Clinical Note

Methaemoglobinaemia in an infant after eating vegetable puree

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ABSTRACT

Cyanosis is a clinical sign due to the presence of bluish coloration of skin and mucosae, caused by an increase in the reduced form of hemoglobin in the capillaries, or, less frequently, to the presence of methemoglobinemia (ferric form of hemoglobin). Its origin can be contact or ingestion of exogenous oxidating toxic agents like aniline dyes, nitrobencene, drugs or nitrogen compounds from different origin or vegetables with high nitrate content (1 and 2). We report a case of a 8-month-old female infant who was brought to the emergency room with no symptoms except cyanosis of the lips and acral areas (hands and feet) after the ingestion of a mixed vegetable puree, prepared and conserved at room temperature. Her methemoglobin level determined by cooximetry was 22.8%. She was treated during 24 hour with oxygen and observation and evolved satisfactorily.

Key words: *Methemoglobinemia. Cyanosis. Cooximetry. Mixed vegetable purees.*

RESUMEN

Metahemoglobinemia en una lactante por consumo de puré vegetal

La cianosis es un signo clínico consistente en coloración azulada de piel y mucosas debida a un aumento de la hemoglobina reducida en los capilares, o menos frecuentemente, a la presencia de metahemoglobinemia (forma férrica de la hemoglobina) que puede ser ocasionada por contacto o ingesta de agentes oxidantes exógenos tóxicos como tintes de anilina, nitrobenceno, fármacos o compuestos nitrogenados de diferente procedencia, como son las verduras con alto contenido en nitratos (1 y 2). Presentamos el caso clínico de una lactante de 8 meses que fue traída a urgencias por presentar cianosis labial y de partes acras (manos y pies), sin otro tipo de sintomatología, tras la ingestión de un puré vegetal preparado y conservado a temperatura ambiente. La determinación de metahemoglobina fue del 22,8% mediante determinación por cooximetría. La evolución del lactante fue satisfactoria con tratamiento con oxígeno y observación durante 24 horas.

Palabras clave: *Metahemoglobinemia. Cianosis. Cooximetría. Pures vegetales*

INTRODUCTION

Methaemoglobinaemia (MH) occurs when the oxidation degree of iron in the heme group overwhelms the compensating mechanisms of erythrocytes and is converted to a ferric state that can not bind oxygen and carbon dioxide[3].

Due to their function in the human body, erythrocytes are continually exposed to oxidizing elements, thus, they have compensating antioxidizing mechanisms, such as cytochrome-b5 reductase and NADPH methaemoglobin reductase. However, these mechanisms become exhausted with time since erythrocytes have no cell nucleus or mitochondria to generate new enzymatic proteins.

MH can be congenital – rare - or acquired. Congenital MH can be due to a deficit in cytochrome-b5 reductase –inherited in an autosomal recessive pattern – or to the presence of haemoglobin M which is an abnormal form of haemoglobin generated when there is substitution by an abnormal amino acid in the globin chain in the presence of an exogenous agent - inherited in an autosomal dominant form.

Acquired MH is produced by contact or ingestion of exogenous toxic oxidants such as aniline dyes, nitrobenzene,

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drugs or nitrogen compounds of different origins such as vegetables containing high amounts of nitrates (Table 1)[3-6,10]. In the last 20 years, there have been accounts of series of patients that presented MH while suffering from acute infectious gastroenteritis[2]. This was mediated by the production of nitric oxide induced by swelling and infection and in other cases, as a manifestation of intolerance to cow milk proteins.

Healthy infants of under 4 to 6 months have a greater predisposition to MH due to various factors such as lack of maturity of the methaemoglobin reductase pathway, a greater predisposition of foetal haemoglobin to be oxidized and an elevated gastric pH that promotes bacterial overgrowth due to a higher rate of intestinal transformation of nitrates into nitrites - which are toxic. This predisposition disappears after the above mentioned age as the enzyme levels become similar to those of adults and there is virtually no foetal haemoglobin.

In erythrocytes, non-oxidized molecules bind oxygen with a higher affinity and they shift the dissociation curve to the left, with the corresponding clinical implications. Methaemoglobin can not carry out its functions and thus, generates cyanosis, failure in oxygenation and metabolic acidosis. MH severely impairs tissue oxygenation, not only because it reduces oxygen-binding capacity but also due to the poor oxygen transfer to tissues that it generates.

CLINICAL CASE

An 8-month-old female infant was brought to the Emergency Department after his parents noticed she had bluish colouration when they woke her up from a nap. She also presented vomiting of food. She appeared to be well in general, showing no fever, normal respiratory pattern and an oxygen saturation of 98%. However, she presented cyanosis to the lips and acral parts. Cardiopulmonary auscultation was normal with no respiratory effort and there were no abnormal findings in the ear nose and throat and neurological exams.

Additional tests that were carried out, included normal full blood count and biochemistry and a venous blood gases for co-oximetry test (IL682 Instrumentation Laboratory, IZASA) with pH 7.36, PCO_2 42 mmHg, oxygen saturation 69.4%, COHB 1.1% and methaemoglobin 22.8%.

The mother reported that the infant had had a vegetable puree for lunch that contained carrots, potatoes, leek and chard that had been prepared the previous day and kept at room temperature.

The patient was admitted to the paediatrics department for observation and was treated with oxygen therapy. She was discharged with no symptoms and her parents were advised to avoid giving her foods with high content in nitrates such as chard and spinach.

TABLE 1. Methaemoglobinaemia - inducing agents

Aromatic compounds	Aliphatic and inorganic compoounds	Other compounds
• Aniline	• Sodium nitrite	• Methylene blue
• Aniline ethanol	• Hidroxylamine	• Resorcinol
• Phenacetine	• Dimethylamine	• Hydroquinone
• Acetanilide	• Nitroglycerin	• Chloroquine
• Methyl acetanilide	• Amyl nitrite	• Dapsone
• Sulphanilamide	• Ethyl nitrite	• Sodium valproate
• Sulphatiazole	• Bismuth subnitrate	• Nitric oxide
• Sulphapyridine	• Ammonium nitrate	• Topical anesthetics (benzocaine, prilocaine, lidocaíne)
• Aminophenol	• Silver nitrate	
• Alpha-naphthalene	• Potassium nitrate	
• Para-amino propiophenone		• Vegetables with high content of nitrates
• Phenylhydroxylamine		
• Nitrobenzene		
• Nitrosobenzene		
• Phenylenediamine		
• Para-nitroaniline		

DISCUSSION

MH in children is an acute condition, normally with an only clinical sign – cyanosis – that disappears spontaneously in a few minutes or, usually, within a few hours.

MH can appear as a result of contact with oxidizing agents or due to different causes that can be food-related, genetic or even idiopathic and thus a high level of suspicion is required to make a correct diagnosis and treatment of the condition. The main clinical sign is sudden onset and progressive cyanosis, sometimes distributed by patches which are more visible in the face and limbs and that is enhanced when the patient cries. Sometimes there can also be haemodynamic repercussions such as tachypnoea and polypnoea. Patients with a more severe manifestations may present metabolic acidosis, cardiac arrhythmias and neurological symptoms such as a decrease in the level of consciousness, coma and generalised seizures.

The severity of the condition is related to the level of methaemoglobin in the blood - which in normal conditions is of 0.6% - and cyanosis appears as a first symptom when levels are over 1.5 g/dl - which in a healthy individual constitutes approximately 10-15% of total haemoglobin.

Symptoms appear progressively when methaemoglobin concentration levels are over 20%. Concentration levels of over 50% result in severe hypoxemia and depression of the CNS while concentrations of over 70% are incompatible with life.

Clinical manifestations can also depend on the previous condition of the patient, such as anaemia, respiratory distress,

cardiac failure or acidosis. Patients with these conditions present a manifestation of the symptoms that is more acute than expected for relatively low methaemoglobin levels.In other cases, the causative agent induces other symptoms, such as hypotension generated by nitrite poisoning.

Diagnosis must be based on clinical suspicion, differential diagnosis and determination by co-oximetry test, which this is not available in all laboratories. We must rule out other conditions that induce cyanosis such as respiratory diseases and congenital cardiac conditions that produce cyanosis in the neonatal period. A co-oximetry test provides a determination of abnormal haemoglobins and a measurement of saturation that is more reliable than that determined through pulse oximetry, as high levels of methaemoglobin do not produce important differences in saturation reading by this method. This occurs because the pulse oximeter works at certain wavelengths in which the light absorption rate of methaemoglobin is similar to that of oxyhaemoglobin and reduced haemoglobin. Therefore, their values are mistaken with both fractions and the readings obtained are intermediate or even normal.

We must point out that blood samples from patients with more that 15% of methaemoglobin have a dark brown chocolate colour that does not change with exposure to light.

In terms of treatment, patients with acute secondary MH must be stabilised and given oxygen. When necessary, should be performed gastrointestinal or cutaneous decontamination and in rare cases, oxygen therapy in a hyperbaric chamber must be applied.

The antidote of choice is intravenous methylene blue[3], 1 to 2 mg/kg of weight in a solution of 1 to 2 % in 5 minutes and its effects should appear within the first hour after administration. Doses must not be higher than 4 mg/kg, with a maximum dose of 7 mg/kg. Administration is not indicated when methaemoglobin levels are < 30%. This drug can induce paradoxical haemolysis or MH in patients with glucose-6-phosphate dehydrogenase deficiency and, therefore, it must be avoided in these patients. The treatment of choice in their case is exchange transfusion.

In recent years, there have been many cases of MH induced by food ingested by children or by the preservatives they contain[4,7,8] such as carrots, spinach, vegetable puree with beetroot, green beans, borage and/or chard. This is not due to the presence of nitrates in water for consumption – as was previously thought – whose concentration has been limited to 10 ppm by the WHO. Possibly, vegetables used for making the purees had high levels of nitrates and the poor preservation techniques employed turned them into nitrites - which induce MH when ingested.

Therefore, the best preventive strategy is to not introduce vegetables in infants diet before they are 6 months old and green vegetables, spinach, borage, etc., no earlier than 8-9 months. Moreover, vegetables must be consumed within a few hours of on their preparation or they should otherwise be frozen[4]. Commercial preparations must also be avoided, especially those containing carrots and spinach.

When treating an infant with cyanosis, in emergency medicine, once pulmonary origin has been ruled out, methaemoglobinaemia should be considered.

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