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.

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/mm³, 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
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.
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 type I, associated with amino acid substitution mutations, whereas CMR type II is associated with CMR type I. 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 age 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 some patients.\(^11\) In congenital recessive methemoglobinemia type II, there are no evidence that treatments are effective on the neurological impairment.\(^10\)

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.

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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 data collection. 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.

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