

# A hereditary methemoglobinemia case: Estimation of tissue oxygenation

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### SUMMARY

We present the case of an adult patient presenting with clinical features suggestive of asthmatic bronchitis due to respiratory tract infection and a low pulse oximetry reading, who was finally diagnosed suffering from hereditary methemoglobinemia. Presence of a wide discrepancy in haemoglobin oxygen saturation, as assessed by pulse oximetry (SpO<sub>2</sub>) and arterial blood gas analysis (SaO<sub>2</sub>), along with normal arterial blood partial pressure of oxygen (PaO<sub>2</sub>) are findings highly suggestive of elevated methemoglobin concentration. Measurements of SpO<sub>2</sub> and SaO<sub>2</sub> are, due to technical reasons, unreliable in cases of, either hereditary or due to exposure to an oxidizing agent, Methemoglobinemia and alternative methods estimating tissue oxygenation have to be used.

*Pneumon 2017, 30(3):188-191.*

### CASE REPORT

We report the case of a 48-year-old male, with no previous medical history, who presented with wheezing and symptoms suggestive of respiratory infection at the outpatient Pulmonary Clinic. His physical examination revealed mild expiratory wheezing and a low pulse oximetry reading (SpO<sub>2</sub>) of 86%. His chest X-Ray was normal and spirometry findings were within normal limits (FVC: 86%, FEV<sub>1</sub>: 96%, FEV<sub>1</sub>/FVC: 91%). Bronchodilatation test was negative, though post FEV<sub>1</sub> was markedly increased by 300ml. Given that neither the radiologic nor the spirometry findings were compatible with the patient's low SpO<sub>2</sub>, he was referred for cardiology evaluation and Computed Tomography angiography, both of which were negative for cardiac disease or pulmonary embolism. Arterial Blood gas analysis (ABGs) were pO<sub>2</sub>: 78mmHg, pCO<sub>2</sub>: 36mmHg, pH: 7,41, SaO<sub>2</sub>: 96%, HCO<sub>3</sub>: 22,5mEq/L. Alveolar-arterial Gradient was elevated (27 mmHg). Since SaO<sub>2</sub> and pO<sub>2</sub> were normal, a macrolide antibiotic, as well as inhaled corticosteroid in a fixed combination with a long acting beta adrenoceptor agonist, were prescribed.

Four days later he came back for re-evaluation and significant clinical improvement was noted. However, his SpO<sub>2</sub> reading was still abnormal at

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86%, leading to a new ABGs analysis on a different blood gas analyzer, with the following results:  $pO_2$ : 76mmHg,  $pCO_2$ : 38mmHg, pH: 7,423,  $SaO_2$ : 96,7%,  $HbO_2$ : 83,6%,  $COHb$ : 0,7%,  $HHb$ : 2,9%,  $MetHb$ : 13%,  $HCO_3$ : 24,2mEq/L.

The high methemoglobin (MethHb) level of 13% was consistent with the patient's low  $SpO_2$  reading and suggestive of methemoglobinemia. Upon closer inspection mild peripheral cyanosis of the fingernail beds was noted (Figure 1), which had been observed for years by the patient and his family members, with no apparent worsening recently. Two weeks later and after discontinuation of all medication, patient had fully recovered, while a new ABG sample confirmed the presence of MethHb at high levels. The patient was advised on avoidance of oxidative agents (e.g. local anesthetics, antibiotics and common household products, such as naphthalene) and was referred to an Haematology specialist for further evaluation and genetic testing to confirm the diagnosis of hereditary methemoglobinemia. Unfortunately such genetic testing is not available in any laboratory in Greece.

Given the fact that his MethHb was elevated at two different time points, there had been no prior oxidising agent exposure, comprehensive physical and laboratory testing were normal, and in view of the peripheral cyanosis present for several years according to the patient himself, final diagnosis of hereditary methemoglobinemia was reached.

## DISCUSSION

The most interesting point regarding this case report is the wide discrepancy in haemoglobin oxygen saturation, as assessed by pulse oximetry and arterial blood gas analysis, which are the two most commonly used methods in clinical practice. Haemoglobin oxygen saturation measured by pulse oximetry ( $SpO_2$ ) was 84-86%, while measuring on a blood gas analyzer ( $SaO_2$ ) it was 96-97%. The  $SaO_2$ - $SpO_2$  difference is called the satura-



FIGURE 1.

tion gap, which is normally no more than 5%, whereas higher results should always raise high clinical suspicion of methemoglobinemia<sup>1-3</sup> (in this case: Saturation Gap= $SaO_2$ - $SpO_2$ =96%-85%=11%).

Methemoglobin (MethHb) is produced by haemoglobin oxidation, during which the iron in the heme group (which is in the  $Fe^{2+}$ -ferrous-state) loses an electron and changes to the  $Fe^{3+}$ -ferric-state.<sup>1,2,4</sup> Along with carboxyhemoglobin (COHb) and sulfhemoglobin (SHb), MethHb is one of the dyshemoglobins (dysHb), which are abnormal Hb derivatives incapable of reversibly binding with oxygen.<sup>5</sup> Haemoglobin oxidation to MethHb has two important effects. The first one is that MethHb cannot bind with  $O_2$ , and therefore does not contribute to  $O_2$  transfer to the tissues. Secondly, ferric iron in partially oxidised Hb (by means of allosteric modulation) increases its  $O_2$  affinity, hindering oxygen release to the tissues, and therefore causing a leftward shift of the oxygen-hemoglobin dissociation curve.<sup>1,2,4,5</sup> When MethHb concentration increases, both these mechanisms are responsible for the resulting tissue hypoxia, and the upcoming wide clinical presentation, varying from asymptomatic peripheral cyanosis (when MethHb concentration is up to 15%) to death (when MethHb concentration exceeds 70%).<sup>1,2,4</sup>

Assessing tissue oxygenation in methemoglobinemia is challenging. MethHb absorbs light at both wavelengths used in pulse oximetry (660 and 940nm), at the same or even higher level than oxyhemoglobin ( $O_2Hb$ ) and deoxyhemoglobin (HHb), leading to inaccurate results.<sup>5-7</sup> Animal studies since the '90s have shown that pulse oximetry yields results that lead to either over- or underestimation of tissue oxygenation (depending on whether  $SpO_2$  is over or under 70%). Moreover, pulse oximetry in methemoglobinemia rarely exceeds the value 85%.<sup>6,7</sup>

On the other hand, blood gas analysis is also unreliable as in most commonly used ABGs analyzers,  $SaO_2$  is not directly measured but is rather calculated, by means of the  $PaO_2$  measurement and the normal Hb- $O_2$  dissociation curve.<sup>2</sup> Although  $PaO_2$  is within normal limits in methemoglobinemia, the Hb- $O_2$  dissociation curve is shifted to the left, resulting in false  $SaO_2$  calculation.

The only reliable non-invasive method to detect MethHb and estimate tissue oxygenation at the same time is by means of the new technology CO-oximeters.<sup>1,2,4,5</sup> While the widely used pulse oximeters measure light absorbance in 2 wavelengths, CO-oximeters can reliably detect and measure not only  $HbO_2$  and HHb but also all dyshemoglobulins, by measuring light absorbance in at least 6 wavelengths.<sup>5,7</sup> They are invaluable tools in every day

clinical practice, although their use is still not very popular.

Regarding this case, since there was no CO-oximeter available, we calculate the oxyhemoglobin fraction (FO<sub>2</sub>Hb), by using the data from the second ABGs analysis:

$$FO_2Hb = HbO_2 / (HbO_2 + HHb + COHb + MethHb) = 83,6\%$$

Oxyhemoglobin fraction is a reliable tissue oxygenation index, which is practically equal to SpO<sub>2</sub> and SaO<sub>2</sub>, in the absence of dysHbs.<sup>1,2,5</sup> In this case, FO<sub>2</sub>Hb was approximately 84% of the total Hb, pulse oximetry (SpO<sub>2</sub>) resulted in a slight overestimation (84-86%) and SaO<sub>2</sub> in ABGs was utterly false (96%).

Any oxidising agent (e.g. drugs, smoke, inhaled toxic substances) can theoretically lead to MetHb formation and this practically happens constantly. Natural reducing systems maintain the levels of MetHb under 2%, with the most important system being NADH-Methemoglobin reductase (NADH-NR). NADH-NR is responsible for the endogenous reduction of MetHb, corresponding to 99% of the reducing activity,<sup>1,2,4</sup> by transfer of one electron from NADH to MetHb, thus reducing heme Fe<sup>3+</sup> to Fe<sup>2+</sup>.<sup>1,2,4</sup> NADH-MetHb reductase synthesis is encoded by the CYB5R3 gene in chromosome 22q13qter, whereas more than 40 mutations have been identified in cases of hereditary methemoglobinemia.

Initial misdiagnosis of asthma or Chronic Obstructive Pulmonary Disease (COPD), late diagnosis and lack of laboratory confirmation (due to lack of proper equipment) of the diagnosis are common features among the limited reported cases of hereditary methemoglobinemia diagnosed in adult life.<sup>10-14</sup> In order to overcome these technical difficulties, simple diagnostic tests are proposed in order to reach diagnosis.<sup>2,5,15</sup> The simplest method proposed is by assessing the arterial blood sample colour, which is dark brown (chocolate) when MetHb >20%, as is evident on our patient's sample in figure 2.<sup>1,2,14</sup> Additionally, while HHb (which is also dark coloured) turns bright red when exposed to O<sub>2</sub> (either by enriching the blood sample with 100% O<sub>2</sub> bubbles or by exposing a single blood drop to room air), MetHb maintains its dark brown colour.



**FIGURE 2.**

Although the reported cases of hereditary methemoglobinemia in adults in the literature are limited,<sup>3,9,11-13</sup> the clinical presentation and the diagnostic and tissue oxygenation evaluation methods discussed are also applicable in the far more common cases of acquired methemoglobinemia due to an oxidising agent exposure. It is noteworthy that, in a recent review, 11 cases of acquired methemoglobinemia due to lidocaine use during bronchoscopy were reported, while the reviewers suggest that methemoglobinemia is probably underdiagnosed in every day practice<sup>16</sup>.

In conclusion, high clinical suspicion is the key prerequisite for methemoglobinemia diagnosis<sup>17</sup> and should be high in every case of peripheral cyanosis with normal PaO<sub>2</sub> unresponsive to oxygen therapy.

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