CASE REPORTS

Congenital Methaemoglobinaemia: A Rare Cause of Cyanosis in an Adult Patient

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Abstract
Cyanosis is a physical finding that can occur at any age but presents a great challenge as the causes are multiple and varied. When patients present with cyanosis and dyspnoea that are unrelated to cardio-pulmonary causes, methaemoglobinaemia should be considered as a possible diagnosis although rare. Methaemoglobinaemia can be asymptomatic even when methaemoglobin (metHb) levels are as high as 40% of the total haemoglobin values. Although acquired methaemoglobinaemia caused by environmental oxidizing agents is common; congenital deficiency of the innate reducing enzymes is so rare that very few cases have been documented. We report this case of type I congenital methaemoglobinaemia.

Case Report

A 18 year old Indian male presented with history of cyanosis, headache and exertional dyspnoea since 10 years. He had no history of chest pain, syncope, palpitations, oedema feet or early satiety. He did not give history of addictions, drug intake or exposure to oxidant chemicals. His younger sister has similar complaints.

On examination, he had bilateral ptosis (present since childhood and no diurnal variation or diplopia). Patient also had cyanosis (as shown in Figures 1 and 2) (both central as well as peripheral) and grade 3 clubbing. His vital signs were normal and there were no abnormalities in the examination of cardiorespiratory system. Pulse oximetry reading on room air was 85 per cent. The patient’s venous blood was dark in colour and became dark brown on standing for few minutes at room temperature as shown in Figure 3.

Routine investigations like complete blood count showed a secondary polycythaemia with haemoglobin of 19.2 gm% and haematocrit of 58.8 per cent. Patient was investigated for cardiorespiratory disorders and found to have a normal chest X ray and echocardiography as well as contrast ventriculography (to rule out congenital heart diseases). Arterial blood gases showed a saturation of 92% (SaO₂) and normal oxygen and carbon dioxide content but a methaemoglobin level of 37.4% (normal being less than 1%) with a saturation gap. Haemoglobin electrophoresis was done which did not show evidence of haemoglobin
Hence it was concluded that patient was suffering from cyanosis due to methaemoglobinaemia. Acquired causes were ruled out as there was no history of exposure to oxidising drugs in the near past. He was evaluated further and found to have a deficiency of NADH-cytochrome b5 reductase enzyme levels 14.15 IU/g of haemoglobin (Normal: 30-35 IU /g haemoglobin) in his red blood cells. Karyotyping was done for chromosomal abnormalities which was normal however single gene defects could not be tested.

He was started on ascorbic acid (vitamin C 500 mg thrice a day PO). In view of his secondary erythrocytosis he was started on low dose aspirin (75 mg PO once a day) and pentoxyphylline. Patient also underwent one session of phlebotomy. With these interventions patient became symptomatically better with reduction of cyanosis and decrease in methaemoglobin concentration on arterial blood gases (methaemoglobin levels 17.8 %). He was discharged on oral ascorbic acid and aspirin. Presently he is following up and is symptomatically better. Methaemoglobin levels are presently in the range of 20%. Patient’s sibling who suffers from similar condition could not be tested as she did not come for investigations from her native place.

To conclude this is a rare case of congenital Methaemoglobinaemia type I due to deficiency of cytochrome b5 reductase in the red blood cells.

Discussion

Methaemoglobinaemia is an uncommon clinical problem manifesting as cyanosis. An increased level of methaemoglobin can be attributed to congenital enzymatic defects, alterations in the haemoglobin molecule, or as a result of medications and toxins. Inherited methaemoglobinaemia arises either from structural alterations in the haeme pocket of globin chains which impede normal reduction of ferric haeme or as a result of marked deficiency of an NADH dependent methaemoglobin reducing enzyme. The haemoglobinopathic form or Haemoglobin M disease is inherited as autosomal dominant defect and diagnosed by an abnormal haemoglobin electrophoresis. The inheritance of the metabolic form of methaemoglobinaemia is autosomal recessive. Recessive congenital methaemoglobinaemia (RCM) is a very rare disorder caused by NADH-cytochrome b5 reductase (cb5r) deficiency. Two distinct clinical forms, types I and II, caused by cb5r deficiency have been recognised. In type I, the enzyme deficiency is restricted only to the red blood cells with cyanosis being the only major symptom. In type II, all tissues are affected and hence it causes reduced life expectancy and is associated with neurological impairment, mental and growth retardation, in addition to cyanosis. Methaemoglobin is produced from oxidation of ferrous ions to ferric ions and persistence of ferric ions within the haeme moiety. Methaemoglobin which normally constitutes less than 1% of the total haemoglobin cannot carry oxygen and deliver it to the tissues.

A possible clue to the diagnosis of methaemoglobinaemia is the presence of “saturation gap”.

This occurs when there is difference between the SO₂ that has been measured by means of pulse oximetry (underestimation) and the saturation that has been calculated by means of arterial blood gas analysis. Typically the saturation gap is greater than 5% in cases of methaemoglobinaemia. 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.

Treatment of type 1 methaemoglobinaemia is symptomatic. Phlebotomy is needed if there is
symptomatic secondary erythrocytosis. Vitamin C (ascorbic acid) is used as a reducing agent and is found to be effective. Methylene blue is the antidote used in life-threatening cases with severe hypoxaemia in acute acquired methaemoglobinemia. Our patient demonstrated all the classic features of congenital methaemoglobinemia type 1 on presentation and was well controlled with vitamin C.

To conclude congenital methaemoglobinemia is a very rare but treatable cause of cyanosis that should be kept in mind in a case of cyanosis (central plus peripheral) without cardiorespiratory causes or oxidant chemicals/drugs exposure.

References: