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Acquired methaemoglobinaemia — a case report

Abstract

Methaemoglobinaemia is a rarely diagnosed, life-threatening pathology and involves the presence of more than 1% of oxidised haemoglobin in the blood that is unable to carry oxygen.

We report the case of a 49-year-old male who developed fulminant symptoms of acute hypoxaemic respiratory failure and in whom acute and chronic cardiovascular and respiratory conditions had been ruled out. The discrepancy between oxygen saturation determined by pulse oximetry and oxygen saturation and oxygen partial pressure determined by capillary blood gas analysis, as well as the evident lack of response to oxygen therapy, were important indicators suggestive of a haemoglobinopathy and the diagnosis of methaemoglobinaemia. His methaemoglobin level was 16%. The symptoms resolved spontaneously and the causative factor was not identified.

Key words: methaemoglobinaemia, cyanosis, saturation

Pneumonol. Alergol. Pol. 2010; 78, 2: 153–158

Introduction

Haemoglobin, the principal pigment of the blood, is found in red blood cells and accounts for about 90% of their dry mass. The haemoglobin molecule consists of globin, which is made up of two pairs of polypeptide chains forming a tetramer, and four haem molecules. The globin chains differ in the number and sequence of constituent amino acids. Their synthesis is controlled by genes located in chromosomes 11 and 16. Each of the chains binds with a haem molecule, which is composed of a porphyrin ring containing a centrally placed iron atom. This association confers the ability to carry oxygen and stabilises the haemoglobin molecule. Oxygen is bound without changing the valence of the iron, as it occurs thanks to forces of side valences. Hence the process is referred to as "oxygenation" and the resulting form of haemoglobin is called "oxyhaemoglobin". Oxidation of haemoglobin can, however, occur when the divalent iron undergoes oxidation to the trivalent form with the resulting product being methaemoglobin (MHb). The trivalent iron ion, which is found in methaemoglobin, does not have any oxygen-carrying capacity.

In natural conditions, the blood methaemoglobin level is up to 1% [1]. Erythrocytes are constantly exposed to oxidative stress and oxidation to MHb. Two enzyme systems are involved in the defence mechanism: a larger one involving the cytochrome b5 reductase system, and a smaller one involving NADPH-dependent methaemoglobin reductase. Exposure to drugs or drug metabolites that show potent oxidising properties results, upon the exhaustion of the defence capacities of these enzyme systems, in increased methaemoglobin levels accompanied by the signs and symptoms of acute tissue hypoxaemia [2].

Methaemoglobinaemia is diagnosed when the oxidised haemoglobin level exceeds 1%. The clinical manifestations depend on blood methaemo-

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Received: 27.11.2009 r.

ISSN 0867–7077

globin levels and co-morbidities. Levels of 10–20% result in blue discolouration of the mucous membranes and the skin. When methaemoglobin levels exceed 20% headache, anxiety, and dyspnoea develop. At levels exceeding 30%, malaise, arrhythmias, and confusion ensue, which progress, at 50–70%, to coma, severe arrhythmia, acidosis, and death [2–4].

Below is a presentation of a case of paroxysmal methaemoglobinaemia of unclear origin in an adult male with manifestations of acute tissue hypoxia.

Case presentation

A 49-year-old male was referred to the Department of Internal Diseases of the Chest at the Institute of Tuberculosis and Lung Diseases in Warsaw, Poland, for further investigation of suspected pulmonary embolism.

The patient had otherwise been fine since 2003, was not suffering from any medical conditions apart from varicose veins of the lower limbs, was not being treated for any chronic illnesses, and denied any family history of medical conditions. He was a technician employed by the railway and was responsible for inspecting the tracks. He was a smoker (total exposure: 24 packet-years).

In July 2003, at his workplace, during strenuous physical exertion, he lost consciousness. Several hours before the incident he had experienced chest pain, asthaenia, and dyspnoea. The patient was taken by an ambulance to the nearest hospital, where physical examination revealed cyanosis, tachycardia, and agitation. Laboratory parameters, in particular d-dimers and cardiac markers, were all with in normal range. Head CT, electrocardiogram (ECG), and plain chest X-ray revealed no abnormal findings.

Based on the clinical picture, a suspicion of pulmonary embolism was raised; the decision to initiate thrombolytic treatment was made and the patient received streptokinase. A gradual resolution of the dyspnoea and the cyanosis was observed. No chest CT scan or echocardiogram was performed. The patient was discharged home with a recommendation to use anticoagulant treatment. The patient was receiving low-molecular-weight heparin for six months and was then switched to a vitamin K antagonist. He also ceased smoking.

After this episode the patient developed episodes of dyspnoea accompanied by retrosternal pain, cyanosis of the lips and the tip of the nose, dizziness, calf pain, and blurred vision several times a year. The patient did not associate these episodes with any single triggering factor. They usually developed during physical exertion but also during activities of daily living. The episodes lasted for about 4–5 hours and resolved spontaneously. They prompted the patient to see his GP and seek medical attention at his local hospital. The doctors eventually recommended a more thorough diagnostic evaluation.

The next hospitalisation took place at a cardiology department, where multiple investigations were performed. Their results did not, however, lead to a conclusive diagnosis. During the hospitalisation the patient was additionally diagnosed with mild arteliar hypertension and hypercholesterolaemia. Resting ECG, echocardiogram, ultrasound scans of the lower limb deep veins and of the carotid arteries, plain chest X-ray, spirometry, tilt test, and 24-hour ambulatory ECG were all normal. No ST segment elevation or depression and no arrhythmias were observed in the ECG stress test. Apart from fatigue at maximum exertion with a pulse limit of 89% and workload of 10.5 METs, no other symptoms occurred. Coronary arteriography did not reveal any organic changes in the coronary arteries. In view of suspected Prinzmetal angina and confirmed hypercholesterolaemia and mild hypertension, the patient was prescribed acetylsalicylic acid, a calcium antagonist, a nitrate, and a statin. Anticoagulant treatment was continued.

Despite the treatment the patient continued to experience episodes of dyspnoea and cyanosis, and was referred to the Institute of Tuberculosis and Lung Diseases in Warsaw, Poland, for further evaluation.

The physical examination on admission was unremarkable (apart from varicose veins of the lower limbs). Full blood count, blood coagulation parameters, ESR, CRP, aminotransferases, CPK, CK-MB, troponin, NT-proBNP, urea, creatinine, and thyroid hormones were all normal. No antinuclear antibodies were detected. Arterialised capillary blood gas analysis revealed: oxygen partial pressure (PaO_2) of 76 mm Hg, carbon dioxide partial pressure ($PaCO_2$) of mm Hg, pH of 7.41, bicarbonate (HCO_3) of 22.5 mmol/l, and saturation of 95.4%. Spirometry was normal.

Ultrasonography of the deep veins of the lower limbs did not demonstrate any thrombosis. Echocardiography revealed normal sizes of the cardiac chambers, normal thickness and contractility of both ventricles, impaired relaxation of the left ventricular walls, a normal ejection fraction of 60%, and no echocardiographic signs of right ventricular strain or pulmonary hypertension. In the six-minute walk test the patient walked a distance of 529 m without a reduction in arterial blood oxygen saturation.

The chest angio-CT did not reveal any structural abnormalities within the organs of the chest and demonstrated no occlusion or thrombosis in pulmonary vessels. Perfusion scintigraphy of the lungs did not reveal any tracer accumulation defects. Also, no abnormal findings were revealed in bronchoscopy, abdominal ultrasound, or ultrasound of the lower limb arteries.

In the second week of hospitalisation, during the morning rounds, the patient reported asthaenia, dyspnoea, tightness in the precordial area, vision abnormalities in the form of "black spots", and pain in the calves. The patient was fully conscious with logical verbal contact. Physical examination revealed marked central cyanosis, anxiety, limb tremor, a respiratory rate of 18/min, a normal breathing pattern, and blood pressure of 140/80 mm Hg. Chest auscultation revealed no pathological breath sounds. ECG revealed sinus tachycardia of 130 bpm and no signs of ischaemia. Saturation measured with a finger pulse oximeter was decreased to 89%. Despite administration of oxygen through a nasal cannula, saturation measured with a pulse oximeter did not change. Arterial blood gas analysis revealed a saturation of 97.9%, PaO_2 of 102 mm Hg, $PaCO_2$ of 35 mm Hg, HCO_3 of 3.4 mmol/l, pH of 7.44, and BE of –0.7 mmol/l. Results of the laboratory tests performed during the episode were normal.

The possibility of acute pulmonary embolism was raised. The patient underwent emergency echocardiography but the echocardiogram was similar to the previous one, where no signs of pulmonary hypertension or right ventricular strain were found, and an ultrasound scan of the deep veins of the lower limbs did not show any signs of thrombosis. Suspecting a right-to-left shunt, the patient was given a contrast medium, but no shunting was observed. The patient's condition continued to deteriorate, saturation decreased to 82% and the cyanosis worsened. Oxygen through a 40% Venturi mask was initiated but it failed to have any significant effect on saturation measured with a pulse oximeter, or on the cyanosis.

Because the blood gas analysis parameters were inconsistent with the patient's clinical condition and because of the saturation values measured with a pulse oximeter (high oxygen partial pressure in blood gas analysis and decreased oxygenation measured with a pulse oximeter), the suspicion was raised of an abnormality of oxygen transport resulting from the presence of a pathological haemoglobin. Blood was drawn for methaemoglobin and several hours later the laboratory report arrived showing a blood methaemoglobin concentration of 16%. Administration of methylene blue was considered, but at that time the patient's condition had already started to gradually improve. The entire episode lasted about 4 hours and the symptoms gradually resolved.

According to the patient, the clinical manifestations of the episode were identical to those of the previous episodes, based on which pulmonary embolism was initially being diagnosed. The consulting neurologist ruled out any nervous system disorders.

Over the next days of hospitalisation the patient felt well and did not report any symptoms. Methaemoglobin levels were determined several times and only on one occasion were they elevated to 4.5%. The remaining values ranged from 0 to 1%. No changes in full blood counts, no bilirubin elevations, and no reticulocyte elevations were observed. Anticoagulant treatment was discontinued. The patient was discharged home with a recommendation to avoid any iron-oxidising substances that might increase blood concentration of methaemoglobin.

Over the one year of follow-up the patient's condition did not change significantly. The episodes of cyanosis are now less frequent and milder. The patient continues to be looked after by a haematologist. The multiple tests that have been performed have ruled out the possibility of a congenital form of methaemoglobinaemia and the other haemolytic anaemias.

Discussion

Dyspnoea and cough are two most common symptoms of respiratory and/or cardiovascular diseases. Dyspnoea is a subjective manifestation, in the evaluation of which the physician should be guided by historical information and such "indirect" indicators as: respiration rate, breathing pattern, heart function, and skin colouration. Measurement of saturation using a pulse oximeter and measurement of arterialised capillary blood saturation are also recognised diagnostic methods.

In the case we report here, the symptoms, in the form of paroxysmal dyspnoea accompanied by anxiety, palpitations, and cyanosis, appeared over the few years preceding presentation and were initially attributed to ischaemic heart disease and later to pulmonary embolism. However, the normal angiographic picture of the coronary vessels and the absence of thrombi on chest angio-CT allowed us to rule out, with a high degree of probability, episodes of myocardial ischaemia and high-

risk pulmonary embolism as the causes of the episodes of dyspnoea, cyanosis, and arrhythmia.

Normal breath sounds over the lungs and normal values of peak inspiratory and expiratory flows allowed us to rule out respiratory disorders with a paroxysmal course and the described manifestations. We discovered considerable discrepancies between oxygen saturation measured with a pulse oximeter and oxygen saturation calculated in arterial blood gas analysis (these two measurements were conducted simultaneously). This discrepancy and the lack of increase in oxygen saturation measured with a pulse oximeter when oxygen delivery through a Venturi mask 40% was being increased were the most important tips that allowed us to establish the correct diagnosis.

The significant discrepancy between the saturation value measured by pulse oximetry and the saturation measured by blood gas analysis or the arterial blood oxygen partial pressure (the so-called saturation gap) should prompt the physician to look for the cause of oxygen transport abnormalities, and one such cause is the presence of an abnormal haemoglobin [2, 4].

Measurement of the partial pressure of gases in arterial blood or arterialised capillary blood is based on an electrochemical method and involves the measurement of the difference in the voltage of high-resistance electrodes for the determination of pH and $PaCO_2$. PaO_2 is the partial pressure of oxygen dissolved in the serum and not bound to haemoglobin. Patients with methaemoglobinaemia may have normal PaO_2 values despite a high methaemoglobin concentration, which may put their life at risk. In blood gas analysis, bicarbonate levels and blood oxygen saturation are calculated from pH and $PaCO_2$ values using the Henderson-Hasselbalch equation with the assumption, however, that normal haemoglobin is present. The presence of abnormal haemoglobins (methaemoglobin, sulfhaemoglobin, carboxyhaemoglobin) leads to false results of oxygen saturation measurements [4].

The functioning of the pulse oximeter is based on the absorption of light waves of two wavelengths: 660 and 940 nm. Both oxygenated and deoxygenated haemoglobin absorbs the waves of both wavelengths, and based on that the pulse oximeter determines oxygen saturation. Methaemoglobin equally absorbs the 660 nm and 940 nm waves. When methaemoglobin concentrations reach 30–35%, oxygen saturation measured with the pulse oximeter stabilises at 82–86%, as was observed in our patient. Oxygen therapy does not change the saturation reading [4–6]. We did not have at our disposal a CO-oximeter, which separately measures, by spectrophotometry, four different wavelengths: for oxy-, deoxy-, carboxy-, and methaemoglobin [7].

Methaemoglobinaemia was confirmed by determining the blood concentration of methaemoglobin during an episode, which equalled 16%. This result was consistent with the clinical manifestations. Blood was drawn for testing about 2 hours after the onset of symptoms. According to the literature, methaemoglobin levels gradually decrease at the rate of about 0.15 percentage points per hour [2, 6].

Although we had at our disposal methylene blue for intravenous administration, we decided against using it for several reasons. When we received the confirmation of the diagnosis of methaemoglobinaemia the patient's condition had already improved: the dyspnoea and anxiety had resolved and oxygen saturation measured by pulse oximetry had increased. Also, we did not know the patient's glucose-6-phosphate dehydrogenase (G6PD) status (this enzyme is required for methylene blue to take effect). G6PD deficiency not only prevents the reduction of methaemoglobin by methylene blue, but can precipitate a life-threatening haemolysis. It is also ineffective when haemoglobin M is present [8].

Congenital methaemoglobinaemia is a rare disease which manifests immediately after birth. It is seen in neonates with cytochrome b5 reductase deficiencies accompanied, especially in type II deficiency, by numerous congenital anomalies of the nervous system. A case of methaemoglobinaemia in an adult male has previously been reported at our institute [9]. This also applies to patients with a congenital abnormal haemoglobin structure, the so-called haemoglobin M.

Our patient, who developed his first symptoms at the age of 42, illustrated a case of acquired rather than congenital methaemoglobinaemia. Manifestations of this condition are triggered by exposure to a multitude of drugs, chemicals, or toxins (Table 1).

Among the very numerous causes of acquired methaemoglobinaemia, there are several which may be considered important in the case of our patient. The patient lives in a rural area and uses water from a well. Exposure to contamination with inorganic nitrates is a very common cause of acquired methaemoglobinaemia in infants and small children [10]. Inorganic nitrogen is found in insecticides and pesticides, wood maintenance products, and paints [11, 12]. The patient's work in-

Table 1. The most common causes of methaemoglobinaemia

Drugs	
Benzocaine (spray, ointment, cream)	Metoclopramides
Methylene blue (high doses)	Nitrates
Chloroquine	Nitrofurantoin
Dapsone	Nitroglycerin
Flutamide	Sodium nitroprusside
Phenacetin	Prilocaine
Phenazopyridine	Silver salts
Lidocaine	Sulfonamides
Concomitant diseases	
Sepsis	
Paediatric gastrointestinal infections	
Inhalation of amyl nitrate	
Haemolytic crisis in sickle-cell anaemia	
Other factors	
Paints containing aniline derivatives	
Car exhaust fumes, toxins formed during combustion of wood and plastic materials	
Chemicals: nitrobenzene, nitroethane, glues	
Herbicides, pesticides	
Fuel calorific value enhancers	

volved inspection of railway tracks, which is why he might have been exposed to substances used for the maintenance of railway ties. Our case of methaemoglobinaemia episode cannot, however, be linked to the effects of these substances, as it was observed while the patient was hospitalised. However, the previous episode, which occurred several years before and which was diagnosed as a high-risk pulmonary embolism and managed with thrombolytic treatment without confirmation by imaging studies, occurred at the patient's workplace.

There have been several reports in the available literature of methaemoglobinaemia resulting from mucosal exposure to local anaesthetics used during endoscopy (transoesophageal echocardiography, bronchoscopy) [13–15]. After analysing a group of 886 patients undergoing transoesophageal echocardiography, it was established that methaemoglobin elevation occurred in 4 patients (0.115%) [16]. Our patient did not, however, undergo transoesophageal echocardiography at any of the hospitals that treated him.

Most of the 138 reported cases of acquired methaemoglobinaemia (56 cases) involved immunosuppressed patients who were taking dapsone for the prevention or treatment of an infection caused by *Pneumocystis jiroveci*. The next group comprised patients undergoing surgical procedures and diagnostic investigations, such as cardiac catheterisation. The highest methaemoglobin concentrations were observed in 5 patients in whom a 20% benzocaine spray has been used, one patient subsequently died and three others required long-term treatment [17].

In the case of our patient, the cause of elevated methaemoglobin could not be established. The patient denied having taken any medication.

Acquired methaemoglobinaemia is very likely to be underdiagnosed, with most of the undiagnosed cases being patients with abortive symptoms. Dyspnoeic and cyanotic patients, however, require immediate evaluation and rapid action. Our patient did not require exchange transfusion or use of a hyperbaric chamber, as these measures are reserved for second-line treatment and are utilised when the patient's condition fails to improve or methylene blue cannot be used [6]. Knowledge of the reasons for discrepancies in blood oxygen saturation values assessed by pulse oximetry and blood gas analysis is the key to the correct diagnosis and a favourable treatment outcome.

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