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A 50-YEAR-OLD WOMAN WITH SEVERE RESTING HYPOXIA NOT AMENDABLE TO HIGH-FLOW OXYGEN SUPPLEMENTATION

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ABSTRACT

Introduction: Pulse oximetry is a widely used non-invasive method to measure arterial oxygen saturation (SpO_2). However, haemoglobinopathies, including rare low-oxygen-affinity variants such as haemoglobin (Hb) Lansing can result in falsely low SpO_2 readings due to alterations in the Hb oxygen dissociation curve and spectral properties. Recognising these conditions is crucial to avoid misdiagnosis and unnecessary interventions.

Case description: A 50-year-old female with a history of chronic obstructive pulmonary disease (COPD), hypertension and compensated cirrhosis presented for pre-operative evaluation. Persistent hypoxia (SpO_2 84%), unresponsive to oxygen supplementation, was noted during routine assessment. Diagnostic investigations excluded pulmonary or cardiac shunts, hepatopulmonary syndrome and common causes of methaemoglobinaemia or carboxyhaemoglobinemia. Arterial blood gas analysis using a CO-oximeter revealed a true oxygen saturation of 90%, highlighting a discrepancy with pulse oximetry. Hb electrophoresis demonstrated an abnormal haemoglobin fraction, and subsequent genetic testing identified a heterozygous mutation (HBA1: c.264C>G), confirming Hb Lansing. The patient was asymptomatic apart from mild exertional dyspnoea attributed to underlying COPD and safely underwent planned surgery.

Discussion: Hb Lansing is a rare haemoglobinopathy characterised by low oxygen affinity and high p50, leading to falsely low SpO_2 readings and minimal response to supplemental oxygen. Diagnosis relies on CO-oximetry, Hb electrophoresis and genetic analysis. No specific treatment is required for low-affinity haemoglobinopathies, which generally have a benign clinical course.

Conclusion: Haemoglobinopathies should be considered in the differential diagnosis of unexplained hypoxia. Utilisation of targeted diagnostic tools enables clinicians to ensure accurate diagnosis and appropriate management.

KEYWORDS

Hypoxia, haemoglobinopathy, CO-oximetry, dissociation curve, blood gases

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LEARNING POINTS

- The differential diagnosis of hypoxia, non-amendable to supplemental oxygen in a stable patient mainly includes right to left pulmonary or cardiac shunt, or a haemoglobinopathy with altered oxygen affinity.
- Clinicians should be familiar with instances in which pulse oximetry is not reliable, including poor tissue perfusion, certain nail polish types and haemoglobinopathies, and should obtain arterial blood gas for accurate assessment.
- If haemoglobinopathy is suspected, it is advisable to perform arterial blood gas analysis using a multi-wavelength spectrometer for accurate assessment.
- Early performance of haemoglobin electrophoresis followed by mutational analysis will yield diagnosis and prevent further work-up.
- The clinical course of low-oxygen-affinity haemoglobinopathies is mild, and patients should not be denied necessary surgical interventions due to this condition.

INTRODUCTION

A pulse oximeter provides a non-invasive and accurate estimation of oxygen pressure in the artery. It operates by emitting light at two different wavelengths (red light with a wavelength of 660 nm and infrared with a wavelength of 940 nm). Oxygenated haemoglobin (O_2Hb) absorbs more infrared light whereas deoxygenated Hb absorbs more red light. The fraction of O_2Hb can be calculated based on the fraction of absorbed infrared light. Disorders of haemoglobin structure and function include metHb, COHb and the group of haemoglobinopathies. These disorders might cause a false reading of the pulse oximeter by two mechanisms. Firstly, through changes in oxygen dissociation curve and secondly, by altering the spectral properties of the Hb, thus causing a change in light absorption. MetHb and COHb are easily detected by most laboratories using blood gas analysers. Diagnosis of haemoglobinopathies in adults, however, is often challenging and requires a high index of suspicion. Diagnosis requires performing Hb electrophoresis to detect an Hb fraction with an unusual molecular weight. Genome sequencing allows clinicians to detect the exact mutation and by doing so, can choose appropriate treatment and assess the prognosis. Low-affinity haemoglobinopathies are usually characterised by asymptomatic hypoxia, non-amendable by oxygen supplementation.

CASE DESCRIPTION

A 50-year-old female patient was referred to our pulmonary clinic for pre-operative evaluation before undergoing a cholecystectomy due to an episode of biliary colic. The patient was obese with a body mass index of 34. Her past medical history included hypertension and COPD with moderate to severe airflow limitation (Forced Expiratory Volume in the first second of maximal expiration after a maximal inspiration (FEV1) 50% of predicted) and alcoholic liver disease with compensated cirrhosis, complicated by grade 1 oesophageal varices. The patient complained of shortness of breath when walking two flights of stairs, but not at rest. Repeated measurements using different oximeters showed a low-oxygen saturation (SpO_2) of 84%, with a pulse of 82 beats per minute. Oxygen supplementation of up to 15 litres per minute via a face mask resulted in a rise of SpO_2 to only 89%. Physical examination revealed no cirrhotic habitus, no cardiac murmurs and no abnormal findings on lung auscultation. No peripheral cyanosis was notable, but mild clubbing was apparent.

Laboratory results showed haemoglobin (Hb) 13.6 g/dl, creatinine 0.7 mg/dl, albumin 4.3 g/dl and bilirubin 0.65 mg/dl. Venous blood gas showed pH=7.41 with PCO_2 42 mmHg. Echocardiography showed a preserved ejection fraction with no signs of diastolic heart failure and no signs of pulmonary hypertension. Computed tomography performed eight months previously was normal without emphysema or interstitial lung disease.

Pulmonary function tests demonstrated a moderate to severe airflow limitation (FEV1 52% of predicted), normal lung volumes and a moderate diffusion capacity limitation (DLCO 50% of predicted).

Due to the patient's liver disease, we suspected hepatopulmonary syndrome (HPS) as the cause of the non-amendable hypoxia. However, assessments for shunt via microbubble transoesophageal echocardiography and via lung perfusion scan using macro-aggregated albumin were normal and failed to demonstrate a significant cardiac or pulmonary shunt.

We then performed arterial blood gases with a CO-oximeter, which demonstrated partial pressure of oxygen (PO_2) of 80 mmHg, with a measured oxygen saturation of 90%, and normal levels of metHb and carboxy-Hb. At the same time, the pulse oximeter showed an SpO_2 of 84%.

The combination of non-amendable hypoxia without evidence of a shunt, and the discrepancy between oxygen saturation measured via CO-oximetry and pulse oximetry, has led us to suspect a methaemoglobinaemia and haemoglobinopathy. MetHb was ruled out because of normal blood levels of the substance. An Hb electrophoresis test revealed a fraction of 10% of Hb with a weight close to that of HbA but incompatible with known haemoglobin variants. This finding led us to perform globin chains genome sequencing, which revealed a mutation in alpha-globin. The mutation (HbA1: c.264C>G) had been previously described and is termed Hb Lansing. As mentioned above, low-oxygen-

affinity haemoglobinopathies require no specific therapy. The patient continued follow-up with treatment of her COPD and was referred for pulmonary rehabilitation. Clinically, she is stable. The patient was approved for cholecystectomy and underwent the surgery safely.

DISCUSSION

Hb Lansing is an extremely rare haemoglobinopathy caused by a heterozygote mutation (HbA1: c.264C>G) and has been described as a cause of falsely low readings of oxygen saturation using a pulse oximeter. The mutation was first reported in East Lansing, Michigan, USA in 2009, in a 24-year-old male with asymptomatic hypoxia[1]. Other cases were reported in Thailand[2], Turkey[3], Japan[4] and Oman[5]. The frequency and geographical distribution of the mutation are unknown. All cases described are of a heterozygote mutation, except for the case in Oman, which was homozygous. This instance occurred in consanguineous parents of a deceased newborn presenting with hepatomegaly, cardiomegaly and severe haemolytic anaemia[5]. Homozygosity is assumed to cause in utero or neonatal death.

The mutation is a part of the low-oxygen affinity haemoglobinopathies, characterised by a high p50, meaning that high PO_2 levels are required to bind 50% of the Hb molecules to oxygen. The most common clinical presentation is incidentally found to be asymptomatic hypoxia, without cyanosis or erythrocytosis. Interestingly, the delivery of supplemental oxygen results in a smaller than expected rise in oxygen saturation. This phenomenon is attributed to two mechanisms. The first is the low-oxygen affinity, which requires a very high PO_2 tension to load the Hb level with oxygen. This can be seen by the discrepancy between the PO_2 levels of 80 mmHg, which under normal dissociation curve conditions are supposed to translate to an oxygen saturation of approximately 95%. However, in our patient, the actual measured arterial oxygen saturation was only 90%. The second mechanism is that haemoglobinopathies alter the spectral characteristics of the Hb molecule. A pulse oximeter works by emitting light at two different wavelengths: usually 660 nm (red light) and 940 nm (infrared). Oxyhaemoglobin (O_2-Hb) absorbs more infrared light, while deoxygenated haemoglobin (deO_2-Hb) absorbs more red light. The oximeter calculates the fraction of oxygenated Hb out of the total haemoglobin (O_2-Hb and deO_2-Hb). Pulse oximetry can be affected by haemoglobinopathies due to their unique spectral properties at these wavelengths[6-9]. This second mechanism explains the discrepancy between oxygen saturation of 84% measured via pulse oximetry and the oxygen saturation of 90% measured directly in the arterial blood.

The key to accurate diagnosis depends on two stages. First, performing arterial blood gas using an analyser with multiple-wavelength spectrophotometry, thus allowing to measure Hb oxygen saturation directly in the blood rather than extrapolating oxygen saturation from the measured PO_2 using known formulas that do not account for the unique dissociation curve of haemoglobinopathies. Second, after the diagnosis of low-oxygen affinity is suggested, an exact diagnosis is needed by performing Hb electrophoresis, and if pathological, proceeding to mutational analysis of the globin chains[10]. Notably, at times HbA2 might be borderline but normal even in patients with mutations. Therefore, borderline results in the face of a high clinical suspicion should not deter clinicians from proceeding to genetic analysis.

No treatment for Hb Lansing specifically, and for low-oxygen affinity haemoglobinopathies in general is required[10]. No epidemiological studies report the prognosis of low-oxygen affinity haemoglobinopathies, and we assume the diagnosis does not impact longevity, despite long-term chronic mild end-organ ischaemia.

CONCLUSION

Haemoglobinopathies should be considered in the differential diagnosis of unexplained hypoxia. Hb electrophoresis followed by gene sequencing allow for definitive diagnosis. It is important to distinguish between low-oxygen affinity haemoglobinopathies, that don't require treatment and generally carry good prognosis, and high-oxygen affinity which might be associated with increased morbidity.

REFERENCES

1. Sarikonda KV, Ribeiro RS, Herrick JL, Hoyer JD. Hemoglobin lansing: a novel hemoglobin variant causing falsely decreased oxygen saturation by pulse oximetry. *Am J Hematol* 2009;**84**:541.
2. Trakulsrichai S, Panthan B, Jittorntam P, Niparuck P, Sriapha C, Chantratita W, et al. First identification of hemoglobin lansingramathibodi [α87(F8)His→ GLN; CAC> CAG (HBA1: c. 264C>G)] in a Thai family with spurious hypoxemia. *Southeast Asian J Trop Med Public Health* 2016;**47**:1048–1054.
3. Akar N, Torun D, Öztürk A. Hemoglobin Lansing (Alpha) [HBA2 CD87 (HIS> GLU)(C> A)] in a Turkish individual resulting from another nucleotide substitution. *Turk J Haematol* 2014;**31**:317–318.
4. Ishitsuka K, Uchino J, Kato J, Ikuta M, Watanabe K, Matsunaga A, et al. First reported case of hemoglobin lansing in Asia detected by false low oxygen saturation on pulse oximetry. *Int J Hematol* 2012;**95**:731–732.
5. Hassan SM, Harteveld CL, Bakker E, Giordano PC. Hb lansing (HBA2: c.264C>G) and a new β promoter transversion [−52 (G>T)]: an attempt to define the phenotype of two mutations found in the Omani population. *Hemoglobin* 2015;**39**:111–114.
6. Verhovsek M, Henderson MP, Cox G, Luo HY, Steinberg MH, Chui DH. Unexpectedly low pulse oximetry measurements associated with variant hemoglobins: a systematic review. *Am J Hematol* 2010;**85**:882–885.
7. Chan ED, Chan MM, Chan MM. Pulse oximetry: understanding its basic principles facilitates appreciation of its limitations. *Respir Med* 2013;**107**:789–799.
8. Torp KD, Modi P, Simon LV. Pulse Oximetry. 2017. StatPearls. NIH National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK470348/
9. Patterson S, Sandercock N, Verhovsek M. Understanding pulse oximetry in hematology patients: hemoglobinopathies, racial differences, and beyond. *Am J Hematol* 2022;**97**:1659–1663.
10. Yudin J, Verhovsek M. How we diagnose and manage altered oxygen affinity hemoglobin variants. *Am J Hematol* 2019;**94**:597–603.