Late Diagnosis of Congenital Methemoglobinemia in a 33-year-old Patient, Case Report and Review of Literature

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Abstract

This is a case of recurrent episodes of headache and cyanosis who has never been diagnosed despite frequent visits to the hospital. After excluding cardiopulmonary causes, methemoglobin levels were found to be high, without exposure to any offending agent. Also, we did a literature review about congenital methemoglobinemia.

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Keywords:

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Key clinical message:

Congenital methemoglobinemia is rarely diagnosed and reported as a cause of cyanosis, especially in adults. It is a treatable cause of cyanosis that should be kept in our differential diagnosis.

Abstract:

Cyanosis and dyspnea are common complaints in adults and have broad differential diagnoses, of which rare ones as congenital methemoglobinemia should always be kept in mind. Methemoglobinemia might be acquired or congenital. Patients' symptoms vary from severe shortness of breath, mental status changes, cyanosis to none.

Here we present a rare case of a 33-year-old Indian non-smoker female, who had a long history of recurrent episodes of cyanosis, headache, and fatigue. After excluding cardiopulmonary causes, methemoglobin levels were measured and found to be high, without exposure to any offending agent. Consequently, we suspected a diagnosis of congenital methemoglobinemia and started treatment with ascorbic acid, and she improved.

In this article, we summarized our patient's presentation and did a literature review about congenital methemoglobinemia.

Introduction:

Methemoglobinemia, a form of hemoglobinopathies, is defined as an increased methemoglobin level, where the ferric form of iron is attached to heme instead of ferrous. This will reduce tissue oxygenation[1]. A percentage of hemoglobin will be oxidized to methemoglobin under any oxidative stress, but this is regulated by special enzymes to keep it in normal individuals less than 1.5%. Usually, cyanosis appears when methemoglobin levels exceed 1.5 g/dl, around 15% of total hemoglobin; most adults with methemoglobinemia have the acquired type due to exposure to an offending agent. Whereas having unexplained methemoglobinemia in an adult should raise the possibility of the congenital type, which is extremely rare.

Three genetic causes lie behind congenital methemoglobinemia[2]:

1.*CYB5R3* gene pathogenic variations lead to autosomal recessive cytochrome b5 reductase deficiency. This genetic phenotype causes two types of methemoglobinemia; type 1, RBC type, might be asymptomatic and type 2, other cells, were patients will have neurologic manifestations.

2. Point mutation in alpha-globin gene causing hemoglobin M, an autosomal dominant disease.

3. Cytochrome b5 deficiency, extremely rare.

Our patient presented with shortness of breath of 3 days duration with bluish discoloration of her fingers and lips. Her complaint was not associated with chest pain, cough, wheezes, or any other symptoms. she had recurrent similar episodes since childhood but milder. A mismatch between oxygen saturation by pulse oximetry and blood gases raised the possibility of methemoglobinemia. We suspected the congenital methemoglobinemia type 1 and initiated treatment with a high dose of ascorbic acid; after ruling out the causes of acquired methemoglobinemia, and the patient improved clinically.

Case presentation:

This is a case 33-year-old Indian lady seen in the emergency room for difficulty breathing with bluish discoloration gradually increased over days, with no fever or cough. She mentioned having recurrent similar episodes since childhood, exacerbated by infections, but usually milder. No previous surgical or medical history, except for one admission last year for shortness of breath with cyanosis, required oxygen support for one day and then discharged home with no diagnosis, and chronic headache.

One sister has similar cyanosis symptoms, who had surgery complicated with low saturation and severe cyanosis during anesthesia. Both have never been investigated. Her other three siblings and parents do not have any symptoms.

Physical examination was normal except for central and peripheral cyanosis; the chest was clear, with no wheezes, no crackles. Cardiac examination, no murmurs or abnormal heart sounds. Abdominal examination, no organomegaly appreciated.

Height: 167 cm, weight: 66 kg, BMI: 23.7 kg/m2, SpO2: 90% sometimes dropping to 88% on room air, HR: 77 beat/minute, BP: 105/80 mmHg, RR: 20 breath/min

Investigations:

Patient had normal liver function tests results, G6PD scan: normal other laboratory results and ABG result in table (1).

Peripheral blood smear demonstrated mild erythrocytosis with no other abnormalities. Electrocardiography showed normal sinus rhythm. Chest radiography showed clear lung fields and a heart of normal size and contour. There were no abnormalities of the hilar, mediastinal, pleural, or bony structures.

The patient's clinical picture of cyanosis with no evidence of cardiovascular or pulmonary diseases and the discrepancy between PaO2 and O2 saturation on oximeter required thinking of methemoglobinemia as a possible diagnosis despite the patient's age and the absence of any exposures. Methemoglobin level 20.9% (0-1.5%). Hemoglobin electrophoresis did not detect any abnormal hemoglobin.

The activity of NADH cytochrome b_5 reductase or the level were not done.

Discussion:

Methemoglobinemia is a result of defective regulation of the methemoglobin level by the responsible pathways after oxidative stress. In normal individuals, methemoglobin results from oxidation of ferrous iron that binds to heme to ferric iron, which decreases its ability to bind to oxygen, leading to less oxygen delivery to tissues and left shift in oxygen dissociation curve[11]/17/2020 5:33:00 PM. Affected individuals can have cyanosis, but clinically significant tissue hypoxia is unusual as compensatory erythrocytosis improves oxygen delivery.

Methemoglobinemia might be acquired or congenital. For acquired methemoglobinemia, a myriad of causes has been described in the literature of which: medication as dapsone, lidocaine, nitrates, sulfa drugs [3,4,5]. The clinical consequences depend upon methemoglobin levels in the blood; symptoms will start at a level >10%, then nausea, tachycardia occurs with level<30%, while 50% level leads to neurological deterioration. Higher levels can cause arrhythmia, while more than 70% of methemoglobin is considered fatal[2,3]. The acquired form's symptoms are affected by the speed of the increase in the levels and the half-life of the causative agent. Mostly those patients require treatment with intravenous methylene blue.

Conversely, congenital methemoglobinemia causes milder presentation as it is a chronic elevation in methemoglobin with a physiologic compensatory erythrocytosis. NADH cytochrome b5 reductase deficiency congenital methemoglobinemia is further classified into two subcategories. Type 1, enzyme deficiency in the erythrocytes, those patients are usually asymptomatic or will present late with cyanosis, fatigue, some shortness of breath—treatment for cosmetic reasons mostly[10,23]. Type 2, generalize deficiency of cytochrome b5 in all body tissues, is accompanied by neurological disabilities; however, it is not amenable to treatment at this time.

While acquired methemoglobinemia, triggered by oxidative means, is common, congenital causes are uncommon and rarely documented in the literature[10].

Here we tried to summarize the English published literature about congenital methemoglobinemia in table (2)

Conclusion:

Due to mild symptoms, congenital methemoglobinemia is rarely diagnosed and reported as a cause of the cyanosis, especially in adults. Despite the benign nature of congenital methemoglobinemia, it is crucial to keep it in the differential diagnosis list when assessing cyanotic patients, mainly if he has a normal PaO2. Patients are usually asymptomatic and are treated for cosmetic purposes, but they might suffer from severe complications if exposed to oxidative agents.

In summary, congenital methemoglobinemia is a rare but treatable cause of cyanosis that should be considered in the differential diagnosis of cyanosis.

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Conflict of interest:

None to identify.

*Statement of ethics:*Consent was obtained from the patients. Case was approved by HMC Medical Research Center.

Data availability statement: All data related to this article are available upon request.

Author contribution: MA, MY: were involved in data collection, analysis, and interpretation. MAwrote the manuscript. MYcritically revised the manuscript.

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Table legends:

Table (1) laboratory results

Table (2) literature review summary

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