Unexpected chronic methemoglobinemia diagnosis in a pregnant patient in labor

Diagnóstico de metahemoglobinémia numa grávida em trabalho de parto

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Abstract

Methemoglobinemia is a rare hemoglobinopathy which can complicate pregnancy. The obstetric and anesthetic management of methemoglobin pregnant patients is poorly described. We report a case of a 24-year-old patient admitted in labor, with noticeable cyanosis but no respiratory distress. Oxygen saturation was 86%, remaining unaltered after oxygen therapy. Arterial blood gas showed normoxemia and 24,4% methemoglobin. Efforts were directed at limiting the physiologic stress and oxygen consumption, initiating epidural labor analgesia, and performing a vacuum-assisted vaginal delivery. Mother and baby were discharged after an uneventful hospital stay. The etiologic investigation of cyanosis in this patient revealed this rare hemoglobinopathy.

Keywords: Cyanosis; Methemoglobinemia; Pregnancy.

Resumo

A metahemoglobinémia é uma hemoglobinopatia rara que pode complicar a gravidez. Na literatura são poucos os casos descritos de grávidas com o diagnóstico de metahemoglobinémia, bem como a sua atuação obstétrica e anestésica. Relatamos o caso de uma paciente de 24 anos internada em trabalho de parto, com cianose, mas sem dispneia. Apresentava uma saturação de oxigénio de 86%, que não se alterou após oxigenoterapia. A gasimetria arterial evidenciou normoxémia e uma metemoglobina de 24,4%. Para limitar o consumo de oxigénio pela grávida foi inicialmente administrado analgesia epidural, e posteriormente realizado um parto instrumentado com ventosa. A mãe e o recém-nascido tiveram alta após um internamento sem intercorrências. A investigação etiológica da cianose revelou esta rara hemoglobinopatia.

Palavras-chave: Cianose; Metahemoglobinémia; Gravidez.

INTRODUCTION

Methemoglobinemia is a rare hemoglobinopathy characterized by the presence of a higher than normal level of blood Methemoglobin (MetHb). The condition occurs either by congenital (chronic) alterations in the hemoglobin synthesis or metabolism, or can be acquired in acute situations where there is an imbalance between oxidizing and reduction agents (exposure to chemical oxidizing agents). In healthy individuals, enzymatic reduction pathways maintain MetHb blood levels under 1 to 2%[2]. The oxidation of

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the iron ions in red blood cells to their ferric (Fe^{3+}) state leads to a left-shift in the oxygen-hemoglobin dissociation curve, thus limiting the oxygen carrying capacity of the hemoglobin molecule, with subsequent functional anemia[1,2].

Acquired methemoglobinemia (acute) is the most common type of the condition and occurs mainly in predisposed individuals with sepsis, falciform crises or other disease states. It can be triggered by contact with drugs, pesticides, herbicides or industrial chemicals with oxidizing potencial. Dapsone, fenacetin derivatives, nitrites, nitrates and local anesthetics (benzocaine, lidocaine) are the most common implicated drugs[3].

The most frequent congenital cause of methemoglobinemia is NADH-methemoglobin reductase deficiency, an enzyme which is responsible for 99% of methemoglobin reduction reactions. Other reduction systems also contribute to the maintenance of normal MetHb levels, namely ascorbic acid, glutathione, and NADPH dehydrogenase.

The most common symptoms are cyanosis, fatigue, headache, dyspnea and tachycardia. Higher MetHb levels (above 50 to 60%) can lead to altered mental state, coma and death[3,4]. Less severe symptoms can resemble some of the expected physiologic changes during normal pregnancy.

Patients are usually asymptomatic and the disease is many times unrecognized Therefore, the exact prevalence of hereditary methemoglobinemia is unknown. There are no structured orientations on the obstetric and anesthetic management of such patients, which brings interest to this case report and literature review. Patient informed consent for this publication was obtained.

CASE REPORT

A 24-year-old female was admitted in the obstetric emergency department in advanced active labor (39 weeks). The initial obstetric evaluation showed intact fetal membranes and 5 cm cervical dilation. The anesthesiologist was called to initiate labor analgesia. Lips and fingerips' cyanosis (Figure 1) was noticeable, but the patient appeared comfortable without signs or symptoms of respiratory distress. The patient had 86% oxygen saturation on room air, respiratory rate of 18 breaths/min, with normal blood pressure and heart rate. Oxygen saturation was double-checked and remained unaltered after supplemental oxygen initation (3 L/minute by nasal cannula). The patient had no difficulty breathing or fatigue during pregnancy, and she denied any exposure to known toxic agents. She recalled having "blue lips" since childhood and rare episodes of dyspnea during moderate exertional activities. When working as a firefighter, she described occasional episodes of dyspnea and subsequent syncope associated with exposure to smoke from fires. The patient had no known family diseases and these symptoms were never adequately investigated.

A cardiology consult was sought, and the patient showed normal electrocardiogram and cardiac ultrasound. The arterial blood sample showed a dark-brown abnormal blood color, which was immediately noticeable (Figure 2). Results showed pH 7.42, 99% oxygen saturation, 115 mmHg PaO_2 (on 3L/min nasal cannula), 35 mmHg $PaCO_2$). Oxyhemoglobin was 75% and methemoglobin was 24,4%. Results also showed an uncommonly high level of hemoglobin (13,7 g/dl) for a pregnant patient. Based on those results and after excluding other causes of cyanosis during the cardiology consult, the diagnosis of Methemoglobinemia was considered.

An epidural catheter was placed and analgesia was instituted (8 ml of 0,2% Ropivacaine and 10 ug Sufentanil) to control pain, the labor-induced metabolic stress and global oxygen consumption. The ICU was contacted for postpartum monitoring. The multidisciplinary team chose a conservative approach with mother and fetal well-being vigilance and no therapy institution. The patient had adequate contractions and labor progressed to vaginal delivery. To limit oxygen consumption during the expulsive efforts, we used a vacuum delivery system (Kiwi®) to shorten the expulsion stage.

The baby was born uneventfully, with APGAR score 9-9-9. Mother was admitted for postpartum vigilance in ICU and discharged uneventfully on the next day. Mother and baby received clearance for hospital discharge on the third postpartum day and were referred for hematology and genetic consultations.

FIGURE 1. Patient with visible cyanosis of lips.

DISCUSSION

Methemoglobinemia is a rare hemoglobinopathy which can be unrecognized until later in life. Obstetric patients can be affected by this condition, however the literature on the combined obstetric and anesthetic management of these patients is scarce.

In healthy adults, the most common type of hemoglobin in red blood cells is HbA_1 (97%), which is composed by four protein chains, two alpha chains and two beta chains. Each hemoglobin molecule is made up of four heme groups surrounding a globin group, forming a tetrahedral structure. The heme group is a metal complex with iron (Fe^{2+}), that can bind and release molecular oxygen. MetHb is an hemoglobin protein variant in which the iron atom is in the Fe^{3+} (ferric) state, impairing the ability of the molecule to offload oxygen in peripheral tissues[2-3]. Physiologically, NADH-Methemoglobin reductase is the enzyme limiting the auto-oxidation processes generating MetHb[2]. When the enzyme is genetically absent or partially defective, the organism lacks the ability to convert MetHb to hemo-globin. MetHb accumulation in erythrocytes causes a left-shift in the oxyhemoglobin dissociation curve, impairing oxygen offload in tissues[2,3]. The main feature of Methemoglobinemia is cyanosis, which is detectable with MetHb levels above 15%. At 30%, dyspnea, headache, fatigue and weakness become common. Tachypnea, metabolic acidosis, cardiac arrhythmias and seizures develop commonly with levels above 50%. Coma and death occur with levels above 60 to 70%[1-4].

Clinical clues for the diagnosis are: 1) the dissociation between low oxygen saturation levels (85-87%) and minimal or absent symptoms; 2) low oxygen saturation that does not improve with an increased administration of oxygen; and 3) the abnormal coloration of the blood observed during phlebotomy (described as dark red, chocolate or brownish)[3].

The differential diagnosis of cyanosis in adult patients includes causes of low circulating oxygenated hemoglobin, namely by the presence of other altered hemoglobin molecules (carboxihemoglobin and sulfhemoglobin), cardiac diseases (atrial or ventricular septal defects, Ebstein anomaly, impaired pulmonary venous drainage) and severe respiratory failure of several etiologies. Diminished peripheral vascular perfusion can also reduce oxyhemoglobin peripheral levels, namely caused by isolated acrocianosis, cold exposure or Raynaud phenomenon. Causes of enhanced oxygen extraction ratio (shock) can also be associated with

FIGURE 2. Collected arterial blood showing dark red color.

cyanosis. Methemoglobinemia is strongly suggested when there is clinical cyanosis and peripheral low oxygen saturation, in the presence of normal PaO_2. The diagnosis is confirmed by a co-oximetry technique[2,3,5].

Chronic methemoglobinemia can have several genetic causes, although it is commonly associated with absence or impairment of the enzyme NADH-methemoglobin reductase, responsible for the reduction reactions of methemoglobin. Chronic methemoglobinemic patients often develop compensatory mechanisms (increased cardiac output, polycythemia, polypnea) which limit the severity of symptoms[5]. Placental blood flow and oxygen demand increase along with gestational age, which explains why this condition can be associated with intrauterine growth restriction[1].

Acutely acquired methemoglobinemia often affects predisposed individuals with sepsis, falciform crises and other hypermetabolic states, after being exposed to oxidizing agents[2,3]. Local anesthetics are the most frequent drugs involved in the acute development of the disease. Acute methemoglobinemia is often severely symptomatic and demands emergent treatment to restore the oxy-reduction balance.

Therapeutic options in this condition include ascorbic acid and methylene blue. Animal studies suggest that ascorbic acid can be useful in toxic or congenital methemoglobinemia[6]. Methylene blue should be administered intravenously when levels acutely reach 20-30% (variable with authors), which constitutes a medical emergency[1,2]. The drug acts as a cofactor in the reduction of MetHb back to oxyhemoglobin. Treatment with methylene blue (1-2 mg/kg IV over 5 minutes) can be lifesaving and reduces MetHb levels in 10-60 minutes[1,6]. A risk-benefit evaluation before any medical treatment is important, assessing the risk of intrauterine hypoxia versus the potential teratogenicity of methylene blue. Its adverse effects during intravenous administration in humans have not been well studied[1].

Mild methemoglobinemia can decompensate in late pregnancy by high oxygen demanding events, such as labor pain and stress, agitation and high states of high oxygen consumption, which should be avoided and early treated[7,8]. Careful vigilance of mother and fetus is important to evaluate the need for emergent delivery[1]. Neuraxial techniques can help reduce the labor stress and pain, minimizing the metabolic oxygen demand during the labor latent and active stages.

The correct peripartum management of patients with chronic stable methemoglobinemia is not established. Cesarean section was the delivery method in all methemoglobinemic pregnant patients described in the literature, attempting to avoid labor stress-induced hypoxemia[4,5,7-9]. We demonstrated that in chronic asymptomatic cases with adequate labor progression and neuroaxial analgesia, instrumented vaginal delivery can shorten the expulsive period and reduce hypoxic periods.

We highlight the importance of the multidisciplinary management on decision making. The early control of labor pain with neuraxial techniques can reduce the hypoxic stress, and an instrumented delivery limits the expulsive phase duration and expulsive efforts. Patients

with known methemoglobinemia should be referred to obstetric and anesthetic consultations, to adequately plan labor and delivery. There is not enough data to establish the correct prenatal management and safest mode of delivery. This case demonstrated that it is possible to obtain good maternal-fetal results with a conservative approach.

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AUTHORS CONTRIBUTIONS

Rute Isabel Branco: conception, analysis and interpretation of data; drafting the article;
Nelson Santos, drafting and revision of the article;
Ana Paula Ferreira supervision and revision of the article

CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article.

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