

Hereditary methemoglobinemia presenting as breakthrough seizures: a case letter

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Methemoglobinemia is a rare condition characterized by elevated levels of methemoglobin (MetHb), a form of hemoglobin with oxidized ferric iron (Fe^{3+}) instead of ferrous (Fe^{2+}), rendering it unable to bind oxygen. This leads to impaired oxygen delivery to tissues, causing hypoxia and cyanosis despite normal arterial oxygen tension.^[1] Methemoglobinemia can be congenital or acquired. Congenital forms result from mutations in genes such as *CYB5R3*, which encodes NADH-cytochrome b5 reductase (*CYB5R*), the enzyme responsible for reducing MetHb to functional hemoglobin.^[2]

There are 2 types of congenital methemoglobinemia. Type I (erythrocytic) is limited to red blood cells and presents with mild cyanosis, while Type II (generalized) affects all tissues and is associated with severe neurological impairment and developmental delay.^[3]

CYB5R maintains redox balance in erythrocytes by transferring electrons from NADH to cytochrome b5, which reduces MetHb.^[4] Mutations such as P144L and L148P in the *CYB5R3* gene impair enzyme stability and activity, contributing to congenital methemoglobinemia.^[5]

The *CYB5R* enzyme assay evaluates enzyme activity in patient samples. Hall et al.^[6] described an antibody-based spot test that sensitively detects *CYB5R* activity in hemolysates and helps identify patients with congenital *CYB5R* deficiency.

The standard treatment for acquired methemoglobinemia is methylene blue, which acts as an artificial electron acceptor for NADPH-dependent MetHb reductase, restoring hemoglobin to its oxygen-carrying state.^[1]

We present the case of a 21-year-old woman with a history of epilepsy, attention-deficit/hyperactivity disorder, depression, and anxiety, who presented to the emergency department (ED) with breakthrough seizures. Two weeks earlier, she was seen in the ED for a single generalized tonic-clonic seizure. Computerized tomography brain and chest X-ray were unremarkable, and she was discharged after observation. No

arterial blood gas (ABG) was obtained, and methemoglobinemia was not suspected.

She returned after experiencing 2 witnessed episodes of generalized tonic-clonic seizures at home. She reported compliance with her antiseizure treatment with levetiracetam (LEV) 750 mg twice daily. In the ED, she was given 1 g of LEV, a computerized tomography brain showed no intracerebral abnormalities or changes since the previous exam, and chest X-ray and electrocardiogram were normal. Her initial vitals were notable for hypoxia with an oxygen saturation in the 80s on room air, which did not improve with supplemental oxygen via nasal cannula. A complete blood count and comprehensive metabolic panel were normal except for total bilirubin 1.6 mg/dL. Urinalysis was unremarkable. ABG on 4 L oxygen showed MetHb 16.9%, above the 5% diagnostic threshold (Table 1). Urine toxicology was positive only for marijuana. Poison control was contacted and recommended methylene blue 1 mg/kg. This resulted in immediate improvement in O_2 saturation and she was admitted to the intensive care unit for observation.

Upon further investigation, the patient denied benzocaine or dapsone use and consumption of beets, mushrooms, or freeze-dried fruit. She reported smoking marijuana from a dispensary days prior. She worked in an office with no exposure to oxidizing agents, used city water at home, and denied any intentional toxin ingestion. Repeat ABG 5 hours later showed MetHb 1.2% (Table 1). Neurology recommended magnetic resonance imaging and electroencephalogram as an outpatient. Electroencephalogram showed no epileptiform discharge or focal cerebral dysfunction. Her antiseizure treatment with LEV was increased to 1000 mg twice daily. Poison control advised no further methylene blue.

Due to no identifiable toxin exposure, a *CYB5R* enzyme assay was ordered. After clinical improvement, she had no further seizures, was downgraded from the intensive care unit, and discharged the next day. The *CYB5R* assay later showed 3.2 units/Hgb (reference range: 7.8–13.1), confirming Type I hereditary methemoglobinemia. The patient was informed to take appropriate precautions.

This case showcases a patient with breakthrough seizures likely secondary to MetHb toxicity. The most common cause of congenital methemoglobinemia is autosomal recessive b5 reductase deficiency, as seen here.^[2] Although no other clear etiology for the patient's methemoglobinemia was identified, this enzyme deficiency predisposes patients to toxic causes due to reduced enzymatic activity. Of the 2 *CYB5R* deficiency types, Type I is more common and consistent with this case. Despite elevated MetHb levels, most patients with Type I remain asymptomatic, while Type II presents with intellectual disability and developmental delay and was not suspected here. Regardless of whether methemoglobinemia is congenital or acquired, management remains the same in patients without G6PD deficiency, and 1–2 mg/kg of intravenous methylene blue typically resolves symptoms.^[7]

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Emergency and Critical Care Medicine (2026) 6:1

Received: 14 May 2025; Accepted: 7 November 2025.

Published online: 11 March 2026

<http://dx.doi.org/10.1097/EC9.000000000000173>

Table 1
Arterial Blood Gas Before and After Methylene Blue Administration

Parameter	14:27 (Before Methylene Blue)	19:33 (After Methylene Blue)	Reference Range
ABG HCO ₃ ⁻ (mmol/L)	21.4 ↓	24.0	22–26
Base excess (BE)	–2.2	–0.2	–2 to +2
Temperature (°C)	37.0	37.0	37.0
Corrected pH	7.425	7.418	7.35–7.45
Corrected pCO ₂ (mm Hg)	33.3 ↓	38.1	35–45
Corrected pO ₂ (mm Hg)	228.9 ↑	100.5	75–100
Total hemoglobin (g/dL)	13.7	13.2	12–16
Deoxyhemoglobin (%)	0.0	2.0	<3
Oxygenated hemoglobin (%)	82.8 ↓	96.2	>95
O ₂ saturation (%)	100.0	98.0	>95
O ₂ delivery device	4 L via nasal cannula	Room air	–
Carboxyhemoglobin (%)	0.3	0.6	<1.5
Methemoglobin (%)	16.9 ↑↑	1.2	<1.5
Glucose (mg/dL)	–	109 ↑	70–100

Methemoglobinemia is a rare blood disorder caused by oxidation of hemoglobin’s ferrous iron (Fe²⁺) to the ferric state (Fe³⁺), preventing oxygen binding and leading to functional hypoxia.^[8] Patients with congenital forms should be counseled on potential triggers, as they are more susceptible than the general population due to reduced enzyme activity. Our patient, who had a known seizure disorder, did not present with cyanosis, masking suspicion for methemoglobinemia until it was confirmed on ABG.

While methemoglobinemia is most commonly acquired through exposure to oxidizing agents such as benzocaine, dapsone, or nitrates,^[9] this patient denied use of such substances. She also had no environmental exposure to well water, contaminated food, or industrial chemicals, which may also precipitate methemoglobinemia. The absence of classic findings—such as cyanosis or chocolate-colored blood—further delayed diagnosis, illustrating how congenital cases can present atypically or subtly.^[11]

The patient’s seizure activity, initially thought to be epileptic, was likely a neurologic manifestation of tissue hypoxia from methemoglobinemia. Although rare, seizures and altered mental status can occur when MetHb exceeds 15%,^[10] as in this case. The key diagnostic clue was a disproportionately low oxygen saturation on pulse oximetry despite a high arterial pO₂ (228.9 mm Hg). This “saturation gap,” showing a disparity between pulse oximetry and ABG oxygenation, should prompt suspicion for dyshemoglobinemia in the absence of pulmonary pathology.^[11]

Following methylene blue administration, the patient’s oxygen saturation improved rapidly, and no further seizures occurred. This temporal relationship supports hypoxia as the precipitant of her seizures. Methylene blue acts as a cofactor to accelerate the reduction of MetHb through the NADPH-dependent MetHb reductase pathway, making it first-line therapy for moderate-to-severe methemoglobinemia.^[12]

What sets this case apart is the confirmed enzymatic deficiency in CYB5R, consistent with Type I hereditary methemoglobinemia. This erythrocytic form is typically limited to red blood cells and manifests mainly with cyanosis, not systemic symptoms, distinguishing it from the more severe Type II form.^[2] However, when additional stressors such as metabolic strain or toxin exposure occur, hypoxia may worsen and trigger neurologic events even in the milder Type I phenotype.

This finding expands the known clinical spectrum of hereditary methemoglobinemia.

This case highlights the importance of maintaining a broad differential when evaluating seizure patients, particularly when hypoxia is unexplained or refractory. It underscores the limitations of relying solely on pulse oximetry, which underestimates oxygen saturation in methemoglobinemia. Recognizing a saturation gap and maintaining suspicion for dyshemoglobinemia—especially in younger patients or those without clear oxidant exposure—can be lifesaving.

This case also emphasizes the need for thorough follow-up and long-term management. Hereditary methemoglobinemia has implications for family screening, genetic counseling, and occupational planning. Although Type I disease generally follows a benign course, affected individuals should avoid oxidizing agents and carry documentation of their diagnosis to prevent mismanagement in emergencies.^[3] In some cases, prophylactic vitamin C or riboflavin can help reduce baseline MetHb levels and minimize the frequency of symptomatic episodes.^[13]

Ultimately, this case adds to the limited literature on congenital methemoglobinemia presenting with seizures, particularly in the absence of characteristic physical findings or known exposure histories. It demonstrates the diagnostic complexity of such presentations and the need for interdisciplinary collaboration between emergency medicine, toxicology, neurology, and laboratory medicine.

Here, we presented a patient with a known seizure disorder who presented with breakthrough seizures and unexplained hypoxia. Central nervous system symptoms, such as seizures, can occur with methemoglobinemia but are often overlooked early in diagnosis. Her failure to respond to supplemental oxygen and her ABG results led to recognition of the disorder. With no toxic exposure identified, further workup revealed CYB5R deficiency, confirming congenital Type I methemoglobinemia. This rare condition, though mild in most cases, can present unexpectedly and complicate neurologic disease, underscoring the importance of careful evaluation in similar clinical scenarios.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Desai P was the attending physician; all authors participated in the writing of the paper.

Funding

None.

Ethical approval of studies and informed consent

The study followed the principles of the Declaration of Helsinki as revised in 2013. The Institutional Review Board of HCA Healthcare guidelines states that the publication of case reports is exempt from ethics approval. The patient's informed consent was obtained in writing.

Acknowledgements

We would like to thank Dr William S. Hart, Medical Writer, who provided writing and copy-editing assistance on an initial version of the manuscript.

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How to cite this article: Zazaian A, Sukin Z, Coro J, Desai P, et al. Hereditary methemoglobinemia presenting as breakthrough seizures: a case letter. *Emerg Crit Care Med.* 2026;6(1):75–77. doi: 10.1097/EC9.0000000000000173