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Methemoglobinemia - A Rare Adverse Effect of Dapsone in A Patient with Normal G6PD Level

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Abstract

A 76 years old female on dapsone since last 15 days for suspected dermatitis herpetiformis presented with central cyanosis. She had normal G6PD levels (tested just before start of treatment and repeated again from different lab afterwards). Investigations were done to rule out cardio respiratory causes of cyanosis and were later found to have raised methaemoglobin levels as the cause. She was successfully managed by oral ascorbic acid and other supportive measures. Methemoglobinemia should be considered in differential diagnoses of cyanosed patient with normal ABGs, PaO2 and cardio-respiratory status. If left untreated, the disease can be fatal.

Introduction

Long-term administration of dapsone at standard doses (100 mg/day) results in methemoglobinemia in about 15% of patients.[1] classically, low pulse oximeter readings are associated with hypoxia, however methemoglobinemia is an important albeit uncommon cause.[2]

The majority of cases of acquired methemoglobinemia described in literature have

resulted from exposure to exogenous oxidizing agents like nitrites used as preservatives in food or as a deliberate poison,[3,4] amyl nitrate used as a recreational agent,[5,6] abuse of paint thinner by addicts,[7] intake of nitrate containing vegetables,[8] use of EMLA cream,[9,10] and Dapsone intake.[11,12]

The peak plasma concentrations of Dapsone are reached within 2-8 hours after ingestion. The mean elimination half-life varies from 10 to up to 80 hours in overdose situations. In healthy erythrocytes, cellular enzymes rapidly reduce any naturally occurring methaemoglobin. An exposure to oxidative medications can overcome these reducing enzymes thus causing an accumulation of methaemoglobin.[2] The role of nitric oxide (NO) in the pathophysiology of methemoglobinemia is also being studied.[13] The presence of methaemoglobin in the erythrocyte prevents the binding of oxygen as also increases the affinity of normal haemoglobin molecules for oxygen, shifting the oxygen dissociation curve to the left, thus further decreasing oxygen delivery to the tissues.[2,14]

The symptoms and signs are proportional to the level of methaemoglobin. Asymptomatic, if less than 15%; cyanosis in levels above15%; headache, dyspnoea, nausea, tachycardia, and weakness in levels above 20%; coma sets in above 45%, and a high mortality rate is associated with levels above 70%.[15]

While cyanosis is a pointer to the diagnosis, varying oxygen saturation seen with pulse oximetry often confuses the issue. Standard colorimetric pulse oximeters show falsely low readings in mild toxicity and falsely high readings in severe toxicity by giving a constant reading in the low 80s in the presence of methaemoglobin.[2] On the other hand, most arterial blood gas analysers calculate the oxygen saturation based on the PaO2 (which is a measure of the dissolved oxygen in plasma) and so give false high values. Therefore, a "saturation gap" between the recorded saturation from the pulse oximeter as compared to the reported saturation in the arterial blood gas may be detected[16] and in the presence of a high index of suspicion, may be the key to diagnosis, especially in the resource limited setting.[3]

Management consists of removing the offending agent, high-dose oxygen, and intravenous methylene blue. Methylene blue (1-2 mg/kg) administered intravenously over a period of 3-5 minutes (contraindicated in G6PD deficiency) produces a rapid conversion of methaemoglobin to haemoglobin. Its use is recommended in all patients with methaemoglobin levels greater than 30% or in symptomatic patients at lower levels. In mild cases and those with G6PD deficiency ascorbic acid in doses of 300-600mg/day may be given. Exchange transfusion and hyperbaric oxygen may also be considered for severe or refractory cases.[18]

This case emphasizes the importance of good history taking, knowledge of drugs likely to cause methemoglobinemia and a high index of suspicion especially in the presence of a "saturation gap".

Case Report

A 76-year-old Asian lady presented to emergency department with short history of bluish discoloration of her skin, primarily over lips, tongue, hands, and feet. She also had complaints of gradually progressive dyspnoea, palpitation, and apprehension. She denied any history of fever, cough or sputum production. For these complaints she visited different health facilities & was given nebulization, supplemental oxygen, but symptoms didn't improve.

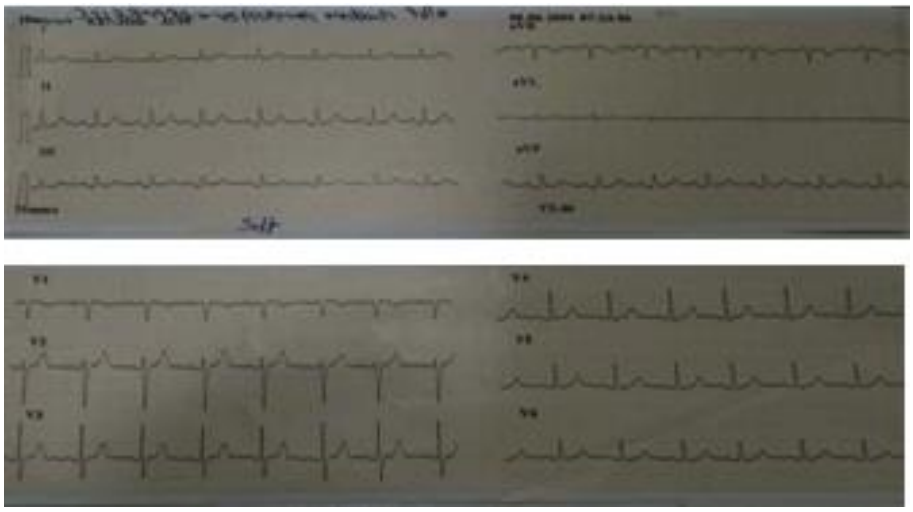
Past history included painful blue-red nodules over extensor surface of lower limbs, which resolved

with steroids use. However, they reappeared many times later and did not regress much with steroids afterwards. Later on she was diagnosed to have Dermatitis Herpetiformis and was started on dapsone 200mg/day after getting the G6PD levels done (which came out to be normal).

On examination, she was dyspnoeic, centrally cyanosed with 86% O2 saturation at room air. Cardiovascular and respiratory examination was unremarkable. She was given supplemental oxygen via face mask but saturation didn't improve more than 88%. All her laboratory investigations (CBC, LFT and RFT) were normal except for haemoglobin which was 9.7 g/dl. Chest Xray, ECG, cardiac enzymes and echocardiography were normal. No circulatory or ventilatory abnormality was found to explain cyanosis.

Figure - 1

Figure - 2



Her haemoglobin fell from 11 to 9.7 g/dl in last 15 days and her reticulocyte count and LDH levels were raised (667U/L) signifying some degree of haemolysis. Her ABGs at maximum O2 revealed PaO2 88 (60–90 mmHg), pH 7.41 (7.36–7.46), PCO2 38.2 (34-46 mmHg), HCO3 26 (22-27 mEq/L). Her cyanosis with normal PaO2 despite low SpO2 on pulse oximetry and haemolysis was the pointer to the diagnosis.

Serum methaemoglobin level was then done, and it came out to be 18.7%. This led to the final diagnosis of Dapsone induced Methemoglobinemia.

G6PD levels were tested again from different lab, they again turned out to be normal.

She was managed on Tablet ascorbic acid 600mg/day and hyperbaric O2 support, and dapsone was stopped. Her O2 requirement gradually reduced from 12L/min to 2L/min in 5 days and she started maintaining SpO2 on room air on 5th day with resolution of her symptoms. Her methaemoglobin levels declined steadily from 18.7% to 3.6% on 6th day and then she was discharged. She is doing fine on follow-up.

Discussion

Oxygen in blood is carried by haemoglobin. When this haemoglobin gets oxidized (due to hereditary defects or by oxidative stress) it forms methaemoglobin, resulting in tissue hypoxia.

Our body has the capability to reduce this methaemoglobin to haemoglobin via certain enzymes such as cytochrome b5 reductase. In its acquired form, exposure to various oxidizing agents can also result in conversion of normal haemoglobin to methaemoglobin. These oxidizing agents include drugs like benzocaine, lidocaine, prilocaine, antibiotics like dapsone, chloroquine, nitrites, some toxins, aniline dyes etc.

Methaemoglobin, formed when haeme iron becomes oxidized from the ferrous state to the high spin ferric valence, is incapable of binding oxygen.[21] In addition, methaemoglobin causes a left shift in the oxyhaemoglobin dissociation curve, making the release of bound oxygen to tissues more difficult. Methaemoglobin is continually formed at a steady rate within normal erythrocytes through auto-oxidation.[20,21] However, normal levels remain less than 1% due to four separate reduction pathways. The principal pathway is an NADH-dependent methaemoglobin reductase system which accounts for 67% of conversion to reduced haemoglobin.[19,20,21] A nicotine adenine dinucleotide phosphate (NADPH reductase) dependent methaemoglobin reductase system also exists but is responsible for only 5% of the conversion. Additionally, glutathione can directly reduce methaemoglobin and is responsible for 15% of the conversion, whereas ascorbic acid may convert up to 12% of the methemoglobin.[21,22]

Four principal causes of methemoglobinemia exist: inherited autosomal recessive deficiency of methaemoglobin reductase; haemoglobin M, an autosomal dominant trait leading to congenitally oxidized haeme iron; glucose-6-phosphate dehydrogenase (G6PD) deficiency, an autosomal recessive trait leading to the inability to reduce oxidized NADP in erythrocytes; and toxic exposures, the most frequent cause of methemoglobinemia.[19,20] Multiple agents have been implicated in the induction of methemoglobinemia and include sulphonamides and their derivatives, local anaesthetics, aniline dyes, and nitrates. Important physical properties of methaemoglobin include equal light absorbances at 660 nm (peak absorbance of deoxyhaemoglobin) and 940 nm (peak absorbance of oxyhaemoglobin). Pulse

oximeters function by comparing pulse added absorbencies at 660 nanometres and 940 nanometres. The software is structured such that a ratio of 0.43 yields a pulse oximeter saturation (SpO2) of 100%, a ratio of 1.0 yields an SpO2 of 85%, and a ratio of 3.4 yields an SpO2 of 0%.[24,25] Because methaemoglobin has similar absorbances at the two wavelengths, high methaemoglobin levels will yield a ratio of 1.0, and therefore, an SpO2 of 85%.[23] The measured partial pressure of oxygen is appropriate for the given fraction of inspired oxygen; however, measured oxygen saturation is lower than ex- pected.[24,25] With these considerations, when methaemoglobin is present, pulse oximetry will underestimate the true haemoglobin saturation under nonhypoxemic conditions and overestimate haemoglobin saturation in hypoxemic conditions.

Our patient has normal G6PD levels therefore she may have defect in other pathways which are less common and therefore rarely considered.

Conclusion

In conclusion, acquired methemoglobinemia is a rare blood disorder which can be fatal condition if left untreated. It should be considered in the differential diagnosis of central cyanosis in presence of normal ventilatory and circulatory systems specially in presence of offending drugs like dapsone.

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