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Case report

Children's environmental health: a target for all Pediatricians

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Summary. Methemoglobinemia is caused by a congenital or acquired increase of methemoglobin (MetHb). A 11-months-old child came for episodes of peripheral cyanosis. The only altered exam was MetHb level, but non-pathogenic homozygous mutation of cytochrome B5-reductase gene.
Our patient had begun to show cyanosis since the assumption of vegetable broth. Our case report is a warning to investigate the children's environmental conditions.

Key words: methemoglobinemia, nitrates, cyanosis, children, vitamin C

Introduction

Methemoglobinemia (MetHba) is a clinical syndrome caused by an increase in the blood levels of methemoglobin (MetHb) secondary to both congenital changes in hemoglobin (Hb) synthesis or metabolism, or acute imbalances in reduction and oxidation reactions induced by the exposure to several chemical agents (1).

Its prevalence is difficult to determine because it encompasses a large part of probably under diagnosed mild forms.

Methemoglobin represents the oxidized form of Hb, whose heme ferrous iron is oxidized to ferric iron and, for this reason, cannot bind oxygen. Ferric iron also causes an allosteric change in the heme portion of partially oxidized Hb, increasing its O_2 affinity, hindering the release of O_2 in the tissues.

In theory, hemoglobin is constantly being oxidized. However NADH-Methemoglobin reductase (NADH-NR), a system with two enzymes, cytochrome B5 and cytochrome B5-reductase(CB5R), maintains the levels of MetHb under 2% (2).

MetHba can be congenital, caused by congenital deficiency of CB5R, or acquired from the exposure to several oxidizing agents or secondary to pathologic conditions such as sepsis or sickle cell crisis.

Case presentation

A 11-months-old white female came to our attention for episodes of peripheral cyanosis in the last 3 months.

She was born by cesarean delivery at 38 weeks for breech presentation and at birth (Apgar Score 1': 5, 5': 7) she suffered from mild respiratory distress and she was hospitalized in neonatal intensive care unit with subsequent resolution after 7 days.

At about 8 months she showed an episode of peripheral cyanosis with progressive oxygen desaturation (from 96% to 89%), not always related to other symptoms.

The child was admitted to another hospital and after electrocardiogram, echocardiogram, HCT of thorax, nasal brushing and sweat test, she was then

discharged with a diagnosis of probable gastroesophageal reflux disease (GERD) and therapy with Domperidone.

Because of persistence symptoms it was required evaluation by our Children's Hospital.

The child was in good general condition [Weight: 8,490 kg (25-50°) Lenght: 70 cm (25°)]. Objective exam was normal except for the presence of perioral and subungual cyanosis during the crying.

She performed several laboratory exams that resulted in the normal range (Tab. 1).

Cardiological evaluation and cardiac ultrasound showed only a mild and not hemodynamically significant patency of foramen ovale and chest Xray was perfectly normal.

Our Metabolic Diseases specialist suggested several exams: Ammonium 18 microg/dL (0-75), Lactic Acid 8.1 mg/dL (4-20), Acylcarnitine profile in the normal range and Urinary Organic Acids normal. The only altered exam it was the arterious hemogasanalysis which showed a MetHb of 28.2%.

Table 1. Laboratory baseline exams.

Cell Blood Count	Normal
RCP	<0.05 mg/dl
Erythrocyte Sedimentation Rate	3 mm (0-15)
Glucose	79 mg/dl
Creatinine	0.32 mg/dl
Triglycerides	97 mg/dl
Sodium	139 mEq/L
Potassium	5.15 mEq/L
Clorum	106 mmol/L
Calcium	9.8 mg/dl
Phosphorus	6.3 mg/dl
Magnesium	2.52 mg/dl
Iron	67 microg/dl
Aspartate Transaminase	31 UI/L
Alanine Transaminase	21 UI/L
LDH	475 UI/L
CPK	156 UI/L
IgG	441 mg/dL
IgA	17 mg/dL
IgM	60 mg/dL
alpha1-antithripsin	115 mg/dL
CD3+	55.8%
CD4+	38.3%
CD8+	15.2%
CD19+	37.5%
CD16+CD56+	5.7 %

The child was then monitored constantly. Saturimetry showed frequent but not constant episodes of oxygen desaturation.

Vitamin C blood levels resulted 30.9 micormol/L (26.1-84.6) and G6PD 17.5 U/g Hb (9.4-17.8).

We decided to assess sequencing of CB5R3 gene: it was found the presence of homozygous mutation of c.776G>C nucleotide in the CYB5R3 (DIA)1 gene.

The parents denied any familiarity for any pathologies, but we discovered that they prepared the broth for the child with the vegetables coming from the garden watered with well water next to a landfill.

To reduce the possibility of side effects, a therapy with ascorbic acid (250 mg a day) was preferred to therapy with methylene blue and the child was discharged with the prescription of changing residence and reducing overall intake of marrow, spinach, beets and green beans.

After 30 days of discharge, the parents had followed the prescribed therapy and had not given the child potentially contaminated vegetables. Unfortunately, they had not changed their place of residence because of economic matters.

After one month and after 60 days of discharge, MetHb was 13.2% and 11.8%, respectively. It was also performed hemogasanalysis to the mother and the father and the percentage of MetHb was of 1.4% and 1.1%, respectively.

It was then recommended to continue therapy and to start home oximetry with an oximeter equipped with 4 wavelengths, for the non-invasive detection of the percentage of MetHb in the blood.

After 1 year and 4 months the child shows good general condition and no cyanosis episodes happened. In Figure 1 the details of follow-up.

Discussion

The case report reminds that sometimes cyanosis may not be due to cardio-respiratory problems.

Saturimetry levels are often wrong in methaemoglobinaemia because of the different wavelength of methaemoglobin than that of hemoglobin and deoxyhemoglobin (3).

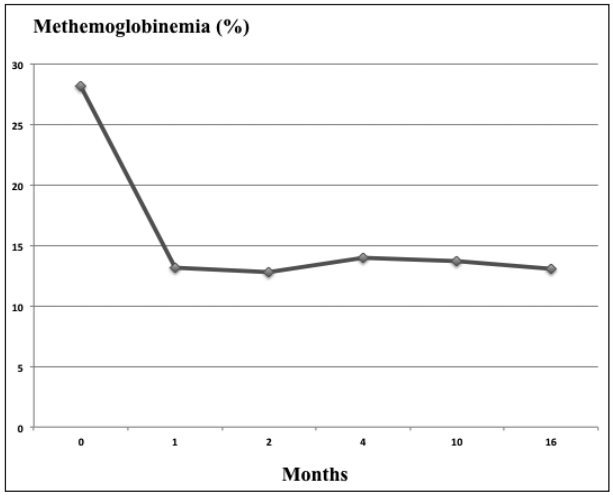

Figure 1. Follow-up

It is also important, to distinguish between congenital and secondary MetHba in order to determine the most appropriate therapy.

In our patient, the c.776G>C nucleotide mutation resulted in the aminoacid change p.Arg259Pro in NADHcytochrome b5 reductase. The physicochemical difference between Arg and Pro is moderate (Grantham score 103 (0-215)) and this mutation is classified as "unclassified variant type 2 (UV2: pathogenicity uncertain).

The relationship between this specific finding and the diagnosis of MetHba is still unclear and the absence of affected family members suggests that MetHba could not be due to the observed genetic changes.

Our patient had begun to show signs of cyanosis, just in time for the first several doses of vegetable broth. This detail was missed to many clinicians who had cared for it.

It is important to remember that children fed with high levels of nitrates develop methaemoglobinaemia only after weaning, when changing the intestinal flora (4).

At this moment, in fact, it is facilitated the transformation of nitrates into nitrites, provoking the oxidation of hemoglobin to methemoglobin.

Children residing in rural settings may encounter environmental hazards derived from agricultural production activities. Health consequences of organic dusts, farm chemicals including pesticides, machinery noise, excess sun exposure, and zoonotic infectious agents have been clearly described among farm-working adults (5).

Some commercially prepared infant food vegetables are voluntarily monitored for nitrate content by private industry, including spinach, squash, and carrots. A target concentration of nitrate nitrogen for food of <100 ppm is desirable for infants. The use of nitrate-contaminated water to prepare food is a well-known risk factor for infant methemoglobinemia since 1947 when Medovy H. et al described two cases, with spontaneous recovery in about three days (5). In our case, the partial resolution of the clinical picture describes how, despite the prescribed diet and therapy, the influence of pollution and genetic predisposition constitute a real threat to the health of the child.

Our case report stimulates new approaches to diagnosis, clinical management and research: it suggests all pediatricians to carefully investigate the environmental conditions where children live.

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