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Unexplained basal oxygen desaturation in a patient with haemoglobinopathy

Desaturare bazală inexplicabilă la un pacient cu hemoglobinopatie

Abstract

Haemoglobinathies are a heterogeneous group of congenital disorders that affect the structure, function or production of haemoglobin. Some of them due to its low affinity to oxygen may be accompanied by cyanosis and mild anemia. For this reason, in the differential diagnosis we should include heart and lung diseases and its presence be suspected in families or young patients with an unexplained basal oxygen desaturation.

Keywords: *haemoglobinathies; basal unexplained oxygen desaturation; congenital heart disease*

Rezumat

Hemoglobinopatiile sunt un grup heterogen de maladii congenitale care afectează structura, funcția sau producerea hemoglobinei. Datorită afinității reduse pentru oxigen, unele se pot însoți de cianoză și anemie ușoară. Din acest motiv, diagnosticul diferențial trebuie să includă maladiile cardiace și pulmonare, iar prezența sa trebuie suspectată în familiile sau la pacienții tineri ce prezintă o desaturare bazală inexplicabilă.

Cuvinte-cheie: *hemoglobinopatii, desaturare bazală inexplicabilă, boală cardiacă congenitală*

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Introduction

In the presence of low oxygen saturation in a patient, we must rule out common etiologies such as hypoventilation, ventilation-perfusion disorders, the existence of a right-to-left shunt due to acidosis, fever, diffusion impairment, or a reduced inspired oxygen tension. Nonetheless, in cases of unexplained cyanosis we must also rule out other causes such as the existence of a haemoglobinopathy which may induce low blood oxygen saturation by alterations of critical molecular regions directly involved in the stabilization of the T (tense) state or destabilization of the R (relaxed) conformation of the haemoglobin.

Low affinity haemoglobinopathies are reflected by an oxygen-haemoglobin dissociation curve shifted towards the right of normal and an increase in P_{50} (oxygen tension at half saturation (50%) of blood). The more the dissociation curve of haemoglobin is displaced to the right, the less readily it picks up oxygen, but the more easily it releases it. This means more oxygen will be released to the cells, but it also means less oxygen will be carried from the lungs in the first place. This may lead to a decreased haemoglobin and/or to a mild cyanosis due to a higher venous blood haemoglobin desaturation.

Case report

We report the case of a 48 year old male patient with no limitation of his physical activities, no cardiovascular risk factors and no breathing problems, who was referred for cardiac evaluation due to a congenital heart disease and a basal oxygen saturation of 83%. The patient also gave a medical history that revealed an asymptomatic 23 year old sister with basal oxygen desaturation and no associated heart defects.

Upon physical examination he had a normal colour of skin and mucous membranes, and the cardiac auscultation revealed a heart murmur in the parasternal region. The electrocardiogram showed a sinus rhythm with no conduction disorders and the echocardiogram evidenced a restrictive membranous subaortic ventricular septal defect with a left-to-right shunt, a normal pulmonary arterial pressure and a dilated coronary sinus in the context of a persistent left superior vena cava drainage (Figure 1A). Meanwhile, agitated saline solution administered via intravenous injection to provide air microbubble contrast in the right heart showed no echocardiographic right-to-left shunt with or without Valsalva maneuvers (Figure 1B). Thoracic computed tomography, except for the existence of a persistent left superior vena cava, was within normal limits as also was the spirometry (FVC 164%; FEV1: 145%; FEV1/FVC: 72%; MMEF 25-75% of 95%) and the diffusion capacity. Blood tests showed a haemoglobin level of 14.4 g/dL and a hematocrit of 42.9%. Also, bilirubin, alpha-2 antiplasmin, haptoglobin, ferritin and erythropoietin (9.3 mU/ml) levels were normal. Meanwhile, the high-performance liquid chromatography (HPPLC) showed an abnormal haemoglobin migration pattern with a profile compatible to Hb D (39%) and normal A2 and F haemoglobins. On the other hand, the basal arterial blood gases showed an oxygen pressure (PaO_2) of 92 mmHg (corresponding to an oxygen saturation (SaO_2) of 83%) which improved to 97% with a reservoir mask at 15 l/min), a $PaCO_2$ of 46 mmHg, a pH of 7.40 and a P_{50} of 53 mmHg. All these data led us to the final diagnosis of an asymptomatic low oxygen affinity haemoglobinopathy as responsible for the low oxygen saturation of our patient.

Discussion

Haemoglobinopathies are caused by point mutations, deletions or insertions in the genes encoding the alpha- and beta-globin chains[1]. Over 150 variants of high and low oxygen affinity variant haemoglobin molecules have been described. Such mutations are usually inherited as an autosomal dominant trait and are usually located at the contact areas of the alpha and beta sub-units or at the junction of the 2,3 bi phospho-glycerate with the beta chain.

Patients with high oxygen affinity variant haemoglobin use to have tissue hypoxia which may favor an increased erythro-

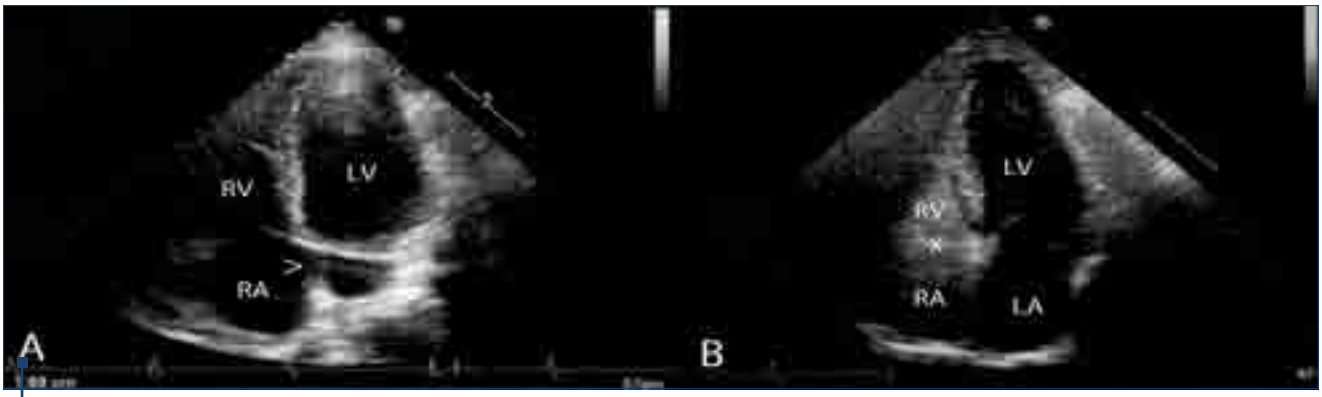

Figure 1. *A. 4-chamber apical echocardiographic view showing a dilated coronary sinus (arrow head) in the context of a persistent left superior vena cava drainage. B. 4-chamber apical echocardiographic view showing air microbubble contrast (asterisk) in the right ventricle with no flow from the right heart to the left cavities through the ventricular septa defect (arrow head). RA: right atrium, LA: left atrium, RV: right ventricle, LV: left ventricle.*

poietin production and secondary erythrocytosis. However, two thirds of them are not associated with erythrocytosis because increased oxygen affinity is only mild or moderate. On the other hand, patients with low oxygen affinity variant haemoglobin (basal oxygen desaturation with normal partial pressure of oxygen) usually are asymptomatic because haemoglobin quickly releases oxygen to the tissues. In fact, patients with a moderately right shifted oxygen equilibrium curve (P_{50} between 35 and 55 mmHg) may be anemic while with further right shift (P_{50} of 80 mmHg) anemia is not present. On the other hand, clinically apparent cyanosis is only observed in carriers of low affinity variants with greatly right shifted curve and in whom the variant portion comprises a substantial portion of the haemolysate. In such cases, cyanosis usually occurs in the first year of life[2].

Within the low oxygen haemoglobinopathies, much less frequent than the high oxygen affinity variant haemoglobins, we may find the Kansas haemoglobin [β 102 (G4) Asn → Thr], the Titusville haemoglobin [α94 (G1) Asp → Asn], the Providence haemoglobin [β82 Lys → Asp and Lys → Asn β82], the Agenogi haemoglobin [β90 (F6) Glu → Lys], the Beth Israel haemoglobin [β102 [G4] Asn → Ser] and the Yoshizuka haemoglobin [β108 (G10) Asn → Asp][3].

Congenital heart defects with initial left-to-right shunts (such as the ventricular septal defect) may also develop oxygen desaturation if there is a shunt reversal secondary to a severe pulmonary arterial hypertension (Eisenmenger syndrome)[4]. These patients, unlike low oxygen affinity variant haemoglobins, often have a reduced partial pressure of oxygen, marked cyanosis and secondary erythrocytosis. Also, we must bear in mind that the blood flow across the ventricular septal defect may favor ventricular septal hypertrophy, right ventricle outflow tract obstruction, flow reversal and the onset of cyanosis without any evidence of pulmonary arterial hypertension[5]. Finally, we must rule out as a cause of hypoxemia the existence of right-to-left shunts through an atrial septal defect or a patent foramen ovale, due to an increased pressure in the right chambers. For this, the intravenous administration of agitated saline solution is useful. In our patient, having both a haemoglobinopathy and a cardiac malformation, the congenital heart defect would not explain basal oxygen desaturation as the left-to-right cardiac shunt produces an abnormal mixture of oxygenated blood from the pulmonary circulation with deoxygenated blood from the systemic venous system, as it was proven by cardiac ultrasound, which does not lead to basal oxygen desaturation. On the contrary, we reached the diagnosis of a low affinity haemoglobinopathy by obtaining haemoglobin HPLC and measuring blood P_{50}.

Low affinity haemoglobinopathies are very rare disorders with an autosomal dominant inheritance. In this context, Verhovsek et al.[6], after a systematic review, identified 45 patients with unexpectedly low pulse oximetry and confirmed variant haemoglobin. In such cases, arterial blood gas and P_{50} evaluations may lead to a proper initial diagnosis while most cases may be detected by starch gel electrophoresis, HPLC or DNA based globin gene analysis. There is no need to intervene medically on patients as oxygen delivery to the tissues is normally adequate. However, early recognition of low affinity haemoglobins in asymptomatic patients may avoid extensive and unnecessary medical investigations and alleviate concern for the patient and family.

Conclusions

Basal oxygen desaturation is often associated with serious conditions such as acute respiratory failure, chronic lung diseases, pulmonary arterio-venous fistulas or congenital heart defects. However, we should consider the presence of a low oxygen affinity haemoglobinopathy (as occurred in our patient) when the patient is young and he/she has an unexplained oxygen desaturation or a family history of basal oxygen desaturation. ■

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