CASE REPORT

HbM methaemoglobinaemia as a rare case of early neonatal benign cyanosis

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SUMMARY

Early neonatal central cyanosis that is unrelated to cardiopulmonary causes, alerts clinicians to possibility of methaemoglobinaemia. Congenital methaemoglobinaemia due to haemoglobin M is an autosomal dominant disorder characterised by lifelong cyanosis. We report a case presentation and review of diagnostic pitfalls of a newborn who presented with central cyanosis; investigations revealed a low methaemoglobin reductase (2.2 IU/g Hb), with normal maternal levels (9.1 IU/g Hb). Therefore, haemoglobinopathy investigations were completed on the mother and her baby, which showed an α -globin variant in both. The maternal $\alpha 2$ globin gene sequencing showed heterozygosity for haemoglobin M Boston ($\alpha 58$ His $\rightarrow$ Tyr).

BACKGROUND

Early neonatal cyanosis is characterised by a blue skin colour due to lack of oxygen in the blood. Sepsis, congenital heart disease with right to left shunt, congestive heart failure, pulmonary disorders, sulphaemoglobinaemia and haemoglobin variants such as the M group of haemoglobins should be considered in the differential diagnosis of central cyanosis.¹ Cyanosis caused by abnormal forms of haemoglobin can be life-threatening, and early recognition is necessary to prevent delay in management.²

CASE PRESENTATION

A baby boy was born to a 33-year-old (G3, T1, A1, P1, L1) mother at 34⁺⁶ weeks' gestation. The parents were new immigrants to Canada, originally from India. A family history of 'brown blood' in the grandmother, two aunts and the baby's older sibling, was reported (figure 1). The delivery was by caesarean section for ultrasound diagnosed placenta accreta. Antepartum brown vaginal spots and a previous caesarean section were additional indications. The infant was assigned Apgar scores of 5 and 7, at 1 and 5 min, respectively. All his growth measurements were between the 75th and 90th centiles. He received positive pressure ventilation for 4 min due to poor respiratory effort. Thereafter, he started having grunting respiration and was placed on NCPAP for approximately 24 h with a maximum FiO₂ of 100%. After the first 24 h, he tolerated room air. His oxygen saturation remained 40–50% on all measurements in spite of NCPAP with 100% O₂ supplements (figure 2).

INVESTIGATIONS

In view of respiratory distress and persistent cyanosis, chest X-ray, echocardiogram, glucose-6-phosphate dehydrogenase (G6PD) screens, ferritin and peripheral blood film were carried out in addition to routine laboratory investigations; all were reported as normal. The newborn metabolic screen was also normal. Consequently, congenital methaemoglobinaemia was entertained as a diagnostic possibility. Investigations indicated a falsely low oxygen saturation and methaemoglobin measuring error, which occurred with several Co-oximeters. Simultaneous arterial samples were sent to regular ABG analyser and I-STAT analyser, which, surprisingly, showed that O₂ saturation was 94% on room air. Repeated oxygen saturation measurements by Co-oximetry consistently gave results between 40% and 60%, while pO₂ was $\approx$ 76 mm Hg. The baby had persistent cyanosis, but was otherwise clinically stable (figure 3). Haemoglobin electrophoresis, NADH-cytochrome b5 reductase activity and methaemoglobin levels were sent for both the baby and his mother after consulting the paediatric haematologist. The baby gradually worked up to taking his feeds on demand and was discharged home with an appointment for paediatric haematologist follow-up after 3 months.

DISCUSSION

Methaemoglobinaemia is a clinical syndrome caused by either an increase of methaemoglobin in the blood due to congenital changes in haemoglobin synthesis and metabolism or an acute adverse drug reaction (acquired methaemoglobinaemia).

Methaemoglobin is an oxidised form of haemoglobin in which the original ferrous atom (Fe²⁺) is

Figure 1 Baby's blood sample showing chocolate brown appearance.

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Figure 2 Baby on NCPAP with 100% O₂ supplements.

oxidised to a ferric atom (Fe³⁺). The ferric atom then causes an allosteric change in the heme portion of the oxidised haemoglobin molecule causing an increase in its oxygen affinity but a functional decrease in its oxygen binding capacity.³ Not only is the tissue hypoxia due to a leftward shift of the oxygen saturation curve but it can also be related to the reduction of free haemoglobin to transport oxygen to the tissues (a relative anaemia). Clinically, these two mechanisms will produce central cyanosis that is unresponsive to oxygen therapy.³ In addition, the absorption spectrum of methaemoglobin differs from that of reduced haemoglobin, giving the blood a chocolate-brown colour when present in sufficient amounts.³

The signs and symptoms of methaemoglobinemia vary depending on the amount of methaemoglobin present. Cyanosis and brown blood may be present with 10–20% methaemoglobin levels; dyspnoea, nausea and tachycardia may be present at 30% methaemoglobinemia; and lethargy, syncope, loss of consciousness and coma may occur at levels approaching 55%.³ Levels above 70% are incompatible with life. An enzyme called methaemoglobin reductase (also known as NADH-cytochrome b5 reductase) normally reduces the iron in haemoglobin, maintaining 98% of haemoglobin in the reduced state.⁴ So the methaemoglobin concentration remains <2% in normal conditions.

Family history is very useful in differentiating hereditary methaemoglobinemia due to methaemoglobin reductase deficiency from HbM disease; the former has an autosomal recessive mode of inheritance while the latter has a dominant mode. All the earlier reported variants have had an autosomal dominant inheritance.⁵ The family pedigree of our case revealed that, in each generation, cyanosis was noted, suggesting a dominant mode of inheritance.

Figure 3 Baby on room air with central cyanosis on the second day of life.

The positive family history of brown blood led to suspicion of a congenital cause for the methaemoglobinemia. The patient's methaemoglobin reductase activity was found to be low at 2.2 IU/g Hb. Adult levels of enzyme function are attained by 3 months of age (8.2–19.2 IU/g Hb), and, in neonates, methaemoglobin reductase levels are normally 60% of the normal adult value.⁶ The maternal methaemoglobin reductase activity in this case was within the reference range at 9.1 IU/g Hb, ruling out methaemoglobin reductase deficiency. Investigations for a haemoglobinopathy were then initiated.

Haemoglobin analysis by high-performance liquid chromatography showed a characteristic pattern of α chain globin variants, for both mother's and baby's blood.

However, initial haemoglobinopathy studies may not be definitive. Interestingly, the chromatography profile did not resemble that of any M haemoglobin found in two independent databases of haemoglobin variants.⁷ The best accepted match according to both of these databases was haemoglobin Q (HbQ) India. Subsequently, Q India and haemoglobin M overlap has been described recently by Estey *et al* (2015), for the same baby and his mother.⁸ Therefore, α -globin gene sequencing was also performed. The results indicated heterozygosity for HbM Boston (α 58 His→Tyr), a rare variant.⁹ The resultant amino acid change leads to a conformational change in the α -globin that contributes to the clinical findings observed in this case, including methaemoglobinemia with cyanosis and the characteristic brown blood that is associated. In addition, the conformational change alters the absorption spectrum of HbM Boston relative to both haemoglobin A and methaemoglobin A,¹⁰ and therefore affects the apparent oxygen saturation measured by Co-oximetry. While this is also the case for other M haemoglobins, it is not typical of acquired methaemoglobinemia or methaemoglobin reductase deficiency.¹⁰ Treatment is not required for this HbM variant. Finally, the importance of early diagnosis is imperative to avoid unnecessary investigations and to alleviate concern for the patient and the family.¹⁰

Learning points

- ▶ Early neonatal methaemoglobin reductase measurements may be unreliable for diagnosis of deficiency, as there is no stabilised reference for this age.
- ▶ Repeating decreased levels after a few months may be necessary (low nicotinamide adenine dinucleotide cytochrome b5 reductase level in the baby is most likely an age-related decrease in enzyme levels, not a true deficiency).
- ▶ Different haemoglobin variants may have similar high-performance liquid chromatography profiles, as is observed for HbM Boston and haemoglobin Q India.
- ▶ Use of arterial blood gases may be helpful in the diagnosis of methaemoglobinemia, especially if Co-oximetry for measurement of oxygen saturation shows error codes.
- ▶ ABG measurement of oxygen saturation and methaemoglobin concentration can be a simple measure to differentiate between the HbM and cytochrome b5 reductase deficiency types of methaemoglobinemia. Haemoglobin M usually results in an error code on Co-oximetry assessment, whereas oxygen saturation measured by blood gas analysis provides a higher (true) oxygen saturation and PaO₂. Cytochrome b5 reductase deficiency would result in an increase in methaemoglobin by Co-oximetry that is mirrored on blood gas analysis.

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Contributors MSE conceptualised and designed the study, drafted the initial manuscript and approved the final manuscript as submitted. MJB and SE reviewed and revised the manuscript, and approved the final manuscript as submitted. GC coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted.

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