Discrepancia entre SpO2 y SaO2: diagnóstico de cuatro generaciones

From SpO_2 and SaO_2 discrepancy to diagnosing four generations

Sandra Lucas, Inés Santos, Filipe Alfaiate, Diogo Dias, Ireneia Lino

Hospital do Espírito Santo de Évora

ABSTRACT

Pulse oximetry measures the peripheral oxy-haemoglobin saturation (SpO2) which is a surrogate marker for arterial oxy-haemoglobin saturation (SaO2). SaO2 estimation is subjected to both oximeter proper functioning, patient characteristicsand haemoglobin disturbances.

A 82-year-old man goes to the emergency with cough, dyspnoea and fever. He has haemolytic anaemia. His kids also have anaemia. Examination showed fine crackles in pulmonary auscultation of the lower two thirds of the right lung and splenomegaly. SpO2 was 80% (FiO2 21%). Arterial blood gas analysis: pH 7.514; PaCO2 23.4 mmHg; PaO2 43.2 mmHg; Hb 13.0 g/dL. Chest X-ray suggested an infectious process. He was admitted to the hospital with the diagnosis of pneumonia. During hospitalization we verify discrepancy between SpO2 and SaO2; haemolytic anaemia. The patient had a respiratory improvement and was discharged to external consult, dying months later.

To clarify the discrepancy between SpO2 and SaO2 results; confirm the hereditary nature and identify the haemolytic anaemia, we conducted a retrospective familiar study based on the patient's clinical processes.

Three children were identified with anaemia. Two of the children have known their anaemia for 35 years - studied in the context of respiratory infections with haemolytic crisis due to Lepore haemoglobinopathy and β-thalassemia, respectively. The patient previously diagnosed with Lepore haemoglobinopathy, currently undergoing hospital anaemia study, was diagnosed with Köln Hb.

The discrepancy between SpO2 and SaO2 in association with a familiar haemolytic anaemia resulted in the diagnosis of autosomal dominant Köln haemoglobinopathy. The advances in the means of diagnosis enabled the probable diagnosis of 19 family members distributed over 4 generations.

Keywords: Anaemia, Köln Hb; Hemoglobinopathies; β-Thalassemia

BACKGROUND

Pulse oximetry (SpO_2) is a simple, non-invasive, and indirect method to estimate arterial oxygen saturation (SaO_2) using spectrophotometry. Different wavelengths, 660 and 940nm, correspond to oxyhaemoglobin and deoxyhaemoglobin[1,2]. SaO_2 reading errors may be related to oximeter malfunction, oximeter poorly adaptation to the patient or patient characteristics - hypoperfusion, cold extremities, painted nails, haemoglobin disturbances. Haemoglobin disturbances responsible for falsely low readings are increased glycated haemoglobin (Hb A_1c), methaemoglobin, sulfhaemoglobin, haemoglobinopathiessuch as sickle haemoglobin (Hb), Hb Lansing, Hb Bonn, Hb Köln, Hb Hammersmith, and Hb Cheverley[1,2].

CASE PRESENTATION

A 82-year-old man goes to emergency service with a 3-day history of cough, dyspnoea and fever. He has anaemia required blood transfusion at the age of 30. His kids also have anaemia.

Examination showed fine crackles in pulmonary auscultation of the lower two thirds of the right lung and splenomegaly, without other abnormalities.SpO2 80% on room air.Arterial blood gas analysis: pH 7.514; $PaCO_2$ 23.4 mmHg; PaO_2 43.2 mmHg; Hb 13.0 g/dL%. Co-oximetry: MetHb 1.4%; COHb 3.6%.Other laboratory results: Hb 12.9 g/dL, Leucocytes 8800 µL; Platelets 56000 µL; total bilirubin 4.32 mg/dL, direct bilirubin 1.39 mg/dL and indirect bilirubin 2.93 mg/dL.Chest X-ray revealed interstitial infiltration of the lower two thirds of the right lung, suggesting an infectious process. The patient was admitted with the diagnosis of community-acquired pneumonia and type 1 acute respiratory failure.

On hospitalization there was always an important discrepancy between SpO_2 and SaO_2.Concerning haematologic state: while in hospital it was found digital clubbing;jaundice attributed to haemolysis aggravated during the respiratory infection;normochromic normocytic anaemia Hb 9-11 g/dL, reticulocyte 6.34%, haptoglobin < 20 mg/dL, total bilirubin 4.32 mg/dL, direct bilirubin 1.39 mg/dL, haemoglobin electrophoresis (HPLC) revealed 2 abnormal peaks: Hb S and a peak unknown, both in low concentrations. These findings correlated with the hereditary anaemia in study.

The patient had a very slow respiratory improvement and was discharged to external consultfor further study, dying months later.

OBJECTIVE

To clarify the discrepancy between SpO2 and SaO2; confirm the hereditary nature and identify the haemolytic anaemia.

MATERIAL/METHODS

Retrospective familiar study based on the patient's clinical processes.

RESULTS

Case 1

56-year-old Portuguese woman, daughter, with Hb 9,7-11,2 g/dL normochromic normocytic anaemia without further characterization. Classified as hereditary anaemia.

Case 2

57-year-old Portuguese man, son. Hospitalized at age 29 in the context of respiratory infection associated with haemolytic crisis. Anaemia study: Hb 10,9 g/dL; MCV 94,0 fL; Platelets 83000 µL (other erythrocytic indices not available at the time); Pyruvate kinase610 mU/million (60-220); glucose-6-phosphate dehydrogenase 157 mU /10^9.eri (118-144), diagnosed as β-thalassemia.

Correspondencia: bee-slgl@hotmail.com

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Fig. 1. Family genogram dating from 1985

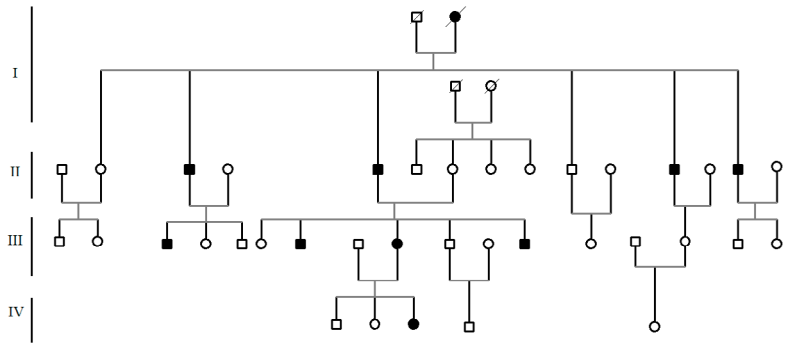
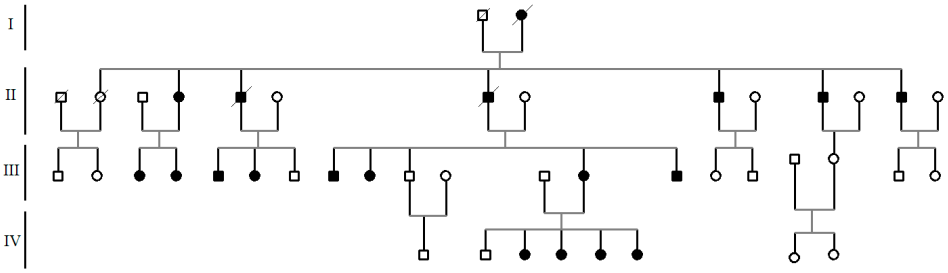


Fig. 2. Family genogram dating from 2020



Case 3

40-year-old Portuguese man, son.Hospitalized 4 times during infancy in the context of respiratory infectionsand fever associated with haemolytic crisis. The anaemia study started at the age 8 culminating in the diagnosis of Lepore hemoglobinopathy. The following genogram was found (fig. 1).

In 2019 the 40-year-old initiated a new anaemia study: Hb 12,5 g/dL; MCV 96.4 fL; MCH 28.4pg; Platelets 101000 µL; blood smear describesslight anisocytosis. Haemoglobin electrophoresis (HPLC) showed 2 abnormal peaks: Hb S and a peak unknown. Molecular study revealed heterozygous mutation of the Beta-globin gene Val98Met (GTCATG). Glycated hemoglobin (A1C) 2,8% glycemia estimated 33,66mg/dL. In 2020 an updated genogram was produced(fig. 2).

DISCUSSION

Clinically and haematologically this family history resembles a dominant hereditary haemolytic anaemia, having haemolytic crisis documented.

The previous diagnostic of both brothers - Lepore haemoglobinopathy and β-thalassaemia - falls into the group of β-thalassaemic syndromes. β-thalassaemic syndromes can be subdivided in major, intermediate and minor, according to clinical severity[3-5].β-thalassaemia intermedia matches patients with moderate severity diseases, it can be associated with a number of autosomal recessive genetic defects as in Hb Lepore, with slight changes in β globin chains or autosomal dominant β-thalassaemia[3,4]. Lepore haemoglobinopathy would be highly unlikely in this case since it plays no influence on oxygen affinity and it is autosomal recessive. However, about 35 years ago the diagnosis would have been appropriate if we take into account how rare is autosomal dominant β-thalassaemia intermedia as a result of an unstable haemoglobinopathy[4].

The existence of an unstable haemoglobin should be investigated in β-thalassaemic individuals when both parents are haematologically normal or in families that display an autosomal dominant transmission pattern of β-thalassaemia intermedia[4]. Unstable haemoglobinopathies result from amino acid mutations affecting the globulin structure rendering it less soluble or more susceptible to oxidation, which leads to the formation of Heinz corpuscles that will damage the erythrocyte membrane[5-7]. Removal of Heinz corpuscles in the spleen originates splenomegaly and shortening of the half-life of the erythrocyte, which translates into haemolytic anaemia of variable severity[5,8].

Today, molecular techniques allow the diagnosis of Köln haemoglobinopathy as the haemolytic anaemia present in all 4 generations of this patient family, previously classified as β-thalassaemia and Lepore hemoglobinopathy. Both β-thalassaemia and Lepore hemoglobinopathy haemoglobin electrophoresis may be mistaken with Hb Köln because this – is an unstable haemoglobin presenting on electrophoresis as multiple peaks expressed in low concentrations.

Köln haemoglobinopathy [$\beta^{98Val\rightarrow Met}$] is originated in an autosomal dominant mutation of the β-globin gene (GTG→ATG) Val98Met, located on chromosome 11, on the protein region of β-globin where heme group is inserted[7,9]. The partial absence of heme groups in some Hb Köln tetramers is responsible for low reliability of pulse oximetry values – Hb will absorb different wavelengths causing the discrepancy between SpO_2 and SaO_2[1,10]. The presence of 5,4% Hb Köln is responsible for an error of 8-11% in pulse oximetry and,

similarly to our case, for a discrete rise of methaemoglobin and carboxyhaemoglobin[11].

An important distinctive Köln haemoglobinopathy feature is its high affinity to oxygenresulting in less oxygen availability to tissues in the presence of normal PaO_2 levels[1,5,9,10]. High haemoglobin affinity to oxygen explains the occurrence of haemolytic crisis mostly associated with respiratory pathology since there is a decrease in PaO_2 and an increase in oxidative stress[8].

On Köln haemoglobinopathy thrombocytopenia is a consequence of splenic sequestration[12]. The elevated activity of Pyruvate kinase and glucose-6-phosphate dehydrogenase, may be due to the expansion of the youthful population of erythrocytes[13].

Köln haemoglobinopathy interferes with the assay of HbA_1c, as can be seen in case 3 in which HbA_1c 2.8% was documented[8]. In fact, inconsistent results from HbA_1c suggest the possibility of hemoglobinopathy - alternative tests should be used as the dosage of fructosamineor the usual glycaemic test[14].

CONCLUSION

Discrepancy between SpO_2 and SaO_2 associated with the report of an unknown familiar history of haemolytic anaemia allowed to carry out a retrospective clinical study that culminated in the diagnosis of 19 patients in 4 different generations, thanks to technological advances of the complementary diagnostic methods.The diagnosed Köln hemoglobinopathy responsible for the SpO_2 and SaO_2discrepancies corresponds to an autosomal dominant mutation of the β-globin gene with a 50% risk of transmission to offspring in each pregnancy.The knowledge of the pathology is not only important in the prevention of future haemolytic crisis - allowing to avoid drugs and foods that increase oxidative stress - it also allows a haematological screening of the remaining family members and genetic counselling in the case of patients intending to have progeny.

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