Congenital methemoglobinemia in old age

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ABSTRACT

Chest infections and ischemic heart disease are the most common causes of shortness of breath and cyanosis in old age. However, the hemoglobinopathies should be considered if the cardiac cause is ruled out, and cyanosis is not responding to oxygen therapy and antibiotic treatment. A 75-year-old retired soldier was admitted to the inpatient department of a tertiary care hospital with symptoms of cyanosis, shortness of breath, and fever. Cyanosis was acrocyanosis in nature and not relieved by oxygen therapy.

The initial diagnosis was lower respiratory tract infection. However, the cyanosis did not improve. An alternate diagnosis was considered, and the patient was started on a treatment regimen for ischemic heart disease that included nitrates that led to worsening his condition. Blood methemoglobin levels were raised, which established the diagnosis of methemoglobinemia. The fast-moving dark brown color band of Hb M on gel electrophoresis confirmed the diagnosis of Hb M. The patient was started on IV ascorbic acid and improved within 36 hours.

Patients presenting with unexplained acrocyanosis should not be treated with oxidizing agents like nitrates, irrespective of age and management of another disease, unless the cause of cyanosis has been established.

Keywords: Aged, cyanosis, congenital methemoglobinemia, shortness of breath

INTRODUCTION

Methemoglobinemia (MetHb) is a rare hemoglobinopathy resulting in increased MetHB in blood. Based on the etiology, it is classified into two forms: congenital and acquired. The acquired form is more prevalent, with a single-center study suggesting its incidence to be 0.067%, but the prevalence of the congenital form has not been determined. The acquired form is often caused by exposure to oxidizing agents, like dapsone, benzocaine and nitrites; infections, such as COVID-19 and severe sepsis, may also induce MetHb. Congenital MetHb has three genetic etiologies: an autosomal dominant point mutation in the any of the globin genes that causes hemoglobin M, an autosomal recessive mutation in the CYB5R3 gene that results in cytochrome b5 reductase deficiency, or an extremely rare autosomal recessive NADH-cytochrome b5 reductase deficiency.[1] The most common genetic etiology is cytochrome b5 reductase (cb5r) deficiency.[2] It includes two subtypes of autosomal recessive disorders. Type 1 is less severe and causes a cb5r enzyme deficit in mature red blood cells. Life expectancy is equal to that of healthy individuals. However, type 2 affects all cell types and is a severe genetic disorder. Ten to fifteen percent of patients with congenital cb5r deficiency have type 2, which can cause mental retardation and neurological complications.[4] Another cause of congenital MetHb is mutation in any of the chains of Hb.[3] It is relatively less severe and is asymptomatic. These patients have normal life expectancy. However, the presence of oxidizing agents and infections may increase levels MetHb levels and cause symptomatic MetHb, as it happened in our case.

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DOI: 10.12746/swrccc.v13i54.1377

Table 1. Methemoglobin Disorders

MetHb Level	Signs	Symptoms	Causes
<10%	Low pulse oximeter readings, alteration of the skin color (pale, gray, blue)	Asymptomatic	Acquired
10%–30%	Cyanosis, dark brown blood	Asymptomatic/confusion	Enzymopenic methemoglobinemia, HbM, acquired
30%–50%	Dyspnea, dizziness, syncope	Confusion, chest pain, palpitations, headache, fatigue	Acquired ± hereditary
50%–70%	Tachypnea, metabolic acidosis, dysrhythmias, seizure, delirium, coma	Confusion, chest pain, palpitations, headache, fatigue	Acquired ± hereditary
>70%	Severe hypoxemia, death	–	Acquired ± hereditary

Acquired causes of MetHb include exposure to medications and poisons that have the potential to oxidize hemoglobin and raise MetHb levels. Previous studies have demonstrated that drugs, such as primaquine, dapsone, and benzocaine, are the primary causative agents.[3] Sickle cell crisis, gastrointestinal infections in children, and exposure to other toxins or oxidizing agents can also cause acquired MetHb.[3,5]

Common symptoms include grayish-blue-tinted skin and asymmetric acrocyanosis. However, the patient may remain asymptomatic in MetHb. The symptoms also depend upon the levels of MetHb levels in the blood (Table 1).[3,5] Almost all cases of congenital MetHb are detected during early childhood and are generally benign. However, our patient who was 77 years old at the time of diagnosis is the sixth person above the age 50 to be diagnosed as a case of congenital MetHb[2,6,7] and based on a current literature is the first person to be diagnosed with Hemoglobin M disease above 70 years of age.

Case

A 77-year-old man was in his usual state of health until 10 days prior to presentation when he developed a low-grade fever with rigors and chills, productive cough, and undocumented weight loss. He had no known comorbidities. The patient had no previous hospitalization episodes. Upon initial clinical examination, the patient was well oriented and alert. Vital signs were blood pressure 86/84 mmHg, pulse rate 88 beats/min, respiratory rate 18 breaths/min, and $Sp0_2$ 90%. General physical examination revealed cyanosis with no clubbing or pedal edema. Chest examination revealed reduced breath sounds and fine crackles bilaterally. Heart sounds were normal. He was previously admitted to a secondary care hospital for six days with similar complaints and was referred to our tertiary care hospital due to his persistent symptoms. The patient was subsequently admitted to the pulmonology ward of the inpatient department. A preliminary diagnosis of lower respiratory tract infection was made. Blood tests showed a normal total leukocyte count with neutrophilia (75%), elevated hemoglobin levels (18.2 g/dL), and an increased ESR. Renal tests showed an elevated urea level (18.2 mmol/L) with urea: creatinine ratio of 19. Sputum analysis was unremarkable. During hospitalization, the patient had an episode of atrial fibrillation. Due to this episode, he was investigated for cardiovascular origins of cyanosis. However, it turned out to be negative.

The patient was treated for lower respiratory tract infections, but his condition showed only minimal improvement. The patient had persistently low $Sp0_2$ levels despite adequate face-mask ventilation. He was then started on treatment of ischemic heart disease that included nitrates. The patient's condition deteriorated further. Persistent cyanosis and dyspnea prompted the search for an alternate diagnosis. Methemoglobin levels were ordered and were found

to be 37.9%. The patient was diagnosed as a case of MetHb and was started on ascorbic acid 2 g with IV infusion three times daily for next 48 hours.

Follow-up and outcome

The patient's cyanosis and cough improved within 36 hours of ascorbic acid administration. No unanticipated events were observed after ascorbic acid administration. A detailed family history revealed that the patient's siblings also had similar symptoms of central cyanosis. The patient was followed after treatment to determine the type of MetHb. Electrophoresis showed Hemoglobin M, confirming the congenital cause of the disease.

Informed consent was obtained from the patient for publication of this case report.

Discussion

This is the first reported case of congenital MetHb caused by Hb M in Pakistan. A study published in the *Journal of the Pakistan Medical Association* reported a case of congenital MetHb. However, the Hb M nature of the disease in that patient has not been established.[8] Few cases of congenital MetHb have been reported in older patients. A medical literature search revealed a single reported case of congenital MetHb at or above the age of 70; the case reported was due to deficiency of cytb53 reductase rather than Hb M disease. Studies to determine the type of Hb M were not conducted due to the limited capacity and resources for both genetic and chromatographic studies.

Hemoglobinopathies are very rare causes of patients presenting with cyanosis, especially at older ages. Most common causes that present with cyanosis include cardiovascular and pulmonary causes.[11] However, after workup on cardiovascular and pulmonary causes have negative findings, hemoglobinopathies should be considered as possible etiology. It is unusual for hemoglobinopathies to present at old age, especially if the cause is congenital. Nonetheless, the hemoglobinopathy can be missed or ignored simply due to the benign nature of disease and may later present in life. The late presentation can be due to declining pulmonary reserves, superimposed infection, administration or ingestion of drugs that promote the oxidized form of iron.

Methemoglobinemia can be broadly classified into deficiency of reducing enzymes or a defect in globin chains surrounding heme, which makes the ferric form of iron more structurally stable. Note that the ferric form of iron is unable to carry oxygen and reduces the oxygen carrying capacity of blood. The resulting hemoglobin chains are known as Hb M. A literature review suggests that there are 7 different types of Hb M, each resulting from mutation in alpha (Hb M Boston, Hb M Iwate),[9,10] Beta (Hb M-Saskatoon, Hb M-Hyde Park, Hb M-Milwaukee),[13,17–19] and gamma (Hb M Fort Ripley).[12,16,17] MetHb disease with alpha chain defect present with cyanosis usually at birth as an alpha chain is a constituent of Hb-F and also persists throughout life, within the structure of HbA (alpha2 beta2). Conversely, Hb M disease resulting from a beta chain defect present with cyanosis after 4–6 months of life as the Hb-A (alpha2 beta2) takes time to gain concentration in the body. The MetHb resulting from gamma globulin chains results in cyanosis at birth, but neonates recover as the Hb-F concentration in the body is shifted in favor of Hb A production. This could give the clinician or hematologist a diagnostic clue into the type of Hb M disease.

After a detailed family history was obtained, it was found that the patient had four brothers and three sisters; two brothers and one sister had similar bluish discoloration of the skin. Further diagnostic confirmation with electrophoresis also supports the autosomal hemoglobin M nature of MetHb. However, the family history did not reveal similar symptoms in preceding or succeeding generations. This may suggest de-novo mutation, resulting in an unstable globin chain and eventually leading to MetHb.

Although a case of congenital MetHb was detected in a 79-year-old Japanese man, this case report indicates that a patient with MetHb is often undetected or undiagnosed during the neonatal and infant periods. This may be due to a lack of facilities and screening in several countries, particularly developing countries. As a result, they may present later in their lives with cyanosis and dyspnea exacerbated by oxidizing

agents or infections such as respiratory tract infections. Therefore, MetHb should be included in the differential diagnosis of patients presenting with cyanosis, irrespective of age, and after ruling out common etiologies of cyanosis, which includes CHF, asthma, and a cyanotic heart disease, especially if not corrected by respiratory support.

Furthermore, a patient should not be started on oxidizing agents such as nitrates until the cause of central cyanosis has been established.

Article citation: Sherani T, Ali K, Rehman L. Congenital methemoglobinemia in old age. The Southwest Respiratory and Critical Care Chronicles 2025;13(54):35–38
From: Army Medical College (TS), Rawalpindi, Pakistan; Pakistan-Emirates Military Hospital (KA), Rawalpindi, Pakistan; United Medical and Dental College (LR), Karachi, Pakistan
Submitted: 9/22/2024
Accepted: 12/23/2024
Conflicts of interest: none

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