CASE REPORT

MYH9-related disorders: a rare cause of neonatal thrombocytopaenia

Maria Inês Marques,^{1,2} Luísa Carrington Queiró,¹ Ana Rita Prior,³ Madalena Lopo Tuna³¹Paediatric Department, Centro Hospitalar de Lisboa Ocidental EPE, Lisboa, Portugal²Paediatric Department, Centro Hospitalar Tondela-Viseu, Viseu, Portugal³Neonatal Intensive Care Unit, Centro Hospitalar de Lisboa Ocidental EPE, Lisboa, Portugal

Correspondence to

Dr Maria Inês Marques, mariainesmarques@gmail.com

Accepted 11 July 2018

SUMMARY

Myosin heavy chain 9-related disorders (MYH9RD) are a genetic condition characterised by large platelets and thrombocytopaenia. The May-Hegglin anomaly (MHA), an uncommon condition with a potential risk of bleeding complications once thought to be separate, is now known to be part of MYH9RD.

There are very limited data on the clinical course and neonatal/paediatric outcome in children with MHA. We present the case of a newborn with a normal physical examination whose mother had MHA. Peripheral blood examination revealed a platelet count of $16 \times 10^9/L$ with giant platelets and neutrophils containing Döhle bodies. Neonatal brain ultrasound examination showed no haemorrhage. The infant received three platelet transfusions during the first 29 days of life, remaining asymptomatic. The genetic molecular test was positive for MYH9RD. It is important to identify at-risk infants with this condition and to initiate therapy to prevent related complications, if needed, in a multidisciplinary team approach.

BACKGROUND

Thrombocytopaenia is relatively rare in the general newborn population. It is typically defined as a platelet count of less than $150 \times 10^9/L$ and further subdivided into mild, moderate and severe. The latter is associated with bleeding and significant morbidity.^{1,2}

Causes of neonatal thrombocytopaenia can be classified by several methods, including platelet size, mode of acquisition, early or late onset, gestational age or underlying pathological mechanisms. The aetiology is either increased destruction of platelets (the most common mechanism) or decreased production of platelets.

Causes of neonatal thrombocytopaenia due to decreased platelet production include genetic disorders,² one of which is myosin heavy chain 9-related disorders (MYH9RD). The May-Hegglin anomaly (MHA), an autosomal-dominant disease characterised by macrothrombocytopaenia and inclusion bodies in the white blood cells, is one of this spectrum of disorders.^{1–5} MYH9RD is caused by mutations in the MYH9 gene, located in the long arm of chromosome 22q, which encodes the non-muscle myosin heavy chain—that appears to be an important cytoskeletal contractile protein in haematopoietic cells.^{3,5–9}

There are no specific guidelines on platelet transfusion for asymptomatic neonates with this

condition. By reporting this case, we want to show our own experience on the management of this rare disease.

CASE PRESENTATION

After an uneventful term pregnancy, a small for gestational age female baby was delivered. The mother, maternal grandmother, maternal great-uncle and maternal great-grandmother were affected with MHA, though none with regular follow-up. The infant was born by caesarean section due to stationary delivery. The mother had a $32 \times 10^9/L$ platelet count before surgery, requiring platelet transfusion.

INVESTIGATIONS

The newborn was subjected to a regular physical examination and showed no signs of bleeding, petechiae or congenital abnormalities. However, given her family history, she had laboratory investigation on the first day of life. The infant's initial platelet count was $16 \times 10^9/L$ 4 hours and $11 \times 10^9/L$ 7 hours after birth. She was therefore admitted for a 20 mL/kg platelet transfusion. Peripheral blood examination revealed giant platelets and neutrophils containing irregular sky-blue intracytoplasmic inclusions similar to Döhle bodies. A neonatal brain ultrasound showed no signs of haemorrhage.

DIFFERENTIAL DIAGNOSIS

In the past, the conditions included in MYH9RD used to be categorised in distinct syndromes that include, in addition to MHA, the Fechtner, Sebastian and Epstein syndromes. They were all characterised by thrombocytopaenia with giant platelets, and on the basis of morphological aspects of Döhle-like bodies and different combinations of the other manifestations of MYH9RD: hearing loss, glomerular nephropathy and cataracts—summarised in table 1.^{3,5–7} The clinical distinction between these disorders was difficult, its pathophysiology was not clearly understood and there may be variable expressions at different ages.^{1,5,8} Ultrastructural features of leucocyte inclusion bodies differentiate Sebastian syndrome from MHA.⁷ Therefore, these syndromes are now recognised to be related disorders, and it has been suggested that they should be referred to as MYH9-related disorders.^{6,7}

OUTCOME AND FOLLOW-UP

Haematology consultation recommended platelet transfusions during the neonatal period when the

© BMJ Publishing Group Limited. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Marques MI, Carrington Queiró L, Prior AR, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2018-224510

Table 1 MYH9-related disorders

Syndrome	Macrothrombocytopaenia	Neutrophilic inclusions	Sensorial hearing loss	Nephritis	Cataracts
May-Hegglin	Present	Present	Absent	Absent	Absent
Sebastian	Present	Present	Absent	Absent	Absent
Fechtner	Present	Present	Present	Present	Present
Epstein	Present	Absent	Present	Present	Absent

platelet count dropped below $30 \times 10^9/L$ with weekly surveillance in the first month. During this period, the baby remained asymptomatic. However, her platelet count remained low ($93 \times 10^9/L$ at day 2 and $65 \times 10^9/L$ at day 4 after birth) during the 4-day hospital stay, but with no need for further transfusion. She was monitored during the first month as recommended, requiring additional platelet transfusions at days 11 (platelet count of $23 \times 10^9/L$) and 29 (platelet count of $9 \times 10^9/L$). A genetic analysis identified a heterozygous variant c.4270G>A in the MYH9 gene, which confirmed the diagnosis of MYH9RD. Ophthalmological and audiological abnormalities were excluded.

DISCUSSION

MHA (OMIM #155100)⁵ is an autosomal-dominant disease first reported in 1909 by Richard May and later by Hegglin.^{4 8} It is characterised by a triad of giant platelets, mild to moderate thrombocytopaenia and leucocyte Döhle-like inclusion bodies.^{1–5}

Data on MHA or MYH9RD incidence worldwide are scarce. Clinical manifestations vary from mild to severe bleeding episodes, including epistaxis, easy bruising, gum bleeding, heavy menstrual bleeding and bleeding after surgery.^{6 8} Although life-threatening cases of haemorrhage have been reported, bleeding diathesis generally tends to be mild.³ Thrombocytopaenia may develop in utero and rarely causes fetal or neonatal intracranial haemorrhage.¹

The diagnosis of MHA is made by a careful assessment of the peripheral blood film in order to recognise its characteristic morphological findings on white blood cells and platelets.^{1 4 5 8} In patients without leucocyte inclusion bodies, immunofluorescence study of neutrophils can be an alternative. In MHA, platelet function is frequently preserved, and the cause of thrombocytopaenia is thought to be abnormal fragmentation of megakaryocytes.^{3 8} Confirmatory diagnosis is made by molecular testing for the MYH9 gene.^{6 8}

A systematic review of MHA during pregnancy revealed a neonatal outcome including 78 live neonates and two intra-uterine fetal deaths. Thirty-four neonates had thrombocytopaenia and subsequently were diagnosed with MHA. Three of them required platelet transfusion prophylactically, as they developed very low platelet counts. No obvious bleeding complications were reported.⁸

Like in all autosomal dominant disorders, a fetus born to a mother with MYH9RD/MHA has 50% chance of being affected with a low platelet count,^{6 8} which means they have a potential risk of bleeding complications including intracranial haemorrhage. Due to the rarity of this condition and the lack of available data, this risk is unquantified. A blood sample via cordocentesis can be used to evaluate platelet count and help deciding about the optimal mode of delivery. However, this prenatal procedure is controversial, invasive and can be responsible for fetal bleeding.⁸

Patients with MYH9RD are usually managed with local measures for minor bleeding; occasionally they may require platelet transfusion to stop or prevent serious haemorrhage.⁹ Bleeding and severe thrombocytopaenia in these neonates

are clear indications for the need to perform platelet transfusions.^{1 2} Abnormalities in platelet function are not necessarily predictive of the possibility of clinical bleeding.² Nevertheless, some authors recommend that prophylactic platelet transfusions are required only when the platelet count falls below $50 \times 10^9/L$ during the first week and below $30 \times 10^9/L$ after that. Larger volumes (20 mL/kg) are usually well tolerated and seem to produce a more significant increase in platelet count compared with minor volumes (10 mL/kg).¹ This is not consensual, and there is no recommendation regarding the optimal dose of platelets to administer or when to administer further transfusions for asymptomatic neonates with MYH9RD.^{1 2 8} Most physicians (both paediatricians and haematologists) treat asymptomatic thrombocytopaenic neonates whenever the platelet count is below $10 \times 10^9/L$, regardless of age.⁸

In our case, due to the fact that we were dealing with a neonate, with no specific guidelines for this condition on this population, and by suggestion of the paediatric haematologic department, the authors decided to administer prophylactic platelet transfusions in the first month of life whenever platelet count was below $30 \times 10^9/L$.

Learning points

- Myosin heavy chain 9-related disorders (MYH9RD) are often under-reported and frequently misdiagnosed. A careful assessment of the peripheral blood smear is important, and its triad could help in the correct diagnosis of this condition, along with family history.
- There are very limited data in the literature on the clinical course and neonatal/paediatric outcome in children with MYH9RD.
- Their diagnosis is challenging during the neonatal period, and a misdiagnose can be associated with adverse neonatal outcomes such as thrombocytopaenia which presents a potential risk of bleeding complications. As a result, it is important to identify at-risk infants, and if needed, initiate therapy to prevent associated complications.
- Joint management by neonatologists and paediatric haematologists is required to minimise risk.
- Future studies should define more clearly the safe lower limit for platelet counts within these different groups of neonates in order to establish which neonates could benefit from platelet transfusion.

Acknowledgements The authors wish to thank Dr Anabela Morais from Paediatric Haematology Department and Dr Juliette Dupont from Genetic Department, both from Centro Hospitalar Lisboa Norte.

Contributors All authors, in addition to being involved in the patient's care, made an individual contribution to the writing of this article and approve the version submitted. MIM, ARP, MLT: were present at the birth of this child, which forced us to research and inspired us to share this challenge. LCQ: followed up the patient during her hospitalisation. MIM, LCQ: did the main research for this article, its design and conception. ARP, MLT: reviewed the article. All authors reviewed and agree with all the changes suggested by the reviewers.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Roberts I, Stanworth S, Murray NA. Thrombocytopenia in the neonate. *Blood Rev* 2008;22:173–86.
- 2 Fernandes CJ. Causes of neonatal thrombocytopenia. 2016 www.uptodate.com (accessed 31 Jan 2017).
- 3 Scurlock D, Nguyen A, Wahed A. Pathologic quiz case: twin neonates with thrombocytopenia. May-Hegglin anomaly. *Arch Pathol Lab Med* 2005;129:111–2.
- 4 Elhassani SB, Gilbert-Barness E. Pathological case of the month. May-Hegglin anomaly. *Am J Dis Child* 1992;146:1097–8.
- 5 Drachman JG. Inherited thrombocytopenia: when a low platelet count does not mean ITP. *Blood* 2004;103:390–8.
- 6 Savoia A, Pecci A. MYH9-Related Disorders. In: Adam MP, Ardinger HH, Pagon RA, eds. *GeneReviews® [Internet]*: Seattle (WA) University of Washington, Seattle:1993–2018.
- 7 Ban BH, Shah V. MYH9-Related Thrombocytopenia. *Mayo Clin Proc* 2017;92:1169–70.
- 8 Hussein BA, Gomez K, Kadir RA. May-Hegglin anomaly and pregnancy: a systematic review. *Blood Coagul Fibrinolysis* 2013;24:554–61.
- 9 Alarcón PA, Werner EJ, Christensen RD. Platelet disorders. *Neonatal hematology: pathogenesis, diagnosis, and management of hematologic problems*. 2nd ed. New York: Cambridge University Press, 2013.

Copyright 2018 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