Early diagnosis of congenital methemoglobinemia type 1 in a 4-year-old child

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Received – 08 November 2018 Initial Review – 25 November 2018 Accepted – 08 January 2019

ABSTRACT

Bluish discoloration of the skin and mucous membrane is known as cyanosis which is a clinical sign that occurs in many diseases. The causes of central cyanosis are cardiac shunts causing mixing of oxygenated and deoxygenated blood, lung diseases with ventilation-perfusion mismatch, polycythemia, and methemoglobinemia. Methemoglobin is the oxidized form of hemoglobin, which does not bind oxygen and increases the affinity of oxygen for the partially oxidized portion of hemoglobin. Methemoglobinemia may be congenital or acquired (usually drug induced). Congenital methemoglobinemia is a very rarely reported disease that is caused by a deficiency of nicotinamide adenine dinucleotide phosphate-cytochrome b5 reductase enzyme deficiency or by an abnormal hemoglobin called hemoglobin H. Acquired methemoglobinemia is caused by drugs, namely the sulfonamide group and local anesthetics such as benzocaine and prilocaine. Here, we present the case of a 4-year-old girl who presented with complaints of bluishness of the fingers and lips without any other associated symptoms and later on diagnosed as congenital methemoglobinemia.

Key words: Congenital methemoglobinemia, Cyanosis, Hemoglobin.

Methemoglobinemia, a disorder characterized by the presence of high methemoglobin levels in the blood, can occur in congenital and acquired forms. Methemoglobin is an oxidized form of hemoglobin, which has an increased affinity of oxygen and reduced ability to release oxygen to tissues. When methemoglobin concentration is elevated in red blood cells (RBC), tissue hypoxia may occur. This disorder may present with several symptoms such as cyanosis, dyspnea, and headache. Individuals with congenital methemoglobinemia will typically present with cyanosis in the neonatal period. In an arterial blood gas (ABG) analysis, these patients show a normal PaO₂ despite cyanosis which gives clue to diagnosis.

Methemoglobinemia occurs rarely throughout the world. Cytochrome b5 reductase deficiency (type Ib5R) is also endemic in the Yakutsk people of Siberia [1]. The incidence of congenital methemoglobinemia in India is not known [1]. Few cases were reported in the newborn period, few unnoticed till old age. We present a patient who went unnoticed till the age of 4 years for her dusky bluish appearance. She consulted many physicians for this and they found her oxygen saturation in pulse oximetry was low. Multiple echocardiograms and chest X-rays were done and all reports turned normal and so she was referred to Ram Manohar Lohia Hospital, New Delhi.

CASE REPORT

A 4-year-old female child resident of Halwani presented with complaints of bluish discoloration of the tip of all fingers and toes, lips, and mouth since birth. The child was born to a non-consanguinely marriage couple and had no history of dyspnea, palpitation, seizures, limitation of physical activity, or developmental delay. The antenatal, natal, and postnatal periods were uneventful. The child achieved all developmental milestones in the appropriate age. The child is attending kindergarten and there are no issues in school. There was no history of any drug intake of recent procedure involving administration of anesthetic agents. The child had an elder sibling who is a 10-year-old boy who has no such complaints. The child’s paternal grandmother also had such bluish discoloration of fingers and perioral region and she had no other symptoms. The child had consulted local physicians for the same and multiple echocardiograms were done and were found to be normal.

On clinical examination, the heart rate was 102/min, respiratory rate was 26/min, temperature was normal, and pulses were normal. Central cyanosis was present. The child had no pallor, icterus, clubbing, lymphadenopathy, and pedal edema (Figs. 1 and 2). Systemic examination was also within normal limits.

Blood investigations showed hemoglobin 10 g/dL, total leukocyte count - 11,000 cells/mm³ with normal differential count, platelet count - 3.2×10⁹/mm³, RBC - 4.92 million cells/mm³, packed cell volume (PCV) - 34.1%, and mean corpuscular volume - 69.3 fl. Peripheral blood picture showed normocytic normochromic RBC, white blood cell, and platelets. Liver and kidney function tests were normal. SPO₂ off oxygen was 88%, and with oxygen, at high flow mask, 6 lit/min was 90%. ABG
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Vol 5 | Issue 1 | Jan - Feb 2019 Indian J Case Reports

Figure 1: Patient with congenital methemoglobinemia

Figure 2: Cyanosis in the fingers of the patient

analysis without O₂ showed pH - 7.49, PaCO₂ - 25.8 mmHg, PaO₂ - 82.3 mmHg, HCO₃⁻ - 19.8 mmol/L, and SO₂% - 97.2% while ABG with O₂ showed pH - 7.437, PaCO₂ - 27.6 mmHg, PaO₂ - 24.1 mmHg, HCO₃⁻ - 21.1 mmol/L, and SO₂% - 99.5%. High-performance liquid chromatography (HPLC) was within normal limits. Heparin whole blood spectrometry showed 42.8% methemoglobin.

As the patient had cyanosis since birth with no drug exposure, a normal HPLC, and no developmental delay or central nervous system symptoms, a final diagnosis of Type I congenital methemoglobinemia was made. Although she was not symptomatic, due to cosmetic concerns of parents, she was administered IV methylene blue at 2 mg/kg a single dose and was also given oral Vitamin C high dose 1000 mcg/day for a week. Cyanosis disappeared the following treatment.

DISCUSSION

Methemoglobin results from oxidation of ferrous iron (Fe²⁺) to ferric iron (Fe³⁺) within the heme moiety of hemoglobin [2]. Methemoglobin normally constitutes <1% of total hemoglobin. It cannot carry oxygen. Due to allosteric interactions within the methemoglobin molecule, the remaining binding sites show increased affinity to oxygen, which lead to a left shift in the oxygen dissociation curve [3]. These two phenomena lead to a reduction in the oxygen delivery to tissues and when severe enough leads to hypoxemia and lactic acidosis.

Increased methemoglobin content of RBCs occurs as a result of either acceleration of oxidation reaction or fall in a reduction reaction (redox imbalance) [4]. In patients of acquired methemoglobinemia, RBCs present with a huge exogenous oxidant load that overcomes the protective cellular reduction mechanisms. In cases of congenital methemoglobinemia, the enzyme cytochrome b₅ reductase activity is diminished and there is a decrease in the rate of reduction of methemoglobin. The oxidant load in congenital methemoglobinemia is from endogenous sources [5].

A patient described in 1845, by Francois, had an enduring congenital cyanosis and there was an absence of any cardiac or pulmonary dysfunction [6]. Although this was the first case of congenital methemoglobinemia documented in literature, it was in 1932 that Hitzenberger found idiopathic cyanosis to be familial [7]. In the 1940s, Gibson [8,9] showed that there was a reduction in the ability of RBCs to reduce methemoglobin in such cases. In 1959, Scott and Griffith [10] identified the enzyme responsible for reducing methemoglobin in normal erythrocytes. They called this nicotinamide adenine dinucleotide (NADH)-requiring enzyme diaphorase. Now, generally referred to as NADH-cytochrome b₅ reductase, a functional deficiency in this enzyme is universally recognized as the underlying cause of congenital methemoglobinemia.

On extensive review of the English literature for cases diagnosed as congenital methemoglobinemia due to deficiency of cytochrome b₅ reductase, we found 23 cases, 17 cases (~74%) of type I and 6 cases (27%) of type II. There is a male predominance, 73% versus 26% in females. Almost half of the reported cases, 12 cases (52%) were Indian, two Japanese, three English, two Arabic, one case was Spanish, and one case was Italian. The median age of presentation of type I methemoglobinemia was 31 years with cyanosis and shortness of breath being the most common sign and symptom. Six cases of type II methemoglobinemia were reported in English literature with the mean age of presentation at 6 years. Type II is always associated with neurological manifestations and mental retardation [11].

Methemoglobinemia is classified as congenital and acquired. Congenital methemoglobin is further classified as Type I: Cytochrome b₅ reductase deficiency, demonstrable only in the erythrocytes, presents as uncomplicated, benign methemoglobinemia; Type II: Generalized cytochrome b₅ reductase deficiency, demonstrable in all tissues, is accompanied by severe, lethal, and progressive neurological disability, in addition to methemoglobinemia; Type III: Deficiency is limited to hematopoietic cells and resembles Type I clinically; and Type IV: methemoglobinemia clinically presents like the Type I disease and is associated with co factor FAD (flavine adenine dinucleotide) and riboflavin deficiency. Acquired methemoglobin was classified according to the causes as occupational causes: Due to absorption of nitro and amino aromatic derivatives (nitrobenzene), nitrates, and aniline (usually absorbed through lungs) related to ICU hemodialysis: Household causes include
furniture and shoe polish containing marking ink, shoe dyes containing aniline, perfume, and flavoring essence and due to various drugs such as acetaminophen, benzocaine, dapsone, and disulfiram [12].

The clinical features of congenital methemoglobin were classified as Type 1: Methemoglobinemia (Cytochrome b5 reductase deficiency) causing bluish coloring of the skin (cyanosis) and Type 2: Methemoglobinemia (generalized cytochrome b5 reductase deficiency) causing developmental delay, failure to thrive, mental retardation, seizures, and hemoglobin M disease-causing bluish coloring of the skin (cyanosis) [13]. Acquired methemoglobinemia includes bluish coloring of skin, symptoms of anoxia including headache, dizziness, and tachycardia, shortness of breath, muscular cramps, and weakness in chronic occupational cases.

In cases of acute poisoning, vomiting, lethargy, loss of consciousness, circulatory failure, and death can occur. Individuals with congenital methemoglobinemia will typically present with cyanosis in the neonatal period. In managing a cyanotic patient, physicians will often obtain ABG analysis, in addition to monitoring pulse oximetry. Unfortunately, the patient with methemoglobinemia will often have normal values for both. In interpreting ABG data, the clinician must remember that the PaO₂ refers to the amount of dissolved oxygen in the blood and in no way reflects hemoglobin saturation and thus arterial oxygen content. Patients with life-threatening methemoglobinemia may have a normal PaO₂ and a falsely elevated pulse oximetry reading [1].

Unlike a pulse oximeter, which measures light absorbance at two wavelengths (660 nm and 940 nm, corresponding to the absorption of oxyhemoglobin and deoxyhemoglobin, respectively), a cooximeter measures light absorbance at four different wavelengths. These wavelengths correspond to the absorption characteristics of deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin. As a consequence, cooximetry can distinguish between these four configurations while providing a more accurate measurement of oxygen saturation. Therefore, in patients who present with cyanosis of uncertain cause, cooximetry measurements are a valuable diagnostic tool [11].

Hemoglobin electrophoresis is also a very helpful adjunct in differentiating the different causes of congenital cyanosis. It will identify hemoglobin M, a hemoglobin variant that causes cyanosis as a result of structural changes in the α or β chains that stabilize the hemoglobin in the ferric state. These structural changes are attributable to amino acid substitutions at positions close to the heme groups in the hemoglobin molecule. Cyanosis is noticed at birth or within 4–6 months thereafter.

Once the diagnosis of methemoglobinemia has been made, there are various assays available to quantify NADH-cytochrome b5 reductase activity [11]. Adult levels of enzyme function are attained by 2–3 months of age, and in the neonate, methemoglobin reductase levels are normally 60% of the normal adult value [2]. Methylene blue is the treatment of choice for severe methemoglobinemia. In the presence of NADH phosphate, methylene blue is converted to leukomethylene blue, which results in a non-enzymatic reduction of methemoglobin. Ascorbic acid directly reduces methemoglobin, but the rate of the reaction is too slow for it to be effective when used alone [7]. Finally, if the combination of ascorbic acid and methylene blue fails to reduce the methemoglobin level, then hyperbaric oxygen and exchange transfusions are alternative therapy [14]. Our patient was treated with IV methylene blue stat dose at 2 mg/kg/dose and oral Vitamin C 1000 mcg for 7 days. She improved and bluishness of fingers and perioral region disappeared.

CONCLUSION

Congenital methemoglobinemia is a very rarely reported disease. We discussed a case of Type 1 congenital methemoglobinemia who presented for bluish discoloration of fingers and lips without any other symptoms. Based on HPLC, blood spectrometry reports, and clinical findings, a final diagnosis of congenital methemoglobinemia was made.

REFERENCES

Funding: None; Conflict of Interest: None Stated.

How to cite this article: Singh S, Narayani V, Sharma M, Tiotia R, Abinandan S H, Baghel S, Dewan V, Deswal S. Early diagnosis of congenital methemoglobinemia type 1 in a 4-year-old child. Indian J Case Reports. 2019;5(1):36-38.

Doi: 10.32677/IJCR.2019.v05.i01.012