Title:

A novel haemoglobin variant mimicking cyanotic congenital heart disease

An unusual explanation for positive oximetry screening for congenital heart disease.

Positive oximetry screening for congenital heart disease in a healthy newborn: a diagnostic challenge!

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Abstract:

Screening for critical congenital heart defects in newborn babies can aid in early recognition, with the prospect of improved outcome. However, as this universal newborn screening is implemented, there will be an increasing number of false positives results. In order to avoid multiple investigations and uncertainty, an Hb variant must be included in the differential diagnosis in otherwise well newborns with low oxygen saturation by pulse oximetry. Here we describe a novel foetal Hb variant [heterozygous Gγ-globin gene (HBG1) mutation in exon 2 c.202G>A (p.Val68Met)] identified in a newborn with positive pulse oximetry screening for congenital heart disease.

Key-words: pulse oximetry; haemoglobin variant; congenital heart disease; screening; newborn

Introduction

Pulse oximetry is a noninvasive and widely used photometric method to estimate a patient's arterial oxygen saturation [1]. Oxy and deoxy haemoglobin (Hb) show unique absorbance at 660 and 940 nm, respectively, and the pulse oximeter determines oxygen saturation by measuring a ratio of pulsatile light transmission through a cutaneous vascular bed at the two wavelengths [2]. This instrument is of great importance in paediatrics as it can detect disorders in oxygen uptake and distribution [3]. Despite the current widespread use of pulse oximetry we must be aware of its limitations. Measurement anomalies can occur due to motion artefacts, nail varnish, reduced local perfusion, venous pulsation, optical and electrical interfering radiation, Hb variants and anatomical and/or histological conditions [2]. Sometimes, patients are found unexpectedly to have low oxygen saturation by pulse oximetry (SpO2). They may undergo extensive cardiopulmonary investigations since low oxygen saturation is found in many malformations and diseases of the respiratory tract, functional breathing disorders and in congenital heart defects [4,5]. However, when diagnostic cardiopulmonary findings remain ambiguous, arterial blood gas measurements (PaO2 and SaO2) are normal, and SpO2 readings are low, an Hb variant should be considered in the differential diagnosis [6-12].

Hb is a tetrameric protein composed of two α-globin chains and two non-α (β, γ, δ)-globin chains that combine with four haeme groups. In the adult, normal Hb mainly consists of HbA (α2β2), with a small fraction of HbA2 (α2δ2) and an even smaller fraction of HbF (α2γ2). In newborns, the largest fraction is composed by HbF and the changeover to HbA takes place until six months of age. Genetic alterations that conduct to synthesis of Hb with abnormal structure (Hb variants) or to reduced synthesis of globin chains (thalassemias) are known as haemoglobinopathies [10]. Included in 1641 known haemoglobinopathies, of which 131 are of foetal origin, there are α-, β- and γ-globin variants that affect oxygen binding affinity [13]. Mutations in γ-globin genes (HBG1 or HBG2) can cause neonatal symptoms that are transient and will disappear in the first months of life. Mutations in the α-globin gene (HbA1 or HBA2) might cause newborn cyanosis that will persist all lifelong. Mutations in the β-globin gene (HBB) will only become clinically significant months after birth. [14] Hb variants which are known to have low SpO2 measurements are listed in Table 1 [8].

The use of pulse oximetry in universal screening for cyanotic congenital heart defects was recently recommended at national and international level [15-17]. As it is implemented and becoming a nursery routine, an increasing number of asymptomatic patients with unexpectedly low SpO2 will probably be uncovered. In order to reduce patients and parent's anxiety and to avoid inappropriate investigations, an Hb variant must be included in the differential diagnosis [7]. These patients diagnostic work-up should include an arterial blood gas (ABG) sampling, with analysis by co-oximetry, to document the PaO2 status and rule out the presence of significant amounts of methe/carboxyhemoglobin (MetHb/COHb). If PaO2 is normal, an Hb assessment should be made, including electrophoresis, high-performance liquid chromatography and isoelectric focusing. In the presence of an abnormal Hb variant, DNA sequence analysis is necessary to identify and characterize the mutation [8,18].

This report aims to describe a novel foetal Hb variant [mutation in exon 2 c.202G>A (p.Val68Met)] discovered in a newborn found to have SpO2 significantly below normal on pulse oximetry screening for congenital heart disease.

Case Report

We report the case of a late preterm female newborn, with no relevant family history, delivered by caesarean section at 36 weeks because of foetal distress. At birth, the Apgar scores were 9 and 10 at 1 and 5 min. She weighed 2.350 kg, was clinically well and the physical examination was unremarkable.

At the second day of life, pulse oximetry screening for congenital heart disease detected a persistent SpO2 of 83 to 90%. Cardiovascular examination, echocardiography and chest radiography were normal. Computed tomography angiogram ruled out anomalous pulmonary venous return and arterio-venous malformations. Septic and metabolic screenings were negative. Haematological parameters were within the reference intervals, with normal results on standard Hb electrophoresis and methaemoglobin level. Oxygen therapy was started with poor response.

By day 11, she was transferred to the pediatric intensive care unit, for monitoring and further evaluation. Pulse oximetry revealed a low SpO2 despite the absence of arterial hypoxia in the ABG (PaO2 94.8 mmHg and SaO2 97.4%, with SpO2 88%), and a normal hyperoxia test (PaO2 507 mmHg and SaO2 99%, with max SpO2 of 93%). ABG revealed a mild lactic acidosis with lactate 2.3-3.6 mmol/L. She was discharged by day 12 with a normal physical examination and a sustained low SpO2, referred to the haematology outpatient clinic.

Further investigations revealed an unknown Hb F variant (Val68Met - 26.9%) on High-performance liquid chromatography (HPLC). With this diagnostic possibility, polymerase chain reaction (PCR) sequence analysis of the patient's haemoglobin genes was performed and a novel heterozygous γ-globin gene (HBG1) mutation in exon 2 c.202G>A was identified.

Her clinical course was unremarkable and by … months of age her SpO2 was consistently higher than 95%. By the time the paper was written, she had been subsequently healthy.

Discussion

Screening for cyanotic congenital heart defects through pulse oximetry allows early recognition and referral of potentially life threatening conditions to specialized centres. Nonetheless, its widespread use will probably lead to false positive results that can result in extensive investigations and represent a burden to families and health care systems.

With the case presented here we wish to alert for a condition that can mimic a cyanotic heart defect. Haemoglobin variants can have different readings by pulse oximetry. In this case the haemoglobin variant was not detected as oxyhaemoglobin by the pulse oximeter, although the SaO2 measured in blood gas analysis by CO-oximetry was normal. At first, we thought that this was just a technical problem related to limitations in pulse oximetry accuracy and that the patient did not have a problem with oxygen transport or delivery to the tissues. But there was a sign that this could not be so simple. Lactate was mildly elevated in all blood gas analysis. This suggests that the later identified Hb variant has a high affinity to oxygen and compromises oxygen delivery to tissues resulting in tissue hypoxia.

It is quite ironic that the false reading of low SpO2 was actually reflecting a deficient oxygen delivery, not detectable by blood gas analysis and the gold standard CO-oximetry. This is exactly the opposite of what happens in more common conditions such as carbon monoxide

intoxication or methaemoglobinaemia where a falsely normal SpO2 hides the presence of dyshaemoglobins (COHb and MetHb) only detectable by CO-oximetry.

Another interesting point is that the defect was in the γ-globin gene, meaning that it only affects foetal haemoglobin. If a pulse oximetry had not been performed as part of the congenital heart disease screening program this condition would probably never have been diagnosed. This raises the question of how many similar cases will appear with the widespread use of these screening programs.

Judicious use of ancillary tests is advised in the investigation of these cases. Simple and inexpensive tests like blood gas analysis and the hyperoxia test would have excluded a right to left shunt avoiding the need for a CT angiography.

We hope that the case described here will help others when faced with an unexplained low SpO2 measurement in a newborn or even in an older patient.

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Tables

false SpO2 values from pulse oximetry measurements	*Hb Bonn*
	Hb Cheverly
	HbM Iwate
	Hb Köln
	Hb Lansing
methemoglobin formation	*HbM Boston*
	Hb Chile
	HbFM Fort Ripley
	Hb Freiburg
	HbM Hyde Park
	HbM Iwate
	HbM Milwaukee
	HbFM Osaka
	HbM Saskatoon
	Hb St. Louis
low oxygen affinity hemoglobin anomalies	Hb Arta
	Hb Bassett
	Hb Beth Israel
	Hb Canabiere
	Hb Cheverly
	Hb Chico
	Hb Denver
	Hb Hammersmith
	Hb Hope
	Hb Kansas
	Hb Louisville
	Hb Nishinomiya
	Hb Rothschild
	Hb Saint Mandé
	Hb Seattle
	Hb Sunshine Seth
	Hb Titusville
	Hb Venusberg
	Hb Warsaw
	Hb Yoshizuka

Table 1. Hb anomalies with low SpO2 measurements. Hb variants clinically significant in newborns appear in italics. Reprinted from "Oxygen saturation in pulse oximetry in hemoglobin anomalies" by Zur B, Bagci S, Ludwig M et al, 2012, Klin Padiatr, 224, p. 259-265. Reprinted with permission.