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A case report of autosomal recessive methemoglobinemia in a child

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Abstract:

Methemoglobinemia is a rare hematologic disorder characterized by impaired oxygen delivery due to oxidation of hemoglobin iron from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state, leading to elevated methemoglobin (MetHb) levels and cyanosis. We report the case of a 3-year-old female with a history of congenital cyanotic heart disease who presented with worsening cyanosis and was found to have a MetHb level of 49.3%. She responded initially to methylene blue therapy, but levels fluctuated over the following week. Whole-exome sequencing revealed a homozygous missense variant in the cytochrome b5 (CytB5) reductase 3 gene, consistent with autosomal recessive methemoglobinemia due to CytB5 reductase deficiency. The identified variant has not been previously reported and was classified as a variant of uncertain significance. This case underscores the importance of considering hereditary methemoglobinemia in children with unexplained cyanosis and persistent MetHb elevation. Genetic evaluation remains essential in suspected hereditary cases to inform prognosis, guide long-term care, and support family counseling.

Keywords:

Case reports, cyanosis, genetic testing, methemoglobinemia, pediatrics

Introduction

Methemoglobinemia is a rare hematologic disorder, characterized by the oxidation of hemoglobin iron from its ferrous (Fe^{2+}) to ferric (Fe^{3+}) state, which impairs oxygen delivery, leading to functional anemia and cyanosis. While small amount of methemoglobin (MetHb) are naturally produced and efficiently reduced by cellular enzymatic reduction systems, disruptions in these pathways can lead to elevated MetHb levels and reduced perfusion.^[1-3] Acquired forms of MetHb are more frequently encountered. However, congenital methemoglobinemia

remains an important differential diagnosis in patients presenting with unexplained cyanosis, particularly in pediatric patients, in the absence of cardiopulmonary pathology.^[2,4] Inherited cases mostly result from reductive enzyme deficiencies or structural hemoglobin variants, with clinical severity varying according to the underlying genetic defect.^[1,2] Pulse oximetry and arterial blood gases are essential diagnostic tools.^[4]

Here, we present a case of genetically confirmed hereditary methemoglobinemia, contributing to the limited literature on this uncommon condition and highlighting key clinical and genetic considerations.

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Case Report

A 3-year-old female with congenital pulmonary artery stenosis and secondary pulmonary hypertension, not on medications, was brought to the emergency department following a 3-day history of worsening cyanosis. Initially, her mother observed cyanosis around the lips and hands, which became more pronounced on the day of her presentation.

She was first evaluated in a primary care facility, where her oxygen saturation (SpO_2) was 75% while on a nasal cannula, prompting her transfer to a tertiary care center. The details surrounding potential accidental ingestion were unclear; however, the parents mentioned the presence of naphthalene mothballs, but ingestion was not confirmed.

Upon presentation, the patient's vital signs and pertinent labs are summarized in Table 1. The patient was tachycardic, had oxygen desaturation, with acid-base imbalance, and elevated MetHb. Except for cyanosis, her pulmonary, cardiovascular, and other systemic evaluations were normal.

Upon further history collection, the parents reported that the patient had been at her aunt's house for the previous 2 days. She was not on any chronic medication and had not undergone any recent dental procedures involving local anesthetics such as lidocaine. The parents saw her playing with her aunt's bag, which contained medications, but no medication overdose was witnessed. Medications in the house included ciprofloxacin, paracetamol, orphenadrine, ibuprofen, simethicone, and polygynax (niastatin, polymyxin B, and neomycin). When questioned whether they have other oxidizing agents, such as dapsone, phenazopyridine, trimethoprim/sulfamethoxazole, nitrates, nitrites, or others, parents denied exposure. Naphthalene is present in the house and the surrounding environment; the child does not smell naphthalene, but there was a soot-like smell that was noted. The mother reported that they are using charcoal in the house.

She was given methylene blue at a dose of 1 mg/kg intravenously over 30 min after confirming she did not have glucose-6-phosphate dehydrogenase (G6PD) deficiency. After 1 h, her MetHb level decreased to 22% and to 11.4% 2 h later. The decision was made to withhold additional doses of methylene blue, as a repeated dose is indicated if MetHb levels remain >30% or if signs and symptoms persist which were not present in this case. She was advised to be admitted for repeated MetHb levels the following day but was signed out against medical advice due to financial constraints.

The next day, the patient's MetHb dropped to 9%. The child later reported eating a white circle found under the bed, suggestive of naphthalene.

A few days later, the parents brought the patient to a different hospital due to a recurrence of cyanosis. Her MetHb level was 30.5% and she received another dose of methylene blue, where her MetHb level dropped to 8.8%. However, 48 h later, it rose again to 20.6%. Over the next week, her MetHb levels fluctuated between 14% and 22%, during which she remained active and hemodynamically stable.

Genetic testing via whole-exome sequencing indicated that autosomal recessive methemoglobinemia due to a MetHb reductase deficiency caused by homozygous or compound heterozygous mutations in the cytochrome b5 reductase 3 (CYB5R3) gene [Table 2]. A homozygous

Table 1: Summary of the patient's vital signs and arterial blood gas analysis at presentation

Parameter	Results (units)
Vitals	
Respiratory rate	35 breaths/min
Heart rate	144 beats/min
Blood pressure	92/44 mmHg
Temperature	37°C
SpO_2	84% on room air
Arterial blood gas analysis	
pH	7.50
PaCO_2	23.4 mmHg
PaO_2	98.6 mmHg
Others	
MetHb level (%)	49.3

MetHb: Methemoglobin, PaO_2 : Partial pressure of oxygen in arterial blood, PaCO_2 : Partial pressure of carbon dioxide in arterial blood, SpO_2 : Oxygen saturation

Table 2: Genetic findings in the cytochrome b5 reductase 3 gene associated with autosomal recessive methemoglobinemia

Variant details	Description
Gene ID	CYB5R3
Transcription	NM_000398.7
Location	Chr22:43024235 Rs1244673706
HGVSc sequence name and HGVSp sequence name	c.386A>C P.gLN129Pro
Coverage	0.47
Zygosity	Homozygous
Inheritance pattern	Autosomal recessive
Disease	Methemoglobinemia due to deficiency of MetHb reductase
Classification	Uncertain significance with pathogenic evidence
Classification database	Varsome and franklin

MetHb: Methemoglobin, HGVSc: Human Genome Variation Society coding, HGVSp: Human Genome Variation Society protein, CYB5R3: Cytochrome b5 reductase 3

missense variant was identified in the *CYB5R3* gene, which is associated with methemoglobinemia due to a MetHb reductase deficiency.

Written informed consent to publish this case report has been granted by the patient's next of kin, who understood that the name of the patient will remain anonymous and the data will be published in an international journal.

This case report has been prepared in compliance with CARE (CAse REport) guidelines.

Discussion

In this child, the identified homozygous missense variant in the *CYB5R3* gene has not been reported in the ClinVar database or in the literature. It is classified as a variant of uncertain significance by the Varsome and Franklin databases, based on moderate (PM1 and PM2) and supportive (PP3) pathogenicity evidence under the American College of Medical Genetics and Genomics (ACMG) criteria.

As the variant is present in a homozygous form, the parents are expected to be obligate carriers of the same variant. This is indicative of 25% chance for the same condition to occur in each subsequent pregnancy. Genetic counseling is recommended for future family planning, as parental genetic testing was not performed. Variants are deemed of uncertain significance when they have conflicting or insufficient evidence regarding the predefined ACMG criteria on pathogenicity and benignity. As evidence continues to evolve, variants of uncertain significance may undergo further reclassification. Therefore, these variants should not inform clinical management, as they do not provide definitive pathogenicity classification.^[5]

Methemoglobinemia is a rare, potentially life-threatening condition where hemoglobin iron is oxidized from Fe²⁺ to Fe³⁺, producing MetHb.^[2] MetHb cannot effectively deliver oxygen to tissues, resulting in cyanosis and functional anemia – a clinically significant methemoglobinemia.^[1] During normal red blood cell (RBC) metabolism, oxidative stress generates low levels of MetHb, maintained at concentrations $\leq 1\%$ by RBC counterregulatory mechanisms.^[1-3]

Methemoglobinemia is confirmed when MetHb exceeds 5%. Levels under 10% are usually asymptomatic, while levels between 10% and 20% may cause cyanosis. Symptoms such as dyspnea, tachycardia, and headache appear at levels between 20% and 30%. Symptoms progress to confusion and lethargy at levels near 50%. Higher MetHb concentrations can lead to seizures, arrhythmias, and coma, and levels above 70% are often fatal.^[2,4]

Cytochrome B5 (CytB5) reductase, also called reduced-nicotinamide-adenine-dinucleotide (NADH)-dependent-MetHb reductase, is the primary reduction pathway responsible for the enzymatic reduction of MetHb to functional hemoglobin.^[2,3] This enzyme removes 95% to 99% of endogenous MetHb.^[4,6] A secondary reduction pathway involving reduced- NADH-phosphate-dependent-MetHb reductase also contributes to MetHb reduction. The gene encoding this enzyme is not well-characterized and is negligible under normal physiological conditions. Therefore, its deficiency – as in patients with G6PD deficiency – rarely leads to clinically significant methemoglobinemia.^[3,4,6] However, it can be activated pharmacologically by exogenous factors, so its role becomes significant in methylene blue therapy.^[2,4,6]

Methemoglobinemia develops when an imbalance in MetHb production and reduction occurs; it is either acquired or hereditary. Most cases are acquired, resulting from oxidizing agents such as antimalarial drugs, dapsone, anesthetics such as bupivacaine, sodium nitrite, phenazopyridine, and trimethoprim-sulfamethoxazole.^[4,7,8]

While less common, three genetic causes may cause hereditary methemoglobinemia. The most common autosomal recessive cause is CytB5 reductase enzyme deficiency. Two different phenotypes are associated with the *CYB5R3* mutation: type I (erythrocyte type) and type II (generalized).^[2,7] Type I accounts for most of the *CYB5R3* disease variants and affects only RBC, where most patients have 10%–35% MetHb and remain asymptomatic.^[2,6,7,9-12] Type II affects all tissues and is associated with failure to thrive, severe neurological impairment, and premature death.^[2,7] Carriers of the mutated *CYB5R3* gene are asymptomatic but susceptible to developing cyanosis under oxidative stress.^[2,7] A less common autosomal dominant cause is due to hemoglobin M (HbM) variants. HbM results from a mutation in one of the three globin genes. Thereby, creating structurally abnormal hemoglobin that auto-oxidize iron and are resistant to reduction.^[2,3] CytB5 deficiency is the rarest cause of hereditary methemoglobinemia, whose patients are usually minimally symptomatic.^[4]

Methemoglobinemia should be suspected in any individual with unexplained cyanosis. It is identified by elevated MetHb levels on blood gas analysis. Moreover, it is often accompanied by chocolate-colored blood and SpO₂ of around 85% despite oxygen supplementation. Despite low pulse oximetry readings, the partial pressure of carbon dioxide in arterial blood (PaO₂) remains normal. This helps differentiate it from cyanotic heart disease, where both PaO₂ and SpO₂ are low. Therefore, diagnosis requires a co-oximeter and genetic testing may be needed for inherited forms.^[2,3]

Treatment of acquired methemoglobinemia begins with removing the cause and providing supportive care.^[13] In acquired methemoglobinemia, methylene blue (1–2 mg/kg intravenously over 5 min) is the first-line treatment. It is indicated for symptomatic patients with MetHb $\geq 20\%$, or asymptomatic patients with levels $\geq 30\%$. Those with heart or lung disease, or anemia, may need treatment at MetHb levels $\geq 10\%$. In contrast, most patients with hereditary methemoglobinemia can tolerate MetHb levels up to 30%–40% while remaining asymptomatic. A second dose may be given after 1 h if needed. Severe or unresponsive cases may require exchange transfusion.^[13] Since methylene blue functions by activating the secondary reduction pathway, it is ineffective and potentially harmful in patients with G6PD deficiency. Therefore, ascorbic acid (5–8 mg/kg) serves as an alternative.^[2,3,7] Genetic methemoglobinemia is managed with daily methylene blue or ascorbic acid, while HbM disease is relatively benign and requires no treatment.^[6] Other treatments such as cimetidine, N-acetylcysteine, and ascorbic acid, have been explored with mixed results.^[3,4,7]

A previous report highlighted the case of recessive congenital methemoglobinemia type II.^[14] It was diagnosed prenatally in a Lebanese family whose parents are the heterozygous carriers of a CytB5 reductase mutation. The fetus was expected to have the recessive congenital methemoglobinemia type II symptoms, thereby underscoring the importance of genetic testing.^[14] Nonetheless, our case report is the first in Lebanon to describe a homozygous missense variant in the CYB5R3 gene.

Conclusion

This case report highlights the importance of considering hereditary methemoglobinemia in patients with unexplained cyanosis, particularly in the absence of cardiopulmonary causes. Genetic confirmation facilitates accurate diagnosis, informs prognosis, and guides management and family counseling. Continued reporting of such cases is essential to expand the clinical understanding of this rare condition and to enhance early recognition in similar presentations.

Author contributions statement

AK: writing – original draft (lead), writing – review & editing (equal), data curation (supporting), and formal analysis (equal). DA: writing – original draft (supporting), writing – review & editing (equal), data curation (lead), and formal analysis (equal). PY: writing – original draft (supporting), data curation (supporting), and writing – review & editing (equal). ZK: Conceptualization (equal), project administration (equal), and writing – review & editing (equal). TE: Conceptualization (equal), project administration (equal), supervision (lead), visualization (lead), writing – original draft (supporting), and writing – review & editing (equal). All authors have approved the submitted version. All authors agreed both to

be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Conflicts of interest

None Declared.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal patient identity, but anonymity cannot be guaranteed.

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