

CASE REPORT

A rare cause of cyanosis: Congenital methemoglobinemia

Rahma Guedri¹ | Nada Missaoui² | Leila Essaddam¹ | Saayda Ben Becher¹

¹Department of Pediatrics (PUC), Faculty of Medicine of Tunis, Children Hospital Béchir Hamza of Tunis, University Tunis El Manar, Tunis, Tunisia

²Department of Pediatrics C, Faculty of Medicine of Tunis, Children Hospital Béchir Hamza of Tunis, University Tunis El Manar, Tunis, Tunisia

Correspondence

Rahma Guedri, Department of Pediatrics (PUC), Faculty of Medicine of Tunis, Children Hospital Béchir Hamza of Tunis, University Tunis El Manar, Tunis Jebbari, Tunis, Tunisia.
Email: guedrirahma@yahoo.fr

Abstract

Congenital Methemoglobinemia is a rare condition that may mimic congenital heart diseases. There are two types of congenital Methemoglobinemia. The type I is usually benign. The enzyme deficiency is limited to red blood cells. Clinically, the patient presents cyanosis without neurological disorders. Whereas, in type II, cyanosis is associated with severe neurological impairment.

KEYWORDS

critical care medicine, emergency medicine, genetics, paediatrics and adolescent medicine

1 | INTRODUCTION

Methemoglobinemia is a condition due to the presence in the blood of a methemoglobin level greater than 1%. In methemoglobin, ferrous iron (Fe^{++}) is oxidized to the ferric state (Fe^{+++}), resulting in tissue hypoxia. Methemoglobinemia can be acquired or, more rarely, congenital. Cyanosis is the most common symptom that suggests cardiac origin in the first place. In this article, we report a case of congenital methemoglobinemia in a 13-month-old Tunisian girl.

2 | CASE PRESENTATION

Our patient is a 13-month-old girl, the first child of a first-degree consanguineous couple. The pregnancy was without complications. She was born at full term from vaginal delivery. Apgar's score was 9 at one minute and 10 at 5 minutes. Birth weight was 3300 g.

Since birth, parents noticed a cyanosis of the face that became more marked at the age of 5 months. Psychomotor development was normal. The infant was referred to our department by a general practitioner at the age of 13 months for

exploration of cyanosis. The interview with the parents revealed that the mother worked in the manufacture of jewelry. The infant diet included vegetable purees containing carrots stored for more than 24 hours. The physical examination found normal weight, height, and head circumference. She had cyanosis (Figures 1 and 2). Cardiac and pulmonary auscultation were both normal. The neurological examination was normal. Oxygen saturation was 94% in room air (she was crying). Chest X-ray and cardiac ultrasound were normal. The blood cell count showed polycythemia at $6\,490\,000/\text{mm}^3$, hemoglobin level was 12.7 g/dL. Electrophoresis of hemoglobin, renal, and hepatic status were normal. Methemoglobinemia and other differential diagnosis were considered such as congenital heart disease. The heart examination was normal. However, the level of methemoglobin was very high. It was measured at 39.4% confirming the diagnosis. A specialized investigation concerning the products handled by the mother excluded a toxic cause. The correction of the methods of preparation and conservation of the diet did not improve the cyanosis. The diagnosis of recessive congenital methemoglobinemia type I was strongly suspected. The determination of the enzymatic activity of NADH cytochrome b5 reductase and DNA sequencing is not available in Tunisia. She did not

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Clinical Case Reports* published by John Wiley & Sons Ltd.



FIGURE 1 cyanosis of lips and extremities



FIGURE 3 Immediate disappearance of cyanosis after methylene blue infusion



FIGURE 2 Cyanosis of the lips before treatment



FIGURE 4 Normal lips coloration after methylene blue infusion

develop neurological impairment on outcome, which improve the diagnosis of congenital methemoglobinemia type I. Our patient received an intravenous infusion of 1.2 mg per kg of methylene blue (MB) after eliminating glucose 6 dehydrogenase deficiency. Cyanosis disappeared immediately (Figures 3 and 4). The methemoglobin level dropped to 2.6%. Dietary measures were explained to parents. Four days after the medication, cyanosis reappeared, the methemoglobin level increased to 38.4%. The patient received a second intravenous infusion of MB and then was put on vitamin C at a

dose of 500 mg per day orally. After a 6 months of follow-up and vitamin C treatment, there was a clear improvement. She has mild cyanosis on exercise. Methemoglobin level was 10.9%. She showed no side effects of treatment.

3 | DISCUSSION

Methemoglobinemia is a condition due to an excessive formation of methemoglobin. In this form of hemoglobin, ferrous iron (Fe^{++}) is oxidized to its ferric form (Fe^{+++}). On the one hand, MetHb is unable to bind oxygen and, on the other hand, it increases the affinity of other forms of hemoglobin for oxygen, thus causing a left shift in the oxygen dissociation curve. These phenomena contribute to a reduction in the delivery of oxygen to tissues, hypoxemia, and cyanosis.^{1,2} There are three forms of methemoglobinemia: the acquired form following exposure to an oxidizing agent and this is the most common form. It is reversible by discontinuation of the offending agent. The second form is hemoglobin M disease, due to the presence of abnormal hemoglobin: hemoglobin M. The third and rarest form is congenital recessive methemoglobinemia CMR.^{1,3} It is due to an enzyme deficiency in NADH cytochrome b5 reductase. This enzyme is responsible for the reduction of methemoglobin to deoxyhemoglobin. This enzyme is encoded by a gene located on 22q13.^{4,6} Two forms of this enzyme are known: the soluble form present exclusively in erythrocytes and the membrane-bound form present in all tissues. There are two types of CMR: type I and type II. Type I is usually benign, the enzyme deficiency is limited to red blood cells. Clinically, the patient presents cyanosis without neurological disorders. In type II, the enzyme deficiency is generalized to all tissues and involves both forms. Cyanosis is associated with a severe neurological impairment which onsets by the age of 6 to 9 months. The long-term prognosis is poor due to swallowing disturbances.^{3,7} The diagnosis of methemoglobinemia is suspected by a "chocolate" color of the arterial blood. It is confirmed by the presence of a high MetHb level (above 1 to 3%). The activity of NADH cytochrome b5 reductase is measured spectrophotometrically. Molecular analysis of the cytochrome b5 reductase gene determines mutations. Congenital recessive methemoglobinemia type I is associated with amino acid substitution mutations, whereas CMR type II is associated with nonsense mutations and deletions.^{4,5} Precise prevalence is unknown. It is estimated at 1 per 100 000. A higher prevalence (47 per 100 000) has been reported by Burtseva et al, who collected 43 cases of CRM in the Sakha Republic.⁶ For the management of CRM, the eviction of oxidative products is necessary. The available treatments are methylene blue, ascorbic acid, and riboflavin. Methylene blue is given intravenously in a dose of 1-2 mg/kg. Response and improvement of cyanosis are rapid. Before treatment with MB, it is necessary to eliminate an associated G6PD deficiency because MB has an oxidant potential and can induce hemolysis in this case.¹ Methylene blue can be prescribed orally as maintenance therapy.^{3,8-10} Ascorbic acid directly reduces methemoglobin but at a slow rate. It was used by several teams for the treatment of CRM.^{1,3,8,9} Also, since the 1980s, high doses of

riboflavin (120 mg/day) have been successfully prescribed in some patients.¹¹ In congenital recessive methemoglobinemia type II, there are no evidence that treatments are effective on the neurological impairment.¹⁰

4 | CONCLUSION

Recessive congenital methemoglobinemia is a rare condition. The constant symptom is cyanosis that can cause confusion with congenital heart diseases especially in children and so delay the diagnosis. The high level of MetHb helps diagnosis. Congenital recessive methemoglobinemia type I is responsible for cosmetic damage while type II is severe neurological dysfunction. The treatment is based on the eviction of oxidants and intravenous methylene blue as an attack treatment. The maintenance treatment is not consensual. The physician may use methylene blue, ascorbic acid, or oral riboflavin.

ACKNOWLEDGMENTS

Published with written consent of the patient.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHORS CONTRIBUTIONS

All authors read and approved the final manuscript. They have contributed to the article as follows: RG: carried out the data collection and drafted the manuscript, obtained the patient consent. NM, LE, and SBB reviewed and approved the manuscript.

ETHICAL APPROVAL

Consent for publication: Written informed consent was obtained from the patient's parents for publication.

DATA AVAILABILITY STATEMENT

All data generated during this study are included in the article.

REFERENCES

1. Khade H, Raju U, Deshmukh T, Srivastav G, Kadiri V. Neonatal congenital methemoglobinemia—A case report. *Indian J Med Case Rep.* 2016;5:12-17.
2. Tasci C, Nevruz O, Candir N, Bilgic H. A methemoglobinemia case who was previously diagnosed and treated as asthma. *Respir Med Case Rep.* 2012;6:11-12.
3. Aslan D, Turkoz-Sucak G, Percy MJ. Recessive congenital methemoglobinemia in immediate generations. *Turk J Pediatr.* 2016;58:113-115.
4. Fermo E, Bianchi P, Vercellati C, et al. Recessive hereditary methemoglobinemia: two novel mutations in the NADH-cytochrome b5 reductase gene. *Blood Cells Mol Dis.* 2008;41:50-55.
5. Kugler W, Pekrun A, Laspe P, Erdlenbruch B, Lakomek M. Molecular basis of recessive congenital methemoglobinemia, types

- I and II: Exon skipping and three novel missense mutations in the NADH-cytochrome b5 reductase (diaphorase 1) gene. *Hum Mutat.* 2001;17(4):348.
6. Burtseva TE, Ammosova TN, Protopopova NN, Yakovleva SY, Slobodchikova MP. Enzymopenic congenital methemoglobinemia in children of the Republic of Sakha (Yakutia). *J Pediatr Hematol Oncol.* 2017;39:42-45.
 7. Schwartz L, Franck P, Debruille C, Olivier J, Vigneron C, editors. Méthémoglobinémie congénitale récessive: une cause rare de cyanose du nouveau-né. *Annales de Biologie Clinique*; 2005.
 8. Da-Silva SS, Sajan IS, Underwood JP. Congenital methemoglobinemia: a rare cause of cyanosis in the newborn—a case report. *Pediatrics.* 2003;112:e158-e161.
 9. Bennaoui F, Draïss G, Bourrous M, Bouskraoui M. La méthémoglobinémie congénitale: à propos d'un cas. *J Pediatr Puericult.* 2010;23:198-200.
 10. Cooper MS, Randall M, Rowell M, Charlton M, Greenway A, Barnes C. Congenital methemoglobinemia type II-clinical improvement with short-term methylene blue treatment. *Pediatr Blood Cancer.* 2016;63:558-560.
 11. Hirano M, Matsuki T, Tanishima K, et al. Congenital methaemoglobinaemia due to NADH methaemoglobin reductase deficiency: successful treatment with oral riboflavin. *British J Haematol.* 1981;47:353-359.

How to cite this article: Guedri R, Missaoui N, Essaddam L, Ben Becher S. A rare cause of cyanosis: Congenital methemoglobinemia. *Clin Case Rep.* 2021;9:e04422. <https://doi.org/10.1002/ccr3.4422>