employed to rapidly restore the blood's oxygen-carrying capacity.²³

Ascorbic acid has emerged as a critical alternative therapy for patients with methemoglobinemia in G6PD-deficiency. As a reducing agent, it converts ferric iron (Fe^{3+}) back to its functional ferrous state (Fe^{2+}) within the heme group. Its efficacy is strictly dose-dependent and highly influenced by the route of administration. Pharmacokinetic studies indicate that the IV route is significantly more effective than oral dosing to reach therapeutic thresholds. While oral dosing is limited by a plateau effect from intestinal absorption, IV administration bypasses these constraints, yielding plasma concentrations that increase in direct proportion to the dose.²⁴ Consequently, IV delivery is preferred in acute cases to rapidly achieve the high plasma concentrations necessary for effective MetHb reduction.

A total of 18 cases of concurrent favism and methemoglobinemia were identified in the literature (Table 1), with eight patients receiving ascorbic acid, predominantly via the IV route.^{9-11,15,17} While reported dosages ranged from 0.3 to 6 g/day, our first case used a dosage of 6 g/day with a total of 8 g and achieved rapid recovery; however, the dose-dependency of this response remains uncertain due to confounding factors such as initial MetHb levels and the simultaneous use of oxygen and blood transfusions. Although ascorbic acid typically exhibits a slower onset of action compared to methylene blue, our patients' SpO_2 levels normalized within 2 to 5 hours, likely reflecting a synergistic effect between the direct reducing properties of high dose ascorbic acid and supportive therapies.

The therapeutic dosing of ascorbic acid requires careful consideration, as excessive concentrations can ironically exacerbate the paradoxical conditions they are intended to treat. High serum levels of ascorbic acid can act as a pro-oxidant, facilitating the production of

hydrogen peroxide (H_2O_2). Among patients with G6PD deficiency, this oxidative surge can lead to the direct oxidation of Hb to MetHb and trigger lipid peroxidation of the erythrocyte membrane.¹ The resulting membrane instability culminates in acute hemolysis, effectively worsening the hemolysis as reported from using high dose ascorbic acid among patients with G6PD deficiency.²⁵⁻²⁷ Thirty grams of IV ascorbic acid infusion reportedly caused hemolysis in an adult patient with G6PD deficiency.²⁶ High dose ascorbic acid also promotes urinary excretion of oxalate, precipitating oxalate nephropathy, especially in patients with predisposing renal dysfunction.²⁸⁻²⁹

Literature regarding ascorbic acid use in pediatric methemoglobinemia remains limited. Documented dosages vary widely: 1 g/day orally³⁰, 1-2 g IV followed by 300-500 mg orally³¹, 1 g IV every 6 hours for 4 doses¹⁷, 1 g IV every 4 hours for 8 doses³², and 2.5 g IV for 4 doses.³³

Our first case received 1 g of IV ascorbic acid every 4 hours (6 g/day) for 8 doses (8 g in total). This represents a high, though not the highest, pediatric dose in the literature, as Karaçoban reported a cumulative dose of 10 g.³³ Despite this aggressive dosing, which raised concerns about worsening anemia, we observed no clinical evidence of secondary hemolysis or renal impairment. While high-dose ascorbic acid carries a theoretical pro-oxidant risk, our findings suggest that a short term, intensive IV regimen constitutes a safe, effective therapy for patients with G6PD deficiency and methemoglobinemia when standard treatments are contraindicated.

The genetic profile of our patients, carrying the G6PD Mahidol (487G>A) and G6PD Viangchan (871G>A) mutations, reflects the common variants found in Southeast Asia.³⁴⁻³⁸ Both are categorized as class B variants under the updated WHO classification, characterized by G6PD enzymatic activity < 45% of normal and high risk acute hemolysis induced by oxidative stress.³⁹ The successful recovery in both cases suggests that ascorbic acid therapy is an effective intervention across the common G6PD genotypes found in the Thai population.

Table 1 Reported cases of favism with methemoglobinemia among patients with G6PD-deficiency

Reference, year	Patient's age, sex and ethnicity	Lowest SpO ₂	%MetHb	Lowest Hb (g/dL)	Ascorbic acid use, route and dosage	Time to recovery
Schuurman M, et al. (2009)	1 Y, M, Afghan	70	6.2	6.3	No	Day 4 of illness
Odièvre MH, et al. (2011)	6 Y, M, Algerian	80	8.7	6.0	No	60 h
Leunbach TL, et al. (2014)	4 Y, M, Iraqi	74	11.4	9.0	No	Day 3 of illness
Leunbach TL, et al. (2014)	6 Y, M, Iraqi	78	14.9	6.8	No	ND
Journal of Hospital Medicine (2015)	43 Y, M, Albanian	86	8.0	8.0	Yes, ND	ND
Barent R, et al. (2015)	9 mo, M, Italian	80	7.6	5.5	No	ND
Rehman A, et al. (2018)	30 Y, M, Nepalese	85	35.0	8.4	Yes, IV, 4 g/day	24 h
Ata F, et al. (2020)	43 Y, M, Qatari	82	3.5	7.4	Yes, ND	ND
Ata F, et al. (2021)	56 Y, M, Qatari	70	5.6	6.5	Yes, IV, total 3 g	ND
Pomoni A, et al. (2021)	3 Y, M, Serian	85	7.8	6.0	No	Day 3 of illness
Al-Dubai H, et al. (2021)	47 Y, M, ND	88	3.6	12.0	No	Day 2 of illness
Lertthammakiat S, et al. (2022)	4.5 Y, M, Thai	64	18.6	2.9	No	ND
D'souza M, et al. (2022)	37 Y, M, Yemeni	67	14.0	11.8	Yes, IV, 4 g/day	ND
Zheng DJ, et al. (2024)	1.3 Y, M, ND	77	6.3	5.3	No	ND
Sawaftah MA, et al., (2026)	12 Y, M, UAE	84	6.1	5.7	No	ND
Sawaftah MA, et al., (2026)	14 Y, M, UAE	80	10.0	7.7	Yes, IV, total 4 g (4 g/day)	1 h*, day 3 of illness
This study (2026)	2.8 Y, M, Thai	89	3.3	9.1	Yes, IV, total 8 g (6 g/day)	2 h*, 12 h
This study (2026)	3.2 Y, M, Thai	83	8.0	6.1	Yes, oral, total 1.2 g (300 mg/day)	5 h*, day 2 of illness

*time to normal oxygen saturation

dL, deciliter; G6PD, glucose-6-phosphate dehydrogenase; g, gram; h, hour; Hb, hemoglobin; IV, intravenous; M, male; MetHb, methemoglobin; ND, no data; SpO₂, oxygen saturation; UAE, United Arab Emirates; Y, years, Mo, months

Conclusion

This report demonstrates that while methylene blue is contraindicated in G6PD-deficient populations due to the risk of worsening hemolysis, high dose IV ascorbic acid serves as a safe and effective alternative to treat fava bean-induced methemoglobinemia. Ultimately, while aggressive dosing was well-tolerated in these cases, the therapeutic dosage must be considered to avoid the potential for pro-oxidant damage or oxalate nephropathy, underscoring the need for standardized pediatric protocols in acute oxidative crisis.

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