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CONGENITAL METHAEMOGLOBINEMIA – A RARE CASE OF CYANOSIS

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ABSTRACT

Cyanosis, both peripheral and central, is a very common and important clinical finding seen in many disorders of the cardiovascular and respiratory system. But in addition to the commonly seen causes, there are certain uncommon causes of cyanosis which are overlooked and seldom diagnosed. Many classes of drugs and chemical agents used in regular practice have shown to induce cyanosis in adults. Among the hereditary causes of cyanosis, congenital methaemoglobinemia is a rare cause of cyanosis seen in the absence of any cardiac or pulmonary abnormalities. Usually diagnosed in the neonatal period, most cases go undiagnosed and eventually untreated in our country, to be picked up only during adulthood. There are many subtypes of congenital methaemoglobinema, of which some are fatal while others being only mildly symptomatic. These patients go on to lead normal lives albeit with mild symptoms and obvious cyanosis. Here we present a rare case of Congenital methaemoglobinemia, untreated until he presented to us at 25 years of age. In view of absent cardiac or pulmonary abnormalities as to the cause of his cyanosis, he was thoroughly evaluated and was found to have Type 1 Congenital methaemoglobinemia. He was subsequently treated and is doing well, on a regular follow up with us as well. Type 1 congenital methaemoglobinemia is a treatable cause of cyanosis and should be suspected in all cases of cyanosis without any cardio-pulmonary abnormalities. Type 1 congenital methaemoglobinemia responds well to treatment with methylene blue. Ascorbic acid, cimetidine and hyperbaric oxygen therapy are other alternatives in the treatment of congenital methaemoglobinemia.

KEY WORDS: **Congenital methaemoglobinemia, cyanosis, cytochrome b5 reductase**

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INTRODUCTION

Mr. X, a 25yr old male patient, moderately built, moderately nourished, manual laborer by occupation, of poor socio-economic status presented to our out-patient department with complaints of bluish discoloration of lips, tongue and tips of fingers along with dyspnoea on exertion for the past 15 years. He did not have any history of chest pain, palpitations, syncope or loss of consciousness. He noticed the fore-mentioned complaints when he was around 10 years of age. He had never been hospitalized or evaluated for the same. Patient consumed alcohol occasionally but was not a smoker. On examination, he was comfortable at rest, had cyanosis – both central & peripheral (Figures 1 & 2) along with grade 2 clubbing. His vitals were stable. Patient did not have any pallor, icterus, lymphadenopathy or edema. His oxygen saturation was around 80% with room air ventilation. Systemic examination did not reveal anything significant. Blood samples taken for routine investigations were characteristically dark brown and became darker on standing. Routine investigations revealed a haemoglobin of 17.3 gm% and haematocrit of 60%. Chest X-ray and ECG were normal. Other routine investigations done were within normal limits. ABG revealed a saturation of 90% with normal carbon dioxide content, but there was a significant rise in the level of methaemoglobin (36%). In view of raised methaemoglobinemia, haemoglobin electrophoresis was done, but did not reveal any Haemoglobin M. Echocardiography was normal. Based on the history, physical examination and investigations, a diagnosis of Methaemoglobinemia was made. History did not point as to the cause of the methaemoglobinemia, as there was no history of exposure to chemical agents or any drug intake. He was subjected to further evaluation and was found to have decreased levels of NADH-cytochrome b5 reductase enzyme (13.5 IU/g of haemoglobin). No chromosomal abnormalitites were picked up by karyotyping. In view of having established a diagnosis of congenital methaemoglobinemia, we started him on Vitamin C thrice daily, aspirin 75mg once daily and Pentoxyphylline 400mg twice daily for his secondary erythrocytosis. He became better after starting treatment and his methaemoglobin levels came down to 19.6%. Hence, he was discharged but kept on a regular follow up.

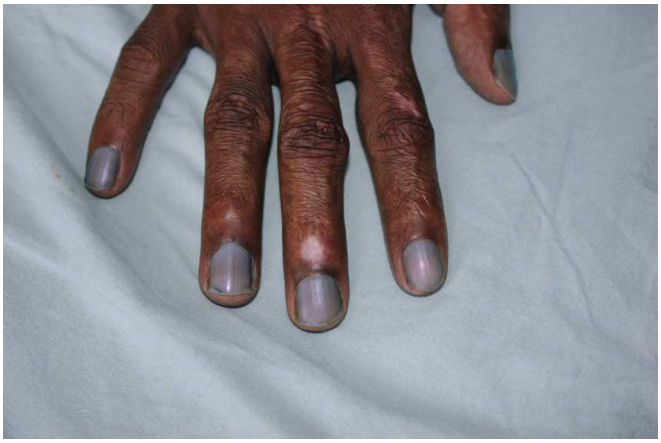

Figure1
Peripheral cyanosis

Figure 2
Central cyanosis

DISCUSSION

Methaemoglobinaemia is a rare clinical manifestation of cyanosis[1]. Methemoglobinemia is characterized by the oxidation of ferrous iron to ferric iron within the hemoglobin complex[2,3]. Once methaemoglobin (MetHb) is formed, the hemoglobin loses its ability to transport oxygen, leading to tissue hypoxia and as a result of allosteric interactions inside the molecule, affinity for oxygen at the remaining binding sites increases, resulting in a shift to the left in the oxygen dissociation curve[4]. Methemoglobinemia is most commonly caused by exposure to an oxidizing chemical, but it may also occur due to genetic or idiopathic etiologies (Table. 1). A certain amount of physiologic Methaemoglobin formation occurs continuously as a result of endogenous oxidation. Several mechanisms occur in the RBCs to reduce Methaemoglobin to deoxyhaemolobin (HHb); therefore, in healthy individuals, methaemoglobin comprises only 1% of total hemoglobin. The primary mechanism of methaemoglobin reduction, of which 99% of methaemoglobin is reduced daily, is the cytochrome b5-methemoglobin reductase (NADH methemoglobin reductase) system[5]. In the year 1959, Scott and Griffith6 identified the enzyme responsible for methemoglobin reduction in normal RBCs and called it the NADH-requiring enzyme diaphorase. Now generally referred to as NADH-cytochrome b5 reductase, a functional deficiency of this enzyme is considered as the cause of congenital methemoglobinemia. Hereditary enzymopenic methemoglobinemia can be classified into 4 different types. Type 1 is the most common and the least severe, involving a deficiency of the cytochrome b5 reductase enzyme, limited to only the RBCs[5,7]. Type 2 congenital methemoglobinemia is associated with a generalized systemic deficiency affecting a multitude of tissues, particularly the central nervous system[7,8,9].After additional study with a more sensitive assay, Type 3 hereditary enzymopenic methemoglobinemia was shown by Nagai et al, which was almost identical to Type 1. Type 4 congenital haemoglobinemia, very rarely reported, is manifested by an attenuated concentration of cytochrome b5 reductase[10].Cytochrome b5-methemoglobin reductase is a two-enzyme system consisting of cytochrome b5 and cytochrome b5 reductase. Other mechanisms of MetHb reduction (ascorbic acid or glutathione reduction & NADPH dehydrogenase) are considered minor pathways under physiologic conditions[11,12], but these minor pathways are capable of reducing large amounts of MetHb when the primary reduction mechanism is compromised. For example, patients with congenital cytochrome b5-methemoglobin reductase deficiencies are able to maintain MetHb of about 50% [2,3].

Table1
Etiologies of Methemoglobinemia

Etiologies of methemoglobinemia.

Hereditary

HbM
NADH-MetHbreductase deficiency

Acquired

Medications
Amyl nitrite
Benzocaine
Dapsone
Lidocaine
Nitroglycerin
Nitroprusside
Phenacetin
Phenazopyridine
Prilocaine
Quinones (chloroquinone, primaquine)
Sulfonamides (sulfanilamide, sulfathiazide, sulfapyridine, sulfamethoxazole)

Chemical agents

Aniline dye derivatives (shoe dyes, inks)
Butyl nitrite
Chlorobenzene
Nitrate-containing foods
Isobutyl nitrite
Naphthalene
Nitrophenol
Nitrous gases
Silver nitrate
Trinitrotoluene
Well water nitrates

Pediatric

Decreased NADH-MetHbreductase activity (<4 months of age)
Associated with low birth weight, prematurity, dehydration, acidosis, and diarrhea

Type 1 congenital methaemoglobinemia presents with little or no visible cyanosis. In spite of the slate gray, bluish appearance of these patients, methemoglobinemia is usually well tolerated. These individuals generally do not become symptomatic until their methemoglobin levels exceed 25% of the total hemoglobin, and the most common symptoms are headache, fatigue, and exertional dyspnea. Type 2 congenital methemoglobinemia constitutes approximately 10% of all cases and usually causes death within the first few years of life[5]. The severity of the disease is due to the global deficiency in NADH-cytochrome b5 reductase activity. The distinguishing feature of type 2 is an unremitting, progressive neurologic deterioration, characterized by mental retardation, microcephaly, opisthotonus, athetoid movements, and generalized hypertonia[7]. Individuals with congenital methemoglobinemia will typically present with cyanosis in the neonatal period. Arterial blood gas analysis and pulse oximetry will usually turn out to be normal inspite of methaemoglobinemia. One must remember that 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. Unlike a pulse oximeter, which measures light absorbance at 2 wavelengths (660 nm and 940 nm, corresponding to the absorption of oxyhemoglobin and deoxyhemoglobin, respectively), a co-oximeter measures light absorbance at 4 different wavelengths. These wavelengths correspond to the absorption characteristics of deoxyhemoglobin,

oxyhemoglobin, carboxyhemoglobin, and methemoglobin. As a consequence, co-oximetry can distinguish between these 4 configurations while providing a more accurate measurement of oxygen saturation. Co-oximetry is the 'gold standard' for diagnosis but arterial blood gas paired with pulse oximetry and serum methaemoglobin levels can confirm the diagnosis clinically[13]. Hemoglobin electrophoresis is also a very helpful 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 or 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 to 6 months thereafter. Once the diagnosis of methemoglobinemia has been made, there are various assays available to quantify NADH-cytochrome b5 reductase activity[14]. In the treatment of hereditary enzymopenic methemoglobinemia, many variables have to be taken into consideration. Often, patients will remain completely asymptomatic. However, methemoglobinemia causes a leftward shift of the oxygen-hemoglobin dissociation curve. Methylene blue is the treatment of choice for severe methemoglobinemia[15,16]. Ascorbic acid directly reduces methemoglobin, but the rate of the reaction is too slow for it to be effective when used alone. Methylene blue is the primary treatment in emergencies of documented symptomatic methemoglobinemia. It is given in a dose of 1-2 mg/kg (up to a total of 50 mg in adults, adolescents, and older children) as a 1% solution in IV saline over 3-5 minutes. Administration can be repeated at 1 mg/kg every half an hour as necessary to control symptoms. Methylene blue itself being oxidant at doses greater than 7 mg/kg may cause methemoglobinemia in susceptible patients; hence, it should be administered carefully. In the presence of nicotinamide adenine dinucleotide phosphate (NADPH), methylene blue is converted to leucomethylene blue, which results in nonenzymatic reduction of methemoglobin[15,16]. Methylene blue is contraindicated in patients with G6PD deficiency because it requires G6PD to work. Additionally, methylene blue administration may cause hemolysis in these patients, and also is not effective in patients with hemoglobin M (Hb M). Patients with mild chronic methemoglobinemia due to enzyme deficiencies may be treated with oral medications to decrease the cyanosis. These include methylene blue, ascorbic acid, and riboflavin. Methylene blue is given in a dose of 100-300 mg/day, ascorbic acid 200-500 mg/day; and riboflavin 20 mg/day. Long-term oral ascorbic acid therapy can cause sodium oxalate stones Hyperbaric oxygen treatment is another option for conditions when methylene blue therapy is ineffective or contraindicated. This approach permits tissue oxygenation to occur through oxygen dissolved in plasma, rather than through hemoglobin-bound oxygen. If the combination of ascorbic acid and methylene blue fails to reduce the methemoglobin level, then hyperbaric oxygen and exchange transfusions are alternative therapy[15]. Cimetidine can be used in dapsone-induced methemoglobinemia to prevent further formation of its metabolite. *N* - acetylcysteine has been shown to reduce methemoglobin in some studies but is not currently an approved treatment for methemoglobinemia.

CONCLUSION

Our patient was a case of Congenital Methaemoglobinemia Type 1, untreated until he presented to us, who recovered well with Vitamin C. His cyanosis & cyanosis regressed well. He became symptomatically better and is on regular follow up with us. With this rare case we conclude that cyanosis in an adult patient in the absence of any cardiac or pulmonary etiology should prompt one to suspect Congenital Methaemoglobinemia.

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