CASE REPORT

Congenital methemoglobinaemia due to Hb F-M-Fort Ripley in a preterm newborn

Satvinder Ghotra, Krista Jangaard, Chantale Pambrun, Conrad Vincent Fernandez

IWK Health Center, Halifax,
Nova Scotia, Canada

Correspondence to

Dr Conrad Vincent Fernandez,
conrad.fernandez@iwk.
nshealth.ca

Accepted 24 February 2016

SUMMARY

Methemoglobinaemia is a rare cause of cyanosis in newborns. Congenital methemoglobinaemias due to M haemoglobin or deficiency of cytochrome b5 reductase are even rarer. We present a case of congenital methemoglobinaemia presenting at birth in a preterm infant. A baby boy born at 29 weeks and 3 days of gestation had persistent central cyanosis immediately after delivery, not attributable to a respiratory or cardiac pathology. Laboratory methemoglobin levels were not diagnostic. Cytochrome b5 reductase levels were normal and a newborn screen was unable to pick up any abnormal variants of fetal haemoglobin. Genetic testing showed a γ globin gene mutation resulting in the M haemoglobin, called Hb F-M-Fort Ripley. The baby had no apparent cyanosis at a corrected gestational age of 42 weeks. Although rare, congenital methaemoglobin aemia should be considered in the differential in a preterm with central cyanosis and investigated with genetic testing for γ globin chain mutations if other laboratory tests are non-conclusive.

BACKGROUND

Methemoglobinaemia is an uncommon cause of cyanosis in newborns, which can be congenital or acquired in origin.¹ The acquired form is more common and occurs secondary to exposure to oxidising agents.^{2–6} Congenital forms are extremely rare and caused either by variant haemoglobins, called M haemoglobins or by deficiency of enzyme cytochrome b5 reductase.^{1 7 8}

M haemoglobins are haemoglobin (Hb) A or F mutants that are partially oxidised to methemoglobin (MetHb) and poorly oxygenated. M haemoglobins are more commonly associated with α or β globin chain variants, but may also arise from γ globin chain mutations. The Hb F-M-Fort Ripley mutation (HBG2: c.227 C>T) is a missense mutation in the γ chain, leading to replacement of the histidine residue at codon 92 with tyrosine.⁸ As result of this, the haeme iron remains stabilised in the ferric state and is relatively resistant to reduction by cytochrome b5 reductase. We report a very preterm infant presenting with cyanosis at delivery secondary to Hb F-M-Fort Ripley mutation. Further, the diagnostic and management challenges of congenital methemoglobinaemia in a very preterm baby are discussed.

CASE PRESENTATION

A male baby was born to a 30-year-old primigravida woman of Scottish origin at 29 weeks and 3 days gestation by urgent caesarean section

indicated for haemolysis, elevated liver enzymes and lower platelets syndrome. The mother received β methasone, magnesium sulfate and morphine prior to delivery.

The baby was born with a heart rate of <60 bpm and poor respiratory efforts. Initial resuscitation was performed as per the neonatal resuscitation guidelines, with positive pressure ventilation. With this, the heart rate improved to >100/min, but the baby was centrally cyanosed with shallow respiratory efforts. A dose of naloxone was administered. Respiratory efforts improved but the baby remained cyanosed with pulse oximetry saturation (SpO₂) around 70% while in room air. He was intubated at 10 min of age and given 100% fraction of inspired oxygen (FiO₂). With this, SpO₂ improved to 84%. Apgar scores were 2 and 7 at 1 and 5 min, respectively.

The baby measured appropriate for gestational age. After admission to the Neonatal Intensive Care Unit, he was started on synchronised ventilation with pressures of 21/6, 60 breaths/min and 100% FiO₂. In view of possible respiratory distress syndrome (RDS), a dose of surfactant was administered. Despite all this, the SpO₂ remained in the low 80's. A trial of lower FiO₂ at 40% was undertaken with no change in the SpO₂.

INVESTIGATIONS

Chest X-ray was consistent with mild RDS, with evidence neither of cardiomegaly nor lung malformation. Echocardiography was normal and no pulmonary arterial hypertension was found. Arterial blood gas revealed respiratory alkalosis with pH 7.43, PaO₂ 86 (on 40% FiO₂), PaCO₂ 33 and HCO₃ 21.6. However, base excess could not be calculated. The oxygen saturation gap could also not be calculated as SpO₂ on arterial blood gases was not measurable due to interfering substances. The results of conventional co-oximetry were not reported by the laboratory due to an unstable measurement possibly secondary to some interfering substances. Hb –177 g/L, haematocrit (49%) and serum lactate (1.2 mmol/L) were normal.

The baby's blood was sent to the Mayo Clinic and it reported a MetHb level of 1.7%, which was slightly above the normal cut-off of 1.5%. Cytochrome B5 reductase enzyme levels were normal for age (4.3 U/g Hb). Glucose-6-phosphate dehydrogenase levels were also normal. The baby was screened for abnormal fetal Hb. There was no variant Hb detected by the newborn screening for haemoglobinopathy carried out by high-performance liquid chromatography (HPLC,

CrossMark

To cite: Ghotra S, Jangaard K, Pambrun C, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214381

Variant nbs BioRad) nor on an alkaline capillary electrophoresis (Capillarys 2 Neonat Fast). Additional testing to rule out variant fetal Hb was performed via γ gene analysis. The results of genetic testing received around 3 weeks of age showed that the baby was heterozygous for the Hb F-M-Fort Ripley mutation.

When discussing the results of the initial haematological tests with the family, the grandmother revealed that the baby's mother also had cyanosis as a newborn, attributed to a heart disease. A review of maternal records revealed the actual diagnosis of methemoglobinemia. The mother was a term baby and the cyanosis resolved within a few weeks after birth. The grandmother also indicated that she herself and 2 maternal great uncles were also 'blue babies' (figure 1). There was no consanguinity. No genetic testing was performed on any of these previous individuals.

TREATMENT

The baby was managed with a presumptive diagnosis of methemoglobinemia. He was successfully extubated to continuous positive airway pressure support with 21% FiO₂ on day 3 of life. However, he went on to develop bronchopulmonary dysplasia and required bi-level positive airway pressure support with 50% FiO₂. Oxygen therapy was guided by PaO₂, which was targeted between 40 and 60 mm Hg. Subsequently, pulse oximetry was titrated to target PaO₂ on blood gases and this gave the baby a target SpO₂ of 78–82%. No specific therapy was administered for methemoglobinemia. He received packed red blood cells on day 18 at a corrected gestational age of 32 weeks of life for a Hb level of 103 g/L. After transfusion, his SpO₂ transiently went up to 92%. He was discharged home on 200cc of 100% FiO₂ at a corrected gestational age of 38 weeks. His SpO₂ at discharge was 85–87%.

OUTCOME AND FOLLOW-UP

The baby had no apparent cyanosis and an SpO₂ of 92% at a corrected gestational age of 42 weeks. The neurological examination and developmental assessment was age appropriate at 12 months corrected age.

DISCUSSION

We described a very preterm baby presenting with cyanosis at delivery secondary to Hb F-M-Fort Ripley. To our knowledge,

this is the first report of congenital methemoglobinemia due to abnormality of a fetal Hb in a very preterm infant.

Hb FM-Fort Ripley was first described in a late preterm baby in 1989, by Priest *et al.*⁸ with a second reported case in a term baby in 1992 by Molchanova *et al.*⁹ Both babies were asymptomatic at birth and presented at a few days of age with no major concerns other than cyanosis. An early presentation at delivery coupled with the extreme preterm birth was a unique feature in our case.

Although co-oximetry has been described as the gold standard for diagnosis of methemoglobinemia, it was not confirmatory in our case. The metHb levels were not significantly elevated. This could be explained by the fact that Hb F-M-Fort Ripley is unstable and, therefore, quantitative analysis for abnormal Hb may not be diagnostic in such cases.^{8 9} Although Hb electrophoresis can identify M haemoglobins derived from the β and α genes, this γ gene variant does not separate by electrophoresis or chromatography, hence it was not detected by the newborn screening for haemoglobinopathy performed on two platforms: HPLC, VariantnbsBioRad and Capillarys 2 Neonat Fast. Genetic testing for γ chain mutations confirmed the diagnosis of congenital methemoglobinemia due to Hb FM-Fort Ripley. Family history was also supportive for congenital methemoglobinemia as the disease follows an autosomal dominant pattern of inheritance with variable penetrance.¹⁰

The presence of methemoglobinemia also complicated the management of underlying respiratory illness in this premature infant. O₂ therapy was guided by PaO₂, as SpO₂ on pulse oximetry was not reliable. Pulse oximeter yields information based on the ratio of light absorbance of oxyhaemoglobin (940 nm) and deoxyhaemoglobin (660 nm). Since MetHb absorbs light equally at both wavelengths (940 and 660), it displays a falsely low SpO₂ on pulse oximetry. Arterial PO₂ reflects the amount of oxygen dissolved in the arterial blood and should be used to guide the need of oxygen therapy. Arterial PO₂ targets (40–60 mm Hg) for preterm babies were used in our case. Subsequently, pulse oximetry was titrated to target PaO₂ on arterial blood gases and SpO₂ was targeted for 78–82%, which is lower than the usual targeted SpO₂ (88–92%) for preterm gestation.¹¹

Treatment of methemoglobinemia depends on the clinical severity and underlying cause.^{12 13} Exchange transfusion may be an option in severe forms. Methylene blue and ascorbic acid are also some of the potential therapies available for treatment, and are recommended when MetHb levels are >30%. However, their role in M haemoglobin is unclear as abnormal Hb may be resistant to reduction.^{7 13} The two cases of Hb F-M-Fort Ripley reported in the literature were asymptomatic other than cyanosis and did not require any therapy. We did not have exact serum measurements of MetHb in our baby. Thus, other markers of tissue hypoxia such as metabolic acidosis or elevated lactate were monitored and no specific therapy was administered for methemoglobinemia as they were normal. A lower threshold for blood transfusion was chosen due to concurrent methemoglobinemia.

The cyanosis was transient and completely resolved at follow-up. Given that Hb F-M-Fort Ripley is caused by a mutation in the γ gene, the symptoms are expected to be transient and gradually improve as the HbF converts to HbA, and less γ globin is produced over the first year of life.

Prenatal genetic testing may be an option in subsequent pregnancies given the autosomal dominant mode of inheritance of the disease. Although prenatal testing is available, given the risk associated with obtaining the amniotic fluid or chorionic villous

Figure 1 Pedigree chart.

sampling and given the lack of prenatal intervention, its role would be very limited.

Learning points

- ▶ Congenital methemoglobinemia should be considered in the differential of a preterm baby with central cyanosis after respiratory and cardiac causes have been excluded.
- ▶ Although co-oximetry has been described as the gold standard for diagnosis of methemoglobinemia, it may not be useful in Hb F-M-Fort Ripley, as this form is unstable.
- ▶ Although haemoglobin electrophoresis can identify M haemoglobin derived from the β and α genes, this γ gene variant does not separate by electrophoresis or chromatography, hence newborn screening for haemoglobinopathy may not be diagnostic in such a case.
- ▶ A family history and genetic testing may prove diagnostic for congenital methemoglobinemia, when co-oximetry results are non-conclusive.
- ▶ Oxygen therapy should be guided by PaO₂, as SpO₂ on pulse oximetry is not reliable in methemoglobinemia.

Acknowledgements The authors are thankful to Drs. Rasoul Koupaei and Sandhya Parkash and Miss Ashley Smith for their valuable contribution in managing this challenging case.

Contributors SG drafted the initial version of the manuscript. All the authors contributed to patient management, revising the manuscript and approving the final version.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Da-Silva SS, Sajan IS, Underwood JP III. Congenital methaemoglobinemia: a rare cause of cyanosis in the newborn—a case report. *Pediatrics* 2003;112:e158–61.
- 2 Hjelt K, Lund JT, Sherling B, *et al.* Methaemoglobinemia among neonates in a neonatal intensive care unit. *Acta Paediatr* 1995;84:365–70.
- 3 Mehler K, Oberthuer A, Weisshaar G, *et al.* Hemolytic anemia and methemoglobinemia in a preterm baby as a complication of antenatal intraamniotic injection of toluidine blue. *Klin Paediatr* 2013;225:263–5.
- 4 Allegaert K, Miserez M, Lerut T, *et al.* Methemoglobinemia and hemolysis after enteral administration of methylene blue in a preterm infant: relevance for pediatric surgeons. *J Paediatr Surg* 2004;39:E35–7.
- 5 Voelker CA, Brown L, Hinson RM. Perioperatively acquired methaemoglobinemia in a preterm infant. *Paediatr Anaesth* 2002;12:284–6.
- 6 Jinnou H, Sugiura H, Kikuchi S, *et al.* Unexplained late-onset hemolysis and methemoglobinemia in a preterm infant. *Paediatr Int* 2011;53:1084–7.
- 7 Glader B. Hemoglobin FM-Fort Ripley: another lesson from the neonate. *Pediatrics* 1989;83:792–3.
- 8 Priest JR, Watterson J, Jones RT, *et al.* Mutant fetal hemoglobin causing cyanosis in a newborn. *Pediatrics* 1989;83:734–6.
- 9 Molchanova TP, Wilson JB, Gu LH, *et al.* A second observation of the fetal methemoglobin variant Hb F-M-Fort Ripley or alpha 2G gamma 2(92)(F8)His—Tyr. *Hemoglobin* 1992;16:389–98.
- 10 Hain RD, Chitayat D, Cooper R, *et al.* Hb FM-Fort Ripley: confirmation of autosomal dominant inheritance and diagnosis by PCR and direct nucleotide sequencing. *Hum Mutat* 1994;3:239–42.
- 11 Manja V, Lakshminrusimha S, Cook DJ. Oxygen saturation target range for extremely preterm infants: a systematic review and meta-analysis. *JAMA Paediatr* 2015;169:332–40.
- 12 Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999;34:646–56.
- 13 Bento C, Magalhães Maia T, Carvalhais I, *et al.* Transient neonatal cyanosis associated with a new Hb F variant: Hb F viseu. *J Paediatr Hematol Oncol* 2013;35:e77–80.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow