

The Saturation Gap as a Diagnostic Clue for Methemoglobinemia in a Child with Persistent Low Oxygen Saturation

Homa Farajkhah

Ardabil University of Medical Sciences

Seyed Hossein Mirlohi

sh.mirlohi2004@gmail.com

Tehran University of Medical Sciences

Mahsa Choroom Kheirabadi

Tehran University of Medical Sciences

Short Report

Keywords: Methemoglobinemia, dyshemoglobinemia, oxygen saturation, hypoxemia, saturation gap, pediatrics

Posted Date: October 12th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10825773/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Persistent low peripheral oxygen saturation in children commonly prompts investigation for pulmonary or cardiovascular disease. However, when oxygen desaturation persists despite an unrevealing cardiopulmonary evaluation, dyshemoglobinemia should be considered.

Case presentation

We report the case of a 7-year-old girl with persistent low peripheral oxygen saturation for approximately five years. Her peripheral oxygen saturation remained between 85% and 89% on room air despite an otherwise normal clinical condition. Extensive investigations, including echocardiography, contrast echocardiography, cardiac computed tomography angiography, chest computed tomography, pulmonary function testing, and neurologic evaluation, did not identify a cardiopulmonary cause for the low oxygen saturation. Arterial blood gas analysis demonstrated a preserved partial pressure of arterial oxygen (PaO_2) of 115 mmHg on room air, increasing to 165 mmHg during a hyperoxia test. The calculated alveolar–arterial oxygen gradient was 2.3 mmHg. The discrepancy between the low pulse oximetry readings and preserved PaO_2 prompted evaluation for a dyshemoglobinemia. Co-oximetry demonstrated a methemoglobin level of 15%, supporting the diagnosis of methemoglobinemia.

Conclusions

Methemoglobinemia should be considered in children with persistent low peripheral oxygen saturation that is disproportionate to their clinical condition and cardiopulmonary findings. Recognition of a discrepancy between pulse oximetry and arterial oxygenation can provide an important diagnostic clue and may help prevent prolonged and unnecessary investigations.

Introduction

Persistent low peripheral oxygen saturation in children generally leads to evaluation for pulmonary parenchymal disease, pulmonary vascular abnormalities, or congenital heart disease. When extensive cardiopulmonary investigations fail to identify an underlying cause, disorders of hemoglobin should also be considered.

Methemoglobinemia is a disorder in which the iron within hemoglobin is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Methemoglobin is unable to bind oxygen normally, and its presence also increases the oxygen affinity of the remaining functional hemoglobin, thereby impairing oxygen delivery to tissues. Methemoglobinemia may be acquired following exposure to oxidizing medications or chemicals or may occur as a congenital disorder associated with abnormalities of hemoglobin or the

enzymatic pathways responsible for methemoglobin reduction, particularly cytochrome b5 reductase deficiency [1, 2].

The clinical manifestations of methemoglobinemia vary according to the methemoglobin concentration, the underlying cause, and the rate at which methemoglobin accumulates. Patients with chronic methemoglobinemia may remain clinically stable despite persistent cyanosis or low peripheral oxygen saturation. A discrepancy between pulse oximetry and arterial oxygen measurements may provide an important clue to the presence of a dyshemoglobinemia [2, 3].

We present a child with persistent low peripheral oxygen saturation over several years who underwent an extensive cardiopulmonary evaluation before methemoglobinemia was identified by co-oximetry.

Case Presentation

A 7-year-old girl was referred to our tertiary pediatric pulmonology center for evaluation of persistent unexplained low oxygen saturation. She had been born at term following an uncomplicated pregnancy and delivery. During infancy and early childhood, she had no significant respiratory symptoms other than intermittent nasal congestion.

At 2 years of age, following an upper respiratory tract infection, low oxygen saturation was incidentally detected during an evaluation for lethargy. Thereafter, repeated measurements demonstrated persistent peripheral oxygen saturation between 85% and 89% on room air. Despite the persistent low readings, she remained clinically well. She had no dyspnea, chronic cough, wheezing, exercise intolerance, recurrent lower respiratory tract infections, cyanotic episodes, or impairment of growth and development.

The patient underwent extensive investigations at different medical centers. Echocardiography and contrast echocardiography demonstrated no structural cardiac abnormality or evidence of intracardiac or intrapulmonary shunting. Cardiac computed tomography angiography demonstrated an anomalous arterial branch arising from the aortic arch; however, this finding was considered incidental and did not provide an explanation for the patient's persistent low oxygen saturation.

Neurologic evaluation, including brain magnetic resonance imaging, magnetic resonance venography, and electroencephalography, was unremarkable.

Polysomnography demonstrated mild obstructive sleep apnea associated with adenoid hypertrophy and chronic sinusitis. Symptoms related to upper airway obstruction improved following corticosteroid therapy; however, the low oxygen saturation persisted. Initial pulmonary function testing demonstrated a mild reduction in lung volumes, whereas repeat spirometry at 7 years of age was normal. Chest radiography and chest computed tomography showed no structural pulmonary abnormality.

At presentation to our center, her resting peripheral oxygen saturation was approximately 89% on room air and increased to 95% with supplemental oxygen. Arterial blood gas analysis demonstrated a PaO₂ of 115 mmHg on room air, increasing to 165 mmHg during a hyperoxia test. These findings, together with

the previous contrast echocardiographic assessment, did not support a significant right-to-left shunt. The calculated alveolar–arterial oxygen gradient on room air was 2.3 mmHg, which was within the expected range.

Because the low pulse oximetry readings were disproportionate to the patient's clinical condition and cardiopulmonary findings, a dyshemoglobinemia was considered. Hemoglobin electrophoresis demonstrated an HbA₂ level of 5.5%, and beta-thalassemia trait was suspected in the context of a positive maternal history. Further assessment with co-oximetry demonstrated a methemoglobin concentration of 15% (reference value < 1.5%), supporting methemoglobinemia as the explanation for the persistent low pulse oximetry readings.

Treatment and Follow-up

Following the diagnosis of methemoglobinemia, the patient was referred to the hematology department for further evaluation and management. Given the chronic nature of the condition, the absence of significant clinical symptoms, and the relatively stable clinical status, conservative management was adopted.

The patient and her family were advised to avoid potential oxidizing agents and medications known to increase methemoglobin formation. Oral vitamin C (ascorbic acid) was initiated as antioxidant therapy. During follow-up, the patient remained clinically stable, with persistent but well-tolerated low peripheral oxygen saturation.

Discussion

Methemoglobinemia is an uncommon but important cause of persistent low peripheral oxygen saturation. Oxidation of hemoglobin iron from the ferrous to the ferric state results in the formation of methemoglobin, which cannot participate normally in oxygen transport. In addition, methemoglobin increases the oxygen affinity of the remaining functional hemoglobin, impairing oxygen release to peripheral tissues [1, 2].

Methemoglobinemia may be acquired or congenital. Acquired forms are generally associated with exposure to oxidizing medications or chemicals, whereas congenital forms may result from defects in the enzymatic reduction of methemoglobin or structural hemoglobin variants [1, 2]. In patients with chronic methemoglobinemia, clinical manifestations may be relatively mild despite persistently low peripheral oxygen saturation.

An important diagnostic clue is the discrepancy between pulse oximetry and measurements of arterial oxygenation. Conventional pulse oximeters estimate oxygen saturation using two wavelengths of light. Methemoglobin absorbs light at both wavelengths and can therefore interfere with conventional pulse oximetry, frequently resulting in readings approaching approximately 85% [2, 3]. In contrast, PaO₂

obtained from arterial blood gas analysis reflects oxygen dissolved in plasma and may remain relatively preserved in patients with methemoglobinemia.

In the present case, the patient's peripheral oxygen saturation remained between 85% and 89% for several years despite an otherwise normal clinical condition. Extensive cardiac and pulmonary investigations did not identify a structural or functional explanation for the low saturation. Importantly, her PaO₂ was 115 mmHg on room air, and the calculated alveolar–arterial oxygen gradient was 2.3 mmHg. This discrepancy prompted consideration of a dyshemoglobinemia and ultimately led to measurement of methemoglobin by co-oximetry.

It is important to distinguish a discrepancy between pulse oximetry and arterial oxygenation from a simple difference between pulse oximetry and calculated arterial oxygen saturation. Standard arterial blood gas analyzers may calculate oxygen saturation from PaO₂ and other parameters, whereas co-oximetry directly measures different hemoglobin species. Therefore, co-oximetry is the preferred laboratory method for confirming methemoglobinemia and other dyshemoglobinemias [3, 4].

The clinical context is also important. The patient had mild obstructive sleep apnea, adenoid hypertrophy, and chronic sinusitis, all of which initially provided potential explanations for abnormal oxygenation. However, improvement of upper airway symptoms without resolution of the low peripheral oxygen saturation, together with normal subsequent pulmonary testing and chest imaging, argued against these conditions as the primary cause of the persistent low saturation.

The patient's HbA₂ level was elevated, and beta-thalassemia trait was suspected based on the laboratory findings and maternal history. However, beta-thalassemia trait alone would not explain the marked discrepancy between the peripheral oxygen saturation and preserved PaO₂. The detection of a methemoglobin concentration of 15% provided a more direct explanation for the abnormal pulse oximetry findings.

Management of methemoglobinemia depends on the methemoglobin concentration, severity of symptoms, rate of development, underlying cause, and individual clinical circumstances. Symptomatic or severe cases may require treatment with methylene blue, whereas management of chronic congenital forms may include avoidance of oxidizing agents and, in selected patients, antioxidant therapy such as ascorbic acid [1, 4, 5]. In the present case, the patient's chronic and clinically well-tolerated condition led to a conservative management approach.

A limitation of this case is that the precise underlying etiology of the methemoglobinemia was not established. Although the chronic course raises the possibility of an inherited disorder, definitive molecular or enzymatic testing for congenital causes was not available as part of the reported evaluation. Therefore, the case should be interpreted primarily as an example of the diagnostic value of recognizing the discrepancy between peripheral oxygen saturation and arterial oxygenation rather than as a report of a genetically confirmed congenital form of methemoglobinemia.

This case highlights the importance of considering dyshemoglobinemia in children with persistent low peripheral oxygen saturation, particularly when the clinical condition is relatively normal and extensive cardiopulmonary evaluation is unrevealing. Recognition of this diagnostic pattern and timely use of co-oximetry may shorten the diagnostic process and prevent unnecessary investigations.

Conclusions

Persistent low peripheral oxygen saturation in an otherwise clinically well child should not always be attributed to pulmonary or cardiovascular disease. When cardiopulmonary investigations are unrevealing and arterial oxygen tension is preserved, dyshemoglobinemia should be considered. Recognition of the discrepancy between pulse oximetry and arterial oxygenation and confirmation with co-oximetry can facilitate the diagnosis of methemoglobinemia.

Declarations

Ethics Approval and Consent to Participate

This case report was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. As this manuscript describes a single case report and does not involve an experimental intervention or prospective research, no formal ethics committee approval was obtained. Written informed consent for participation in this case report was obtained from the patient's parent/legal guardian.

Consent for Publication

Written informed consent was obtained from the patient's parent/legal guardian for publication of this case report and any accompanying clinical information.

Competing Interests

The authors declare that they have no competing interests.

Funding

The authors received no specific funding for this work.

Data Availability

The data generated and/or analyzed during the current study are not publicly available because they contain information that could compromise the privacy of the patient. Further information may be available from the corresponding author on reasonable request, subject to appropriate ethical and privacy considerations.

Acknowledgements

Not applicable.

References

1. Mansouri A, Lurie AA. Concise review: methemoglobinemia. *Am J Hematol.* 2021;96(7).

2. Rehman HU. Methemoglobinemia. *West J Med.* 2001;175(3):193-196.

3. Haymond S, Cariappa R, Eby CS, Scott MG. Laboratory assessment of oxygenation in methemoglobinemia. *Clin Chem.* 2005;51(2):434-444.

4. Perrone J, Hoffman RS. Methemoglobinemia: diagnosis and treatment. *Emerg Med Clin North Am.* 2020;38(3):597-609.

5. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med.* 1999;34(5):646-656.

Table

Table 1. Diagnostic evaluation of persistent low oxygen saturation

Investigation	Finding	Diagnostic implication
Pulse oximetry on room air	SpO ₂ 85–89%	Persistent low peripheral oxygen saturation
Arterial blood gas	PaO ₂ 115 mmHg	Preserved arterial oxygen tension
Hyperoxia test	PaO ₂ 165 mmHg	Does not support a significant right-to-left shunt in the clinical context
A–a oxygen gradient	2.3 mmHg	No evidence of a significant pulmonary gas-exchange abnormality
Echocardiography and contrast echocardiography	No intracardiac or intrapulmonary shunt	Major cardiac/shunt causes not identified
Chest CT	No structural abnormality	No structural pulmonary disease identified
Repeat pulmonary function testing	Normal	No persistent ventilatory abnormality identified
Co-oximetry	Methemoglobin 15%	Supports the diagnosis of methemoglobinemia