CASE REPORT

Haemolytic anaemia after nitrofurantoin treatment in a pregnant woman with G6PD deficiency

Lidewij van de Mheen,¹ Simone M Smits,² Wim E Terpstra,³ Anja Leyte,² Dick J Bekedam,¹ Eline S A van den Akker¹

¹Department of Obstetrics & Gynecology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

²Department of Clinical Chemistry, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

³Department of Hematology, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands

Correspondence to

Lidewij van de Mheen, lidewijvandemheen@gmail.com

Lidewij van de Mheen and Simone M Smits contributed equally to the manuscript and are shared first author of this paper.

Accepted 4 April 2014

SUMMARY

We present a normotensive, pregnant woman with severe haemolytic anaemia in the third trimester of pregnancy. Owing to normal platelet count diagnoses other than HELLP syndrome were considered and investigated. The patient was treated with nitrofurantoin 3 weeks before presentation and she turned out to have a deficiency of glucose-6-phosphate dehydrogenase. After treatment with blood transfusion, vitamin B₁₂ and folic acid the patient recovered completely. Caesarean delivery was performed because of maternal hypertension and fetal distress at 33 weeks' gestation.

BACKGROUND

Haemolytic anaemia is a common problem in the third trimester of pregnancy and is usually a part of HELLP syndrome. However, in atypical presentations one should consider other aetiology of haemolysis. We present a woman with haemolytic anaemia in third trimester of pregnancy that was caused by a deficiency of glucose-6-phosphate dehydrogenase (G6PD) after the patient was treated with nitrofurantoin for urinary tract infection. As this is a widely used drug in pregnant women we think that this case is of high importance for all healthcare professionals that work with pregnant women.

CASE PRESENTATION

A 28-year-old Dutch woman of Negroid ethnicity was admitted to the hospital at a gestational age of 32 6/7 weeks, with haemolytic anaemia. During a previous pregnancy, she had a second trimester loss due to cervical incompetence with operative placental removal and haemorrhagia post partum requiring blood transfusion. In the current pregnancy, because of cervical shortening, a secondary cerclage was applied at a gestational age of 15 weeks. At the same time, weekly intramuscular Proluton injections were started. At a gestational age of 29 weeks she developed cystitis which was treated with nitrofurantoin.

At 32 weeks and 6 days' gestation, our patient was seen at a regular visit. She complained about dizziness and weakness, both existing for a few weeks and being progressive. Other symptoms were decreased appetite, abdominal pain and diarrhoea since 1 day. There was no history of chronic diarrhoea or weight loss and the patient was well nourished, using a normal diet.

The patient was normotensive; she had severe anaemia, normal platelet count and proteinuria.

INVESTIGATIONS

On examination she had a blood pressure 105/65 mm Hg, heart rate 72 bpm and temperature 37.5°C. Abdominal examination showed a non-tender uterus according to the gestational age. Abdominal sonography showed an estimated fetal weight of 1718 g (p20–50), normal umbilical artery Dopplers and oligohydramnion.

A complete blood count revealed normocytic anaemia with haemoglobin (Hb) 3.1 mmol/L (7.5–10.0 mmol/L), mean corpuscular volume 91.2 fL (80.0–100.0 fL), haematocrit 0.15 L/L (0.35–0.45 L/L) and normal white cell count ($7.4 \times 10^9/L$, reference range $4.0\text{--}10.0 \times 10^9/L$) and platelet count ($220 \times 10^9/L$, reference range $150\text{--}400 \times 10^9/L$). Other tests showed alanine aminotransferase 23 IU/L (<35 IU/L); aspartate aminotransferase 85 IU/L (<30 IU/L), creatinine 80 µmol/L (50–95 µmol/L), uric acid 0.57 mmol/L (0.11–0.45 mmol/L), C reactive protein 34 mg/L (<10 mg/L) and venous blood gas (measured after blood transfusion) pH 7.38 (7.35–7.45); partial pressure of carbon dioxide 24 mm Hg (36–44 mm Hg) and bicarbonate 13.9 mmol/L (22.0–29.0 mmol/L). With these laboratory results HELLP syndrome was considered. However, a low platelet count, not seen here, is the best indicator of HELLP¹ and therefore additional blood tests were performed. Haemolysis was revealed by elevated lactate dehydrogenase 5334 IU/L (<250 IU/L), slightly elevated bilirubin 19 µmol/L (<17 µmol/L) and low haptoglobin <0.10 g/L (0.40–2.45 g/L). The direct antiglobulin test was negative. Follow-up testing further revealed high ferritin 979 µg/L, decreased folic acid 3.6 nmol/L and low vitamin B₁₂ 104 pmol/L. Urinalysis demonstrated proteinuria (3+), with urinary protein concentration 0.95 g/L (<0.15 g/L), which increased up to 4.14 g/L the next day. From these results we concluded that the 28-year-old 32 weeks' gravid normotensive woman had presented with a severe non-immune haemolytic anaemia, vitamin B₁₂ deficiency, folic acid deficiency and proteinuria.

To determine the cause of the haemolytic anaemia, Hb variant analysis was performed by high-performance liquid chromatography. A diagnosis of HbAS heterozygosity was made and the patient was heterozygous for the α-thalassaemia type 2 with genotype α₂-3.7/αα. She had ABO type B rhesus D-positive blood; irregular antibodies could not be demonstrated.

DIFFERENTIAL DIAGNOSIS

We present a patient with severe haemolysis in the third trimester of pregnancy who developed

CrossMark

To cite: van de Mheen L, Smits SM, Terpstra WE, et al. *BMJ Case Rep*. Published online: [please include Day Month Year] doi:10.1136/bcr-2013-010087

hypertension and proteinuria. Although we considered the combination of hypertension and proteinuria as being caused by pre-eclampsia, it is notable that our patient was normotensive in the first 5 days of admission while she had severe proteinuria. At the same time, she had severe haemolysis. The most common cause of haemolysis in this situation is HELLP syndrome, normally consisting of haemolysis, elevated liver enzyme levels and low platelet count. HELLP syndrome is a serious complication of pregnancy² and can be considered as a variant of severe pre-eclampsia. Patients can be classified as having partial HELLP syndrome when one or two abnormalities are present.³ Normal platelet levels and the severity of haemolysis in our patient suggested reasons other than (partial) HELLP syndrome for the observed haemolysis. The observed proteinuria was possibly caused by excessive haemolysis which can lead to overflow proteinuria. In these circumstances, the filtered load in the glomerular tubulus is increased to a level that exceeds the normal proximal reabsorptive capacity.⁴

Owing to the ethnicity of our patient she was prone to haemoglobinopathies.

Molecular diagnostics and high-performance liquid chromatography revealed coinheritance of α -thalassaemia (α -3.7/ $\alpha\alpha$) and sickle cell trait (HbAS). When megaloblastic anaemia (vitamin B₁₂ and folic acid deficiency) occurs in combination with a condition that gives rise to microcytic anaemia (α -thalassaemia) the anaemia can be normocytic, as was the case in our patient.

TREATMENT

She was admitted in the hospital and received a blood transfusion of three packed cells, vitamin B₁₂ supplementation and folic acid supplementation. She also received Celestone injections to accelerate fetal lung maturity and fetal condition was monitored with daily cardiotocography scans.

Because of increasing blood pressure (160/100 mm Hg on the fifth day of admission), decreasing variability of the fetal heart rate and deteriorating clinical maternal condition, we decided to terminate the pregnancy by performing an elective caesarean section. A boy of 1660 g (p20)⁵ was born with Apgar scores of 10 and 10 after 1 and 5 min of birth and he was admitted to the neonatology department immediately.

OUTCOME AND FOLLOW-UP

The postoperative period of the mother was complicated by transient aphasia which was interpreted as migraine after intracerebral pathology was excluded by cerebral MRI. Laboratory results all normalised and 7 days postoperative she went home in a good clinical condition with a Hb level of 5.8 mmol/L.

Three months after delivery our patient was still in good clinical condition. Additional screening for G6PD was performed because of severe haemolysis during nitrofurantoin treatment and because of the Negroid ethnicity of the patient. The results revealed a deficiency of G6PD with decreased G6PD activity in the patient's erythrocytes 1.7 IE/g Hb (reference range 3.8–5.9 IE/g Hb). Flow cytometric findings ruled out paroxysmal nocturnal haemoglobinuria.

DISCUSSION

G6PD deficiency is a common hereditary enzyme deficiency with the highest prevalence in malaria endemic areas including Africa, Mediterranean and South East Asia.⁶ Patients are usually asymptomatic, but in case of oxidative stress they can develop severe haemolytic anaemia, which is generally triggered by illness or infection, acidosis, certain foods or medicines.⁶ The

inheritance is X linked, and therefore usually mild in women; however due to asymmetric lyonisation or homozygosity women can also present with severe disease. Our patient was treated with nitrofurantoin, an oxidative compound that can induce haemolysis in susceptible patients with G6PD deficiency.⁷ A typical attack of haemolytic anaemia in G6PD-deficient patients occurs within several days after exposure to oxidative stress, usually no treatment is needed and the patient will recover quickly. However, our patient presented almost 3 weeks after treatment with nitrofurantoin and blood transfusions were necessary. Probably haemolytic anaemia was present for a longer period and maintained by vitamin B₁₂ and folic acid deficiency.^{8,9} The patient responded very well to vitamin B₁₂ and folic acid. Within 3 days after start of therapy her Hb levels were stable. Folic acid acts as an antioxidant and may have helped in decreasing haemolysis in our patient. Moreover, the self-limiting aspect of haemolysis in G6PD deficiency requires sufficient erythropoiesis for which vitamin B₁₂ and folic acid are also necessary. Most episodes of haemolytic anaemia can be prevented by avoiding fava beans, oxidant drugs and oxidant chemicals. A list of oxidising chemicals that are commonly reported in the literature as inducing haemolysis in G6PD-deficient individuals was discussed with the patient. She was also informed that her children and other family members should be screened for sickle cell, α -thalassaemia and G6PD deficiency.

In summary, we can conclude that in pregnant women with haemolytic anaemia who do not fulfil all criteria of HELLP syndrome, other causes of haemolysis should be considered and examined.

Learning points

- ▶ In pregnant women with haemolytic anaemia who do not fulfil all criteria of HELLP syndrome, other causes of haemolysis should be considered and examined.
- ▶ Nitrofurantoin treatment can cause severe haemolytic anaemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- ▶ G6PD deficiency is a common X linked enzyme deficiency among persons of certain ethnicities (Negroid, Mediterranean and Asian).
- ▶ In case of haemolytic anaemia it is important to screen for vitamin B₁₂ and folic acid deficiency.

Contributors With Mrs Meaghan Kelly, LvdM agreed to have six authors: LvdM and SMS wrote the manuscript. WET, A Leyte and DJ Bekedam supervised the haematological, chemistry and gynaecological part, respectively, and ESAvdA supervised the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Magann EF, Perry KG, Meydrech EF, et al. Postpartum corticosteroids: accelerated recovery from the syndrome of haemolysis, elevated liver enzymes, and low platelets (HELLP). *Am J Obstet Gynecol* 1994;171:1154–8.
- 2 Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A review. *BMC Pregnancy Childbirth* 2009;9:8.
- 3 Audibert F, Friedman SA, Frangieh AY, et al. Clinical utility of strict diagnostic criteria for the HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome. *Am J Obstet Gynecol* 1996;175:460–4.

- 4 Barratt J, Topham P. Urine proteomics: the present and future of measuring urinary protein components in disease. *CMAJ* 2007;177: 361–8.
- 5 The Netherlands Perinatal Registry. 2013. http://www.perinatreg.nl/uploads/167/82/PRNreferentiecurve_Jongens_Primiparae.pdf
- 6 Nkhoma ET, Poole CH, Vannappagari V, *et al.* The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. *Blood Cells Mol Dis* 2009;42:267–78.
- 7 Lavelle KJ, Atkinson KF, Kleit SA. Hyperlactatemia and hemolysis in G6PD deficiency after nitrofurantoin ingestion. *Am J Med Sci* 1976;272:201–4.
- 8 Andres E, Affenberger S, Zimmer J, *et al.* Current hematological findings in cobalamin deficiency: a study of 201 consecutive patients with documented cobalamin deficiency. *Clin Lab Haematol* 2006;28:50–6.
- 9 Antony AC. Megaloblastic anemias. In: Hoffman R, Benz Jr EJ, Shattil SJ, *et al.*, eds. *Hematology: Basic Principles and Practice*, 4th ed. Philadelphia: Elsevier Churchill Livingstone; 2005:519.

Copyright 2014 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