

## CASE REPORT

## A novel haemoglobin variant mimicking cyanotic congenital heart disease

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## SUMMARY

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-positive results. In order to avoid multiple investigations and uncertainty, an haemoglobin (Hb) variant must be included in the differential diagnosis in otherwise well newborns with low oxygen saturation by pulse oximetry. We describe a novel fetal Hb variant (heterozygous  $\gamma$ -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.

## BACKGROUND

Pulse oximetry is a non-invasive and widely used photometric method to estimate a patient's arterial oxygen saturation.<sup>1</sup> 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.<sup>2</sup> This instrument is of great importance in paediatrics as it can detect disorders in oxygen uptake and distribution.<sup>3</sup> 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.<sup>2</sup> Sometimes, patients are found unexpectedly to have low oxygen saturation by pulse oximetry (SpO<sub>2</sub>). 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.<sup>4,5</sup> However, when diagnostic cardiopulmonary findings remain ambiguous, arterial blood gas measurements (PaO<sub>2</sub> and SaO<sub>2</sub>) are normal and SpO<sub>2</sub> readings are low, an Hb variant should be considered in the differential diagnosis.<sup>6–12</sup>

Hb is a tetrameric protein composed of two  $\alpha$ -globin chains and two non- $\alpha$  ( $\beta$ ,  $\gamma$ ,  $\delta$ )-globin chains that combine with four haeme groups. In the adult, normal Hb mainly consists of HbA ( $\alpha_2\beta_2$ ), with a small fraction of HbA2 ( $\alpha_2\delta_2$ ) and an even smaller fraction of HbF ( $\alpha_2\gamma_2$ ). In newborns, the largest fraction is composed by HbF and the change-over to HbA takes place over the first 6 months of age. Genetic alterations that conduct to synthesis of

Hb with abnormal structure (Hb variant) or to reduced synthesis of globin chains (Thalassaemia) are known as haemoglobinopathies.<sup>10</sup> Included in 1641 known haemoglobinopathies, of which 131 are of fetal origin, there are  $\alpha$ -globin,  $\beta$ -globin and  $\gamma$ -globin variants that affect oxygen binding affinity.<sup>13</sup> Mutations in  $\gamma$ -globin genes (HBG1 or HBG2) can cause neonatal symptoms that are transient and will disappear in the first months of life. Mutations in the  $\alpha$ -globin gene (HbA1 or HbA2) can cause newborn cyanosis that will persist throughout life. Mutations in the  $\beta$ -globin gene (HBB) will only become clinically significant months after birth.<sup>14</sup> Hb variants known to have low SpO<sub>2</sub> measurements are listed in figure 1.<sup>8</sup>

The use of pulse oximetry in universal screening for cyanotic congenital heart defects was recently recommended at a national and international level.<sup>15–17</sup> As it is implemented and becomes a nursery routine, an increasing number of asymptomatic patients with unexpectedly low SpO<sub>2</sub> will probably be uncovered. In order to reduce patients' distress and parent's anxiety, and to avoid inappropriate investigations, an Hb variant must be included in the differential diagnosis.<sup>7</sup> These patients' diagnostic work up should include an arterial blood gas (ABG) sampling, with analysis by CO-oximetry, to document the PaO<sub>2</sub> status and rule out the presence of significant amounts of methemoglobin (MetHb/COHb). If PaO<sub>2</sub> 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 characterise the mutation.<sup>8,18,19</sup>

This report aims to describe an unknown Hb variant (mutation in HBG1 exon 2 c.202G>A (p.Val68Met)) in order to alert physicians to the novelty of this subject and its true clinical daily practice implications.

## CASE PRESENTATION

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

## INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

On the second day of life, pulse oximetry screening for congenital heart disease detected a persistent



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false SpO <sub>2</sub> values from pulse oximetry measurements	<i>Hb Bonn</i>
	<i>Hb Cheverly</i>
	<i>HbM Iwate</i>
	<i>Hb Köln</i>
	<i>Hb Lansing</i>
methemoglobin formation	<i>HbM Boston</i>
	<i>Hb Chile</i>
	<i>HbFM Fort Ripley</i>
	<i>Hb Freiburg</i>
	<i>HbM Hyde Park</i>
	<i>HbM Iwate</i>
	<i>HbM Milwaukee</i>
	<i>HbFM Osaka</i>
	<i>HbM Saskatoon</i>
	<i>Hb St. Louis</i>
low oxygen affinity hemoglobin anomalies	<i>Hb Arta</i>
	<i>Hb Bassett</i>
	<i>Hb Beth Israel</i>
	<i>Hb Canabiere</i>
	<i>Hb Cheverly</i>
	<i>Hb Chico</i>
	<i>Hb Denver</i>
	<i>Hb Hammersmith</i>
	<i>Hb Hope</i>
	<i>Hb Kansas</i>
	<i>Hb Louisville</i>
	<i>Hb Nishinomiya</i>
	<i>Hb Rothschild</i>
	<i>Hb Saint Mandé</i>
	<i>Hb Seattle</i>
	<i>Hb Sunshine Seth</i>
	<i>Hb Titusville</i>
	<i>Hb Venusberg</i>
	<i>Hb Warsaw</i>
	<i>Hb Yoshizuka</i>

**Figure 1** Haemoglobin (Hb) anomalies with low SpO<sub>2</sub> measurements. Hb variants clinically significant in newborns appear in italics. Reprinted from Zur *et al.*<sup>8</sup> Reprinted with permission.

SpO<sub>2</sub> of 83–90%. Cardiovascular examination, echocardiography and chest radiography were normal. CT angiography ruled out anomalous pulmonary venous return and arteriovenous 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, the baby was transferred to the paediatric intensive care unit, for monitoring and further evaluation. Pulse oximetry revealed a low SpO<sub>2</sub> despite the absence of arterial hypoxia in the ABG (PaO<sub>2</sub> 94.8 mm Hg and SaO<sub>2</sub> 97.4%, with SpO<sub>2</sub> 88%) and a normal hyperoxia test (PaO<sub>2</sub> 507 mm Hg and SaO<sub>2</sub> 99%, with max SpO<sub>2</sub> 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 SpO<sub>2</sub>, and 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, PCR sequence analysis of the patient's haemoglobin genes was performed and a novel heterozygous  $\gamma$ -globin gene (HBG1) mutation in exon 2 c.202G>A was identified. This was the first description of the Val68Met mutation at  $\gamma$ 1-globin chains but the same variant, named Hb Tom River, was already described in the  $\gamma$ 2-globin chains in a new born with cyanosis.<sup>14</sup>

## OUTCOME AND FOLLOW-UP

The baby's clinical course was unremarkable and by 4 months of age, her SpO<sub>2</sub> was consistently higher than 95%. At the time of writing this paper, she is healthy.

## DISCUSSION

Screening for cyanotic congenital heart defects through pulse oximetry allows early recognition and referral of potentially life-threatening conditions to specialised 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 healthcare systems.

With the case presented here, we wish to alert those concerned to an emerging condition that can mimic a cyanotic heart defect. Hb variants can have different readings by pulse oximetry. In this case, this previously unknown Hb variant was not detected as oxyhaemoglobin by the pulse oximeter, although the SaO<sub>2</sub> 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. However, there was a sign that this could not be so simple. Lactate was mildly elevated in all blood gas analyses. 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 SpO<sub>2</sub> 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 SpO<sub>2</sub> hides the presence of dysaemoglobins (COHb and MetHb) only detectable by CO-oximetry.

Another interesting point is that the defect was in the  $\gamma$ -globin gene, meaning that it only affects fetal haemoglobin. This explains SpO<sub>2</sub> normalisation by 4 months of age when Hb F production decreases. If pulse oximetry had not been performed as part of the congenital heart disease screening programme, 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 programmes.

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

We hope that the case described here will alert physicians to this new problem and help others when faced with an unexplained low SpO<sub>2</sub> measurement in a newborn or even in an older patient.

## Learning points

- ▶ We describe a novel haemoglobin variant that can mimic cyanotic congenital heart disease.
- ▶ Screening for critical congenital heart defects in newborns can aid in early recognition of potentially life-threatening conditions.
- ▶ Haemoglobin variants must be included in the differential diagnosis in otherwise well newborns with an unexplained low SpO<sub>2</sub> measurement, in order to avoid multiple investigations, and a burden to families and healthcare systems.

**Competing interests** None declared.

**Patient consent** Obtained.

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