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Case 23-2004: A 50-Year-Old Woman with Low Oxygen Saturation

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PRESENTATION OF CASE

A 50-year-old woman was evaluated in the pulmonary clinic because of low oxygen saturation.

Five years earlier, dysfunctional uterine bleeding and dysmenorrhea had developed. A pelvic ultrasonographic examination at that time had revealed uterine fibroids. Four years later, the woman was found to be anemic; an endometrial biopsy showed no evidence of cancer. A repeated pelvic ultrasonographic examination revealed a slightly enlarged uterus, 11 cm in length, and a posterior submucous uterine fibroid, 35 by 30 by 41 mm, that displaced the endometrium anteriorly. Her symptoms were controlled for a time with ibuprofen. However, the pain increased, and after she did not have a response to treatment with medroxyprogesterone acetate, she was scheduled for dilatation and curettage, hysteroscopy, and possible resection of the fibroid.

A tonsillectomy had been performed 27 years earlier and a tubal ligation 6 years after that. The patient was noted to have coughing and cyanosis in the recovery room after the tubal ligation. She also had hypertension of recent onset; a history of a heart murmur, with a report of an echocardiogram revealing trace mitral regurgitation; a history of atypical chest pain (with a normal electrocardiogram) that had not recurred; and asthma, diagnosed two years previously, after she had wheezing with a respiratory infection. Her medications included atenolol (25 mg daily), ibuprofen, and an iron supplement. There was a family history of asthma and coronary artery disease, including a myocardial infarction in her 72-year-old mother, but there was no family history of any adverse reactions to general anesthesia. She had no allergies, did not smoke cigarettes, and did not abuse drugs or alcohol.

The patient was seen in the outpatient preadmission testing area. The blood pressure was 162/89 mm Hg, the heart rate 97 beats per minute, the respiratory rate 26 breaths per minute, the temperature 37.2°C, the height 153 cm, and the weight 75 kg. Auscultation of the chest revealed prolonged expiration, with clear lungs. The cardiac rhythm was regular, and there was a systolic ejection murmur (grade 2 to 3) at the base. The remainder of the findings on physical examination were normal. Oxygen saturation by digital pulse oximetry (SpO_2) was 93 percent bilaterally while the patient was breathing ambient air. The results of laboratory tests are shown in Table 1. An electrocardiogram showed a normal sinus rhythm with clockwise rotation; there

Table 1. Results of Laboratory Tests.

Variable	Outpatient Evaluation
White cells (per mm³)	7,400
Hematocrit (%)	38.1
Hemoglobin (g/dl)	12.9
Red-cell count (per mm³)	4.19×10^6
Platelets (per mm³)	326,000
Mean corpuscular volume (μm^3)	91
Mean corpuscular hemoglobin (pg/red cell)	30.7
Mean corpuscular hemoglobin concentration (g/dl)	33.7
Red-cell distribution width (%)	13.7
Hemoglobin pattern (as measured by high-performance liquid chromatography)	Normal

was no change from the electrocardiogram that had been obtained 14 years earlier. Chest radiography disclosed clear lungs; a heart of normal size and contour, with no evidence of congestive heart failure; and no abnormalities of the hilar, mediastinal, pleural, or bony structures.

Pulmonary-function tests performed five days after the outpatient examination showed normal lung volumes, normal single-breath carbon monoxide diffusion capacity, and a reduced SpO_2 (91 percent) while the patient was breathing room air. An echocardiogram showed normal left and right ventricular function; there was no evidence of a shunt after an intravenous injection of agitated saline. Slight calcification of the posterior mitral annulus and left atrial dilatation, as well as trace mitral regurgitation (without evidence of mitral-valve prolapse), trace tricuspid insufficiency, and trace pulmonary insufficiency were observed on color and spectral Doppler imaging. No evidence of aortic insufficiency or pericardial effusion was seen. The estimated ejection fraction was 70 percent. The planned operation was postponed, and the patient was referred for a pulmonary evaluation.

Eight weeks later, she was evaluated in the outpatient pulmonary clinic. Additional information on her history was obtained; it was learned that the diagnosis of asthma had been made after she had moved into a dusty office and that her symptoms had resolved after she had moved out of the office. She had not had any other episodes of shortness of breath, and she was physically active. She was originally from Puerto Rico, had two children, and had no other history of occupational exposures to toxins or dust. On physical examination, she appeared well and was not in acute distress. Her lungs and heart were normal on auscultation, her fingers and toes showed no cyanosis or clubbing, and her arms and legs showed no edema. Her SpO_2 while she was breathing ambient air in the supine and standing positions was 91 percent, and it remained in the 91 to 93 percent range with exertion. It increased to 97 to 98 percent while the patient was receiving 6 liters of oxygen by nasal cannula. The results of arterial blood gas studies and oximetry are shown in Table 2.

A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. William E. Hurford: The key findings in this patient's preoperative evaluation were unexpectedly low SpO_2 values on multiple occasions in the absence of known pulmonary or cardiac disease.

PREOPERATIVE EVALUATION WITH PULSE OXIMETRY

The usefulness of pulse oximetry as a preoperative screening tool has never been examined prospectively. In their recent advisories on preoperative evaluation, neither the American Society of Anesthesiologists nor the American College of Cardiology recommends pulse oximetry for routine use.[1,2] Nevertheless, the presumption that hypoxemia may contribute to perioperative morbidity and mortality has considerable empiric validity. The patient under discussion had a history of hypertension, a heart murmur, atypical chest pain, and asthma. She had become cyanotic in the recovery room after a previous operation. She also had a family history of asthma and coronary artery disease. Accordingly, the inclusion of pulse oximetry in her cardiopulmonary assessment was reasonable.

CAUSES OF LOW OXYGEN SATURATION ON PULSE OXIMETRY

The low SpO_2 value (93 percent) while the patient was breathing ambient air is unexpected, given that she did not have severe signs or symptoms of cardiac or pulmonary disease. What might explain this value? Hypoxemia is the most clinically important cause of a low SpO_2, and pulmonary disease is the most common cause of hypoxemia (Table 3). The usual causes of hypoxemia include hypoventilation, mismatching of ventilation and perfusion, right-

Table 2. The Results of Arterial Blood Gas Studies and Oximetry.*

Variable	Value
Hemoglobin (%)	12.9
SpO_2 (%)	94
Fractional saturation (%)	89
SaO_2 (%)	98
Pulse (beats/min)	77
pH	7.43
Partial pressure of arterial oxygen (mm Hg)	98
Partial pressure of arterial carbon dioxide (mm Hg)	33

* SpO_2 denotes the oxygen saturation measured by pulse oximetry and SaO_2 the functional saturation, or the saturation calculated according to arterial blood gas values.

Table 3. Possible Causes of a Low Oxygen Saturation on Pulse Oximetry.

Hypoxemia
Abnormal hemoglobin variants
Methemoglobinemia
Sulfhemoglobinemia
Intravenous dyes (e.g., methylene blue and indocyanine green)
Blue nail polishes (some)
Prominent venous pulsations
Contamination of measurement by ambient light

to-left shunting of blood, and diffusion abnormalities (Table 4). On initial examination, the patient was found to be slightly tachypneic and to have a prolonged expiratory time, but the lung fields were clear. The evaluation proceeded appropriately with chest radiography and tests of pulmonary function. Her chest radiograph was normal, and both spirometric values and the results of testing of the carbon monoxide diffusion capacity of the lung were normal. These tests effectively rule out common diseases such as emphysema or asthma as a cause of hypoxemia.

Cardiac disease can also lead to hypoxemia, particularly when right-to-left shunting of blood or pulmonary edema is present. There was no clinical or radiologic evidence of pulmonary edema in this patient. An echocardiogram was obtained to assess the possibility of ventricular dysfunction or intracardiac shunting, and the images were normal. Right-to-left shunting of blood may also be due to pathologic intrapulmonary shunting, such as that occurring in pulmonary arteriovenous malformations or hepatopulmonary syndrome, but such processes would be unlikely in this patient, given her normal diffusing capacity and echocardiogram. Intrapulmonary shunting would have been detected by early opacification of the left ventricle after the intravenous injection of agitated saline. An explanation of her reduced SpO_2 must lie elsewhere.

LIMITATIONS OF PULSE OXIMETRY

Pulse oximetry does not directly measure oxygen saturation. Diodes on the oximeter probe emit two wavelengths of light (660 nm, which is red, and 940 nm, which is infrared) that pass through tissue (usually a finger or an earlobe). Light that is not attenuated by the tissue bed is detected. The oximeter calculates the ratio of the pulsatile and mean light absorbances at each wavelength to create a pulse-added absorbance signal, which is assumed to reflect changes in the arterial blood volume in the tissue. The SpO_2 value is derived from the ratio of the pulse-added absorbances at the two wavelengths, which is then compared with a table of arterial oxygen saturations and absorbance ratios derived from volunteers exposed to varying degrees of hypoxia (Table 5). Because the device uses only two wavelengths, it can determine values for only two hemoglobin species: oxyhemoglobin and reduced hemoglobin (Fig. 1). The values may be invalid for patients who have hemoglobin species that have different absorbance spectra, since the SpO_2 is based on data derived from normal volunteers with low levels of carboxyhemoglobin and methemoglobin.[3]

The extinction coefficient of methemoglobin at 660 nm is similar to that at 940 nm, resulting in a red-to-infrared ratio of 1:1 (Fig. 1). The corresponding SpO_2 value for this ratio is approximately 85 percent. Hence, as the methemoglobin level increases, the SpO_2 will tend toward this value. When methemoglobin levels are in excess of 30 percent, the SpO_2 will plateau at 85 percent and will be relatively unaffected by the oxygenation status[4-6] (Fig. 2).

CO-OXIMETRY

The oxygen saturation value often reported with arterial blood gas values is derived mathematically from the arterial partial pressure of oxygen (PaO_2), pH, and temperature, and it reflects the concentration of oxyhemoglobin divided by the sum of oxyhemoglobin and reduced hemoglobin concentrations. This saturation value is sometimes termed

Table 4. Possible Causes of Hypoxemia.

Hypoxia
Decreased inspired oxygen concentration
Hypobaric conditions
Carbon monoxide poisoning
Hypoventilation
Right-to-left shunting
Cardiac
Atrioseptal defect
Transposition of the great arteries
Tetralogy of Fallot
Intrapulmonary
Arteriovenous malformations
Pneumonia
Mismatch of ventilation and perfusion
Asthma
Emphysema
Atelectasis
Pulmonary edema
Decreased partial pressure of oxygen in mixed venous blood
Low cardiac output
Shock
Diffusion abnormalities (very rare at sea level)

Table 5. Terms Used to Denote Oxygen Saturation of Arterial Blood.*

Term	Formula
Oxygen saturation by pulse oximetry (SpO_2)	$k \times (AC_{660}/DC_{660})/(AC_{940}/DC_{940}) + b$
Functional saturation of oxygen (SaO_2)	$[HbO_2]/([HbO_2] + [\text{reduced Hb}])$
Fractional saturation†	$[HbO_2]/([HbO_2] + [Hb] + [COHb] + [metHb]) = [HbO_2]/[\text{total Hb}]$

* The letters k and b denote empirically defined constants, AC_{660} and AC_{940} the pulsatile absorption at 660 and 940 nm, DC_{660} and DC_{940} the nonpulsatile absorption at 660 and 940 nm, HbO_2 oxyhemoglobin, Hb hemoglobin, COHb carboxyhemoglobin, and metHb methemoglobin.
† The fractional saturation is the oxyhemoglobin concentration expressed as a percentage of total hemoglobin concentration.

the functional saturation of oxygen (SaO_2) (Table 5). It does not take into account the presence of carboxyhemoglobin, methemoglobin, or abnormal hemoglobin species. Co-oximeters are multiple-wavelength spectrophotometers that measure the levels of hemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin by using at least four wavelengths, and they can report values for fractional saturation. Fractional saturation reflects the concentration of oxyhemoglobin as compared with the total concentration of all measured hemoglobin species, rather than just the concentrations of oxyhemoglobin and reduced hemoglobin (Table 5).

In this patient, the fractional saturation value on co-oximetry was 89 percent and the value on pulse oximetry was 94 percent. Surprisingly, measurement of the PaO_2 failed to confirm a diagnosis of hypoxemia. What could explain the differences among a fractional saturation of 89 percent determined by co-oximetry, an SaO_2 of 98 percent calculated from the arterial blood gas measurement, and the intermediate SpO_2 values? The most likely explanation is that an abnormality of hemoglobin, such as methemoglobinemia, was present, and that it altered the absorbance characteristics of the patient's blood.

METHEMOGLOBINEMIA

Methemoglobin is formed by oxidation of the iron moiety of hemoglobin, which changes from the normal, ferrous state to a ferric state. Ferric heme is incapable of binding oxygen and causes an allosteric change in the remaining heme moieties of the molecule, which impairs the release of oxygen and shifts the oxyhemoglobin-dissociation curve to the left. Cyanosis may be evident at a methemoglobin concentration of 1.5 g per deciliter (about 10 percent of the hemoglobin).[3,7] Dark skin pigmentation and poor ambient-light conditions can make the detection of cyanosis difficult.

Normally, an equilibrium exists between the proportions of hemoglobin and methemoglobin (methemoglobin usually constitutes approximately 1 percent of the total hemoglobin). For clinically significant methemoglobinemia to occur, at least one of the following factors must be present: a greatly increased production of methemoglobin; an abnormal hemoglobin that, once oxidized, is resistant to reduction; or decreased activity of erythrocytic NADH–cytochrome-b_5 reductase, the primary enzyme responsible for methemoglobin reduction.[8,9]

Acquired Methemoglobinemia

Exposure to many chemicals and drugs can, directly or indirectly, cause methemoglobinemia, which occasionally can be severe and life-threatening. Rarely, sulfhemoglobinemia can also be induced by exposure to drugs or environmental agents. The clinical picture is similar to that of methemoglobinemia, and pulse-oximetry values can be inaccurate.[10]

Hemoglobin Variants

Hemoglobin M variants have an amino acid substitution at or near the heme group, such that methe-

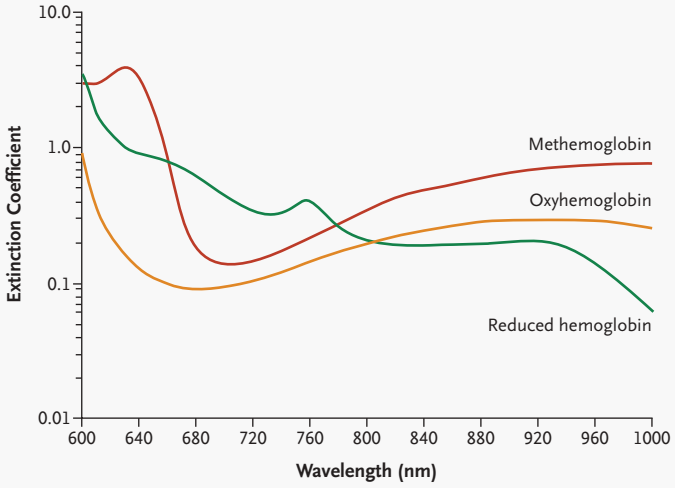

Figure 1. Extinction Curves for Various Hemoglobin Species.

Oxyhemoglobin and reduced hemoglobin have different absorptions at 660 and 940 nm, whereas methemoglobin has similar absorption at the two wavelengths. The extinction coefficient is shown on a logarithmic scale.

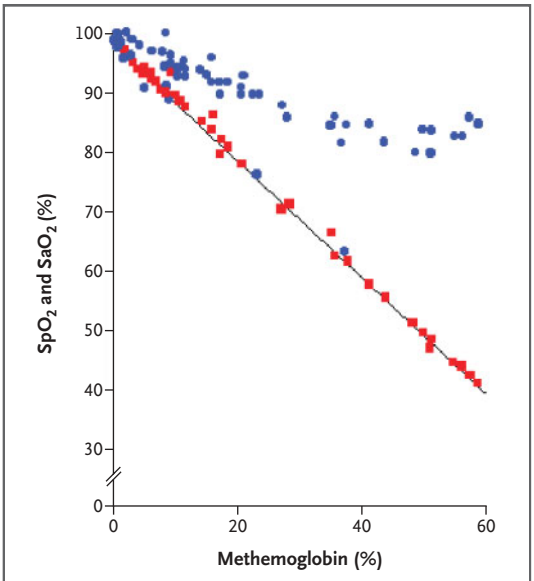

Figure 2. Effect of Methemoglobin on Oxygen Saturation as Measured by Pulse Oximetry.

The ratio of absorbance of methemoglobin at 660 and 940 nm is approximately 1:1, corresponding to a value for oxygen saturation, as measured by pulse oximetry (SpO_2), of approximately 85 percent. As the methemoglobin level increases, the SpO_2 approaches 85 percent. At a methemoglobin level of 30 percent, the SpO_2 plateaus at 85 percent and is unaffected by oxygenation status. Blue circles represent SpO_2, and red squares functional saturation (SaO_2). Adapted from Barker et al.[4]

moglobin becomes unusually resistant to reduction. Inheritance typically follows an autosomal dominant pattern. The presence of hemoglobin M may be suspected when there is a history of parent-to-child transmission of long-standing, unexplained cyanosis.[9] Since the absorption spectrum of hemoglobin M is abnormal, pulse oximetry is an unreliable assessment tool in such patients. In one reported case of anesthetic management in a patient with hemoglobin M_{Iwate} ($\alpha_2{}^{87Tyr}\beta_2$), a pulse oximeter indicated either no value or a reading of 31 to 36 percent, despite a normal PaO_2 value and a normal calculated oxygen saturation.[11] Definitive diagnosis of the presence of hemoglobin M can be made by electrophoresis of the methemoglobin and amino acid analysis.[12] Unexpectedly low SpO_2 readings have been noted in patients with unstable hemoglobin Köln ($\alpha_2\beta_2{}^{98Met}$).[13,14] The low values were also attributed to the altered absorbance spectrum of the abnormal hemoglobin as compared with the spectrum of normal hemoglobin. Finally, other rare hemoglobin variants that have decreased oxygen affinity, which could lead to cyanosis or have decreased rates of methemoglobin reduction, have been described.[9,12]

Recessive Congenital Methemoglobinemia

NADH–cytochrome-b_5 reductase is present in a membrane-bound isoform that is found in all cells and in a soluble form that is present mainly in erythrocytes. The membrane-bound isoform is involved in the desaturation and elongation of fatty acids, in the biosynthesis of cholesterol, and in drug metabolism. The soluble isoform is responsible for methemoglobin reduction. Both isoforms are encoded by a single gene, and more than 30 mutations that affect enzyme activity have been described.[9,15,16] Inheritance of deficiencies of cytochrome-b_5 reductase typically follows an autosomal recessive pattern and leads to recessive congenital methemoglobinemia.[9] Hereditary deficiencies of cytochrome-b_5 reductase have been divided into two types. In type 1, the enzyme deficiency is limited to the soluble form in erythrocytes. A cyanotic appearance usually is the only clinical abnormality. Treatment is usually unnecessary, but patients in whom this deficiency is diagnosed are more susceptible to the effects of methemoglobin-inducing agents.[17]

Ten to 15 percent of patients with recessive congenital methemoglobinemia have deficiencies of both the soluble and bound isoforms of the enzyme (type 2 of the disorder) and have not only methemoglobinemia but also progressive, severe neurologic abnormalities, for which there is no effective therapy.[9,15] Congenital methemoglobinemia can also be caused by a cytochrome-b_5 deficiency, but only a single case has been reported.[18]

SUMMARY AND CONCLUSIONS

This patient had low SpO_2 values on repeated evaluations by pulse oximetry and a decreased fractional oxygen saturation as measured by co-oximetry, despite her healthy appearance and normal PaO_2 and calculated (functional) oxygen saturation. She did not appear cyanotic, but she had had a previous episode of unexplained cyanosis. Overall, the clinical picture is consistent with the presence of methemoglobinemia. Oximetry values and the absence of cyanosis suggest a methemoglobin level of approximately 10 to 15 percent. Acquired causes can be reasonably ruled out by her history of cyanosis, persistently low SpO_2 values, and absence of exposure to methemoglobin-inducing agents. An abnormal hemoglobin is unlikely given the negative family history as well as the normal hemoglobin pattern found on high-performance liquid chromatography. Therefore, the probable diagnosis is a congenital deficiency of erythrocytic cytochrome-b_5 reductase activity (recessive congenital methemoglobinemia, type 1). Appropriate further diagnostic testing would include multiple-wavelength co-oximetry to quantify the degree of methemoglobinemia, and this test could be followed by the measurement of erythrocytic cytochrome-b_5 reductase activity if an elevated methemoglobin level was detected.

DISCUSSION OF MANAGEMENT

There are several case descriptions of the perioperative care of patients with hereditary methemoglobinemia.[8,19,20] Reasonable preoperative recommendations include the maintenance of an increased oxygen concentration in the perioperative period; reliance on arterial blood gas tensions and values obtained by co-oximetry, rather than pulse oximetry,[20] to determine the adequacy of oxygenation; avoidance of methemoglobin-inducing drugs[9]; and treatment with methylene blue if clinically significant methemoglobinemia occurs.

Methylene blue (given intravenously at a dose of 1 to 2 mg per kilogram of body weight) can be used to treat severe cases of methemoglobinemia (in which methemoglobin levels are above 30 percent or there are signs or symptoms of hypoxia). Methylene blue acts as a cofactor that increases the rate of NADPH-dependent methemoglobin reduction. Since the action of methylene blue is dependent on NADPH, the treatment will be ineffective if NADPH levels are low (as they are in glucose-6-phosphate dehydrogenase deficiency) or if NADPH–methemoglobin reductase deficiency is present. High concentrations of methylene blue can act as an oxidant and worsen methemoglobinemia and can cause hemolysis, which may be severe in patients with glucose-6-phosphate dehydrogenase deficiency.[17] Ascorbic acid and riboflavin have been used to reduce methemoglobin levels gradually and may be considered for cosmetic treatment of chronic methemoglobinemia caused by a NADH–cytochrome-b_5 reductase deficiency.[9] Exchange transfusion and hyperbaric oxygen can be considered for refractory life-threatening cases.

In this patient, awareness of her condition, avoidance of drugs known to produce methemoglobin, and the use of methylene blue if necessary should have been sufficient precautions to preclude complications during her operation.

A Physician: Do you think that her initial episode of cyanosis at surgery was caused by her deficiency and a drug that was given?

Dr. Hurford: It is a possibility. She would have been more sensitive to desaturation than someone with normal enzyme function because of the shift in her oxyhemoglobin curve and the increased amount of methemoglobin.

Dr. Nancy Lee Harris (Pathology): Dr. Medoff, you saw this patient in the clinic. Please summarize your thoughts before she had the diagnostic procedure.

Dr. Benjamin D. Medoff (Pulmonary and Critical Care): In my office, the most remarkable thing was how normal she appeared. A normal chest radiograph, normal results on initial pulmonary-function tests, and an unremarkable echocardiogram had ruled out intracardiac or intrapulmonary shunts. I thought that she might have a shunt that was affected by position. I measured her oxygen saturation while she was in various positions, and it never changed. At that point, I considered a hemoglobinopathy or an enzyme deficiency leading to methemoglobinemia as possible diagnoses. I referred her

for a co-oximeter test and hemoglobin electrophoresis.

CLINICAL DIAGNOSIS

Methemoglobinemia due to congenital deficiency of erythrocytic cytochrome-b_5 reductase.

DR. WILLIAM E. HURFORD'S DIAGNOSIS

Methemoglobinemia due to congenital deficiency of erythrocytic cytochrome-b_5 reductase (recessive congenital methemoglobinemia, type 1).

PATHOLOGICAL DISCUSSION

Dr. Alexander Kratz: The diagnostic procedure was co-oximetry, which showed a methemoglobin concentration of 8.6 percent (reference range, 0.4 to 1.5). This methemoglobin level could account for the variability among the values from finger oximetry, calculated saturation, and co-oximetry saturation. To determine the cause of the methemoglobinemia, a specimen of blood was sent to a reference laboratory for evaluation for methemoglobinemia.

The reference laboratory repeated the spectrophotometric measurement of methemoglobin and found a methemoglobin concentration of 5.5 percent. Since methemoglobin levels can decline by 40 percent per day and the specimen had been approximately one day in transit, this result was consistent with the original measurement at our hospital. The reference laboratory then performed a series of tests to determine the cause of the methemoglobinemia. These included determination of the hemoglobin M ratios, hemoglobin electrophoresis, repeated evaluation by high-performance liquid chromatography, and an assay for the presence of cytochrome-b_5 reductase.

Methemoglobinemia due to hemoglobin M does not have the absorbance peak in the range of 630 to 635 nm that is associated with other forms of methemoglobinemia.[21] By converting all hemoglobin to methemoglobin by the addition of potassium ferricyanide and assessing absorbances at 500, 600, and 630 nm, it is possible to determine the presence or absence of hemoglobin M.[21] In this patient, both the A630:A600 ratio and the A500:A600 ratio were in the normal range. This finding argued strongly against the presence of hemoglobin M. To rule out the presence of hemoglobin M definitively, hemoglobin electrophoresis and repeated high-performance liquid chromatography were performed. Hemoglobin electrophoresis showed a pattern of hemoglobins normal for adults; quantification of the hemoglobins by high-performance liquid chromatography indicated that they were present in normal proportions.

Finally, an assay to determine cytochrome-b_5 reductase activity was performed. Cytochrome-b_5 reductase has very strong NADH–ferricyanide reductase activity. The reaction can be summarized by this formula: $K_3Fe(CN)_6 + NADH + H^+ \xrightarrow{\text{cytochrome-}b_5\ \text{reductase}} K_3HFe(CN)_6 + NAD^+$. The results of this assay can be followed spectrophotometrically at 340 nm.[22,23] This method has been advocated as the easiest way to measure enzyme activity.[21] The level of cytochrome-b_5 reductase in the patient under discussion was determined to be 6.9 IU per gram of hemoglobin (reference range, 10.1 to 19.4), consistent with reduced activity of the enzyme.

In summary, on the basis of the elevated methemoglobin level, the normal methemoglobin M absorbance ratios, the normal hemoglobin electrophoretic pattern, the results of high-performance liquid chromatography, and the reduced cytochrome-b_5 reductase activity, the diagnosis of cytochrome-b_5 reductase deficiency was made.

Dr. Harris: If the same gene encodes both the membrane-bound and soluble forms, how can a mutation result in an abnormal soluble form but a normal membrane-bound form?

Dr. Kratz: Some mutations lead to a decrease in the catalytic activity of the protein, which affects both isoforms and causes type 2 disease. Other mutations leave the catalytic activity of the protein intact but cause impaired stability of the enzyme. Since mature erythrocytes (in contrast to other tissues) do not have the ability to synthesize new enzymes, these mutations will be manifested as type 1 disease.[9,24]

Dr. Harris: Did the patient have the planned operation?

Dr. Medoff: With this determination, the anesthesiologist was consulted and the patient underwent surgery. During surgery, methylene blue was kept on hand, and any agents that might cause methemoglobinemia were avoided. There were no complications during the operation, and the patient recovered uneventfully.

Dr. Harris: Is this the kind of inherited susceptibility you would want patients to know about so they can avoid exposures that might be a problem?

Dr. Medoff: This woman now wears a bracelet that says "methemoglobinemia." Her children have begun to undergo the screening process, and her son has been found to have normal oxygen saturation.

PATHOLOGICAL DIAGNOSIS

Methemoglobinemia due to congenital deficiency of erythrocytic cytochrome-b_5 reductase.

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