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CASE REPORT

Sulfhemoglobinemia: A case report

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Abstract

Sulfhemoglobin (SHb) is formed through the oxidation of hemoglobin (Hb) with the incorporation of sulfur atoms, leading to reduced oxygen affinity and rendering it incapable of transporting oxygen to tissues. Causes include environmental and pharmacological factors, as well as intestinal hydrogen sulfide production in constipated patients with certain gut bacteria. Affected individuals present with cyanosis and low oxygen saturation without significant clinical implications, necessitating a high index of suspicion for diagnosis. Acid-base status measurements using multiparameter devices with co-oximetry to assess Hb fractions can indicate the presence of sulfhemoglobinemia and aid in its diagnosis. We present a case and its progression to emphasize the importance of a multidisciplinary approach.

SULFOHEMOGLOBINEMIA: A PROPÓSITO DE UN CASO

Resumen

La sulfohemoglobina (SHb) se genera por la oxidación de la hemoglobina (Hb) y posterior adquisición de átomos de azufre, provocando una disminución de la afinidad por el oxígeno de la Hb, haciéndola incapaz de transportarlo a los tejidos. Las causas pueden ser ambientales, farmacológicas y también pueden ocurrir en pacientes constipados portadores de bacterias intestinales productoras de sulfuro de hidrógeno. Los afectados presentan cianosis y saturación de oxígeno baja sin repercusión clínica, siendo necesario un alto índice de sospecha. La medición del estado ácido base en equipos multiparamétricos que utilizan cooximetría para medir las fracciones de Hb alertan la presencia de sulfahemoglobinemia y pueden resultar útiles para el diagnóstico. Presentamos un caso clínico y su evolución a fines de discutir la importancia del trabajo multidisciplinario.

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INTRODUCTION

Sulfhemoglobin (SHb) forms through the oxidation of hemoglobin (Hb) and the subsequent incorporation of sulfur atoms. This modification results in Hb with a low oxygen affinity, leading to clinically evident cyanosis[1], reduced pulse oximetry (PO) readings, and normal arterial oxygen pressure[2]. It is an uncommon condition with a pharmacological cause[2] (Table 1). Currently, no routine method exists to quantify SHb; however, co-oximetry available in multiparametric equipment can identify its presence. This study aims to describe a case of sulfhemoglobinemia and emphasize the importance of interdisciplinary collaboration in interpreting results and achieving an accurate diagnosis.

TABLE 1. Pharmacological causes of sulfohemoglobinemia2[2-5].

Environmental
• Well water (nitrates and nitrites)
• Sulfur dioxide
Pharmacological
• Phenazopyridine
• Metoclopramide
• Sulfasalazine
• Ferrous sulfate
• Sulfonamides
• Zopiclone
Others
• Constipation with colonization by *Morganella morganii* (a hydrogen sulfide-producing bacterium)
• Hydroxylamine sulfate

CASE REPORT

With parental consent, we present the case of a 10-year-old girl diagnosed with Steinert's disease (a myopathy associated with myotonia, muscle atrophy, and weakness). During routine follow-up visits, she was noted to have cold, cyanotic extremities and perioral cyanosis. Consequently, she was admitted for further evaluation and treatment with oxygen.

On her first day of hospitalization, perioral cyanosis persisted despite the administration of supplemental oxygen while remaining clinically stable, with vital signs within normal limits for her age, except for a peripheral oxygen saturation of 85%. The complementary studies conducted during her hospitalization are summarized in Table 2.

Due to the discrepancy between peripheral oxygen saturation of 85% (measured by PO) and arterial oxygen saturation of 96% (measured by co-oximetry), in the context of an arterial partial pressure of oxygen (PaO_2) of 128 mmHg, a hemoglobinopathy with low oxygen affinity was proposed as a diagnostic hypothesis.

In a patient presenting with hypoxia and central cyanosis, but without hypoxemia, hypercapnia, or clinical signs of respiratory distress, a multidisciplinary approach was undertaken, involving a toxicology specialist and biochemists from the critical care team.

The hospital is equipped with an ABL800 FLEX multiparameter device (Radiometer)[6], which is part of the point-of-care testing (POCT) system. The arterial acid-base status was measured again, and in addition to the result, the following alarm was triggered: "Warning: SHb detected."

The mother was further interviewed on the medical history of the child to identify any exposure to sulfate groups that could explain the presence of SHb. It was learned that treatment with ferrous sulfate had been initiated two months earlier due to anemia, and that polyethylene glycol was being administered at maintenance doses as a regular medication for her daughter's chronic constipation.

Taking into account the pathophysiology and the absence of other potential causes for the clinical presentation, it was decided to discontinue the ferrous sulfate. The patient evolved favorably, with the resolution of perioral cyanosis and an increase in peripheral oxygen saturation (Table 2). No new symptoms were observed during post-discharge follow-up, so guidelines to prevent exposure to sulfate groups

TABLE 2. Clinical and laboratory course.

	Day 1 of hospitalization	Day 3 of hospitalization	Discharge
Laboratory	Arterial blood gases: • **pH** 7.43 • **PaO_2** 132 mmHg • **$SatO_2$** 95% Arterial co-oximetry: • **MetHb:** not measurable • **COHb** 0.3% Blood count: Hb: 12 g/dl	Arterial blood gases: • **PaO_2** 128 mmHg • **$SatO_2$** 96% Arterial co-oximetry: • **MetHb** 0.5% • **COHb** 0.2%	Arterial blood gases: • **PaO_2** 141 mmHg • **$SatO_2$** 96% Arterial co-oximetry: • **MetHb** 0.3%
Images	Chest X-ray no lesions Echocardiogram: No structural heart disease, preserved systolic function, no signs of pulmonary hypertension		
Clinical features	Central and peripheral cyanosis Pulse oximetry 85%	Perioral cyanosis Pulse oximetry 85%	Asymptomatic Pulse oximetry 97%

PaO_2: Partial pressure of oxygen; $SatO_2$: Oxygen saturation; COHb: Carboxyhemoglobin; MetHb: Methemoglobin.

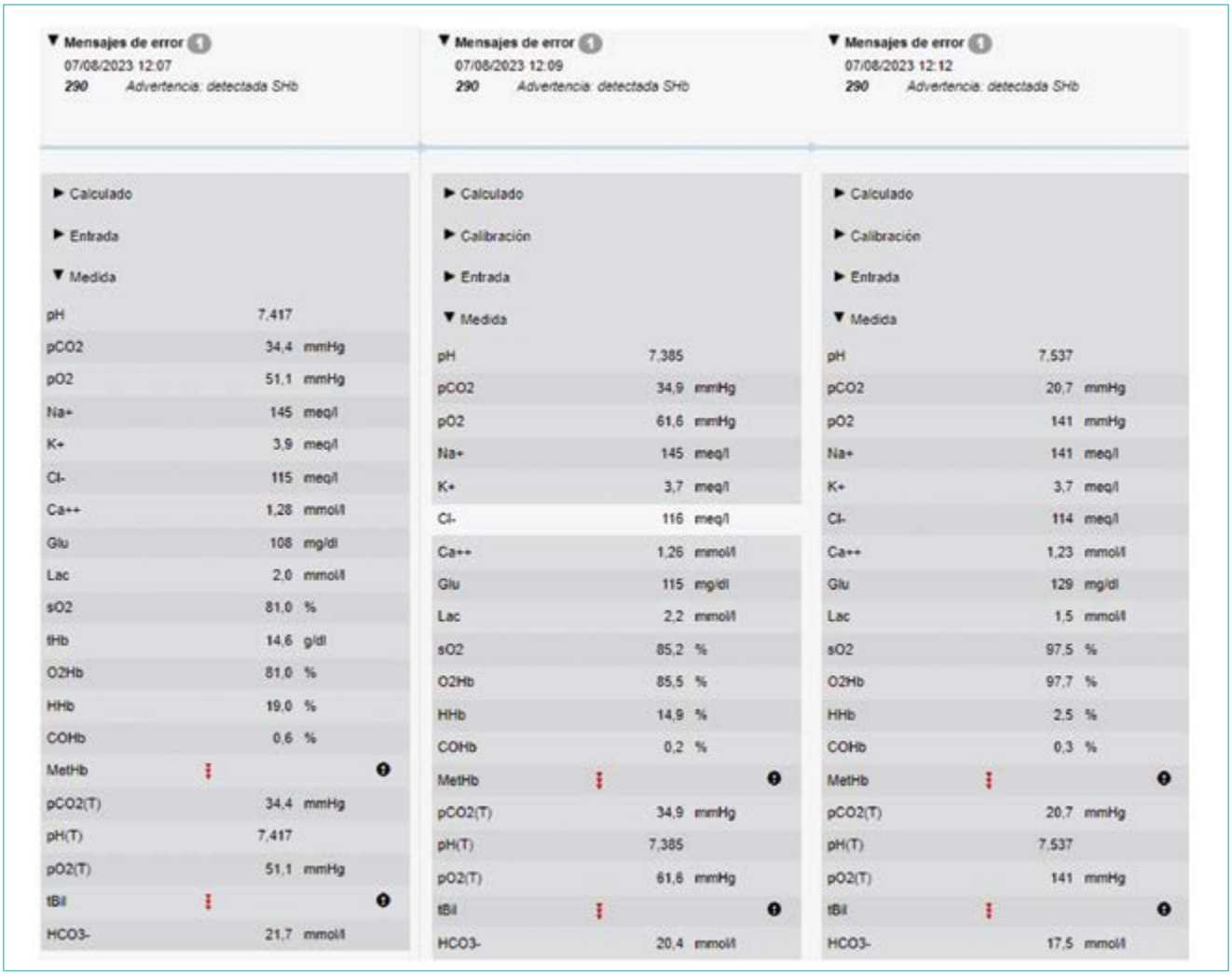

FIGURE 1. Arterial ABE with "Warning: SHb detected". Reference: ↓ MetHb < 0.1%.

were reinforced, and she continued to be monitored by her multidisciplinary team.

DISCUSSION

Total hemoglobin concentration (ctHb) measures the total potential oxygen-carrying capacity of the blood. The fractions of hemoglobin that are effective in oxygen transport are oxyhemoglobin (O_2Hb) and deoxyhemoglobin (HHb). Other fractions, known as dyshemoglobins, are ineffective in transporting oxygen to the tissues. A ctHb result (measured spectrophotometrically) within the reference range does not necessarily ensure adequate oxygen transport. Therefore, it is crucial to determine the different hemoglobin fractions through co-oximetry[7,8].

SHb is produced by the interaction of a sulfur donor group with Hb and can form two distinct structures: in one form, it binds reversibly to the iron in Hb, while in the other, it binds irreversibly to the porphyrin ring. Both forms are considered equivalent and are collectively referred to as sulphohemoglobin[9]. This alteration decreases Hb's oxygen affinity, rendering it unable to transport oxygen to the tissues. The condition persists until physiological elimination of SHb from the erythrocyte occurs.

Patients with sulfhemoglobinemia typically present with central cyanosis, decreased pulse oximetry readings, and normal PaO_2 levels, in the absence of cardiovascular or respiratory disease. The blood acquires a green-greyish appearance, leading to a more pronounced cyanotic presentation compared to similar levels of methemoglobinemia. However, methemoglobinemia is more common and represents the primary differential diagnosis for sulfhemoglobinemia. Both conditions can be distinguished using co-oximetry[2].

In sulfhemoglobinemia, the Hb dissociation curve shifts to the right, increasing the expected p50 values (partial pressure of O_2 required to achieve 50% Hb saturation), increasing the delivery of O_2 to the tissues. As cellular hypoxia does not occur, it does not improve with oxygen therapy. Consequently, dyspnea is absent unless SHb levels are exceptionally high. In contrast, methemoglobinemia has a greater clinical impact[2] as hemoglobin is unable to bind and transport oxygen effectively, causing a leftward shift in the hemoglobin dissociation curve.

The spectrophotometric technique used to determine ctHb and its main fractions—O_2Hb, HHb, fetal hemoglobin (HbF), carboxyhemoglobin (COHb), and methemoglobin (MetHb)[3]—is called co-oximetry. This method employs an optical system consisting of a 128-wavelength spectrophotometer with a measurement range of 478–672 nm. This

method is based on the Lambert-Beer law, which states that the absorbance of a substance is directly proportional to its concentration and the length of the light path through the sample[6]. SHb and MetHb have an absorption peak near 626 nm. Analyzers using co-oximetry do not provide a quantitative value for SHb but warn of its presence. The optical system in ABL800 FLEX analyzers corrects for SHb interference by suppressing its spectrum and generating a SHb detection warning. If the detection range is below 10%, the analyzer issues an "SHb detected" alarm, applies the correction for interference, and reports the MetHb value. However, if the detection exceeds 10%, the warning changes to "SHb too high," indicating compromised measurement accuracy. In such cases, the analyzer does not perform the correction or report MetHb values, and a repeat measurement is recommended[6]. It is important to note that the presence of SHb does not cause falsely elevated MetHb values. As previously mentioned, any interference is corrected by the analyzer. If correction is not possible, the MetHb value is not reported.

CONCLUSION

Sulfohemoglobinemia is a rare condition, and its diagnosis can be challenging due to limitations in measuring SHb in routine practice. The inability of co-oximeters to quantify SHb may result in misinterpretation of results, emphasizing the importance of teamwork and interdisciplinary collaboration, particularly the involvement of a biochemist, for timely diagnosis. While no specific antidote exists, strict clinical monitoring and supportive treatment are recommended, considering the half-life of erythrocytes.

REFERENCES

1. Price DP. Methemoglobin inducers. En: Nelson LS, Howland M, Lewin NA, Smith SW, Goldfrank LR, Hoffman RS. Goldfrank's Toxicologic Emergencies, 11th ed. McGraw-Hill Education; 2019. p. 1703-12.
2. Benavente R, Parada N, Sánchez B, Meneses R, Torres S, Pineda C, et al. Sulfohemoglobinemia secundaria a zopiclona. Casos clínicos. Rev Med Chile. 2022; 150(10): 1401-6.
3. Murphy K, Ryan C, Dempsey EM, O'Toole PW, Ross RP, Stanton C, et al. Neonatal sulfhemoglobinemia and hemolytic anemia associated with intestinal Morganella morganii. Pediatrics. 2015; 136(6): e1641-5.
4. George A, Goetz D. A case of sulfhemoglobinemia in a child with chronic constipation. Respir Med Case Rep. 2017; 21: 21-4.
5. Gharahbaghian L, Massoudian B, DiMassa G. Methemoglobinemia and sulfhemoglobinemia in two pediatric patients after ingestion of hydroxylamine sulfate. West J Emerg Med. 2009 10(3): 197-201.
6. Manual del usuario: Analizador de gases en sangre ABL800 FLEX - Radiometer.
7. Oliver Sáez P, Buño Soto A, Galán Ortega A, Díaz García R, Guevara Ramírez P, Guillén Campuzano E, et al; Sociedad Española de Bioquímica Clínica y Patología Molecular. Comité Científico Comisión Magnitudes Biológicas relacionadas con la Urgencia Médica. Recomendaciones para el estudio de la cooximetría. Documentos de la SEQC; 2010.
8. Chan IH, Au AC, Kwok JS, Chow EY, Chan MH. Co-oximetry interference. Pathology. 2015; 47(4): 392-3.
9. Stepanenko T, Zając G, Czajkowski A, Rutkowska W, Górecki A, Marzec KM, et al. Sulfhemoglobin under the spotlight - Detection and characterization of SHb and HbFeIII-SH. Biochim Biophys Acta Mol Cell Res. 2023; 1870(1): 119378.