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Case Report

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Prenatal diagnosis of Hb H hydrops fetalis caused by haemoglobin adana

Abstract

We present a rare case of Hb H disease with hydrops fetalis phenotype where the fetus was compound heterozygous for α0-thalassaemia and the severe non deletional α+-thalassaemia mutation on the α2-globin gene that results in Hb Adana (genotype --FIL/αAdanaα). This patient presented following two pregnancies that had a normal outcome. The fetus in this pregnancy developed hydrops at 22 weeks and delivered as still birth at 28 weeks. This case highlights Hb Adana as uncommon but clinically significant variant of α-thalassaemia.

Keywords: thalassaemia, pregnancy, hydrops fetalis, haemoglobin adana

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Abbreviations: Hb H, haemoglobin H; MCH, mean corpuscular haemoglobin; RBC, red blood cells; MCV, mean corpuscular volume; NHS, National health service

Introduction

α-Thalassaemia is the most common inherited disorder of Haemoglobin (Hb) production in Southeast Asia, resulting from deficient synthesis of the α-globin chain component of the haemoglobin molecule due to deletion or inactivation of one or more of the normal four alpha-chain genes. The severity of the condition depends on the number of genes inactivated. The severest form is Hb Barts hydrops fetalis syndrome, due to loss of all 4 genes, which is generally incompatible with life. The mildest form is α+-thalassaemia trait due to inactivation of one gene which is completely asymptomatic, with loss of 2 or 3 genes resulting in cases of intermediate severity (i.e. 0, 1, 2 and 3 functional α−globin genes respectively).[1] Rare variants of α-thalassaemia such as Hb Adana may be missed by the routine screening provided by the NHS and may need to be screened for in high prevalence population.

Case presentation

We report the case of a Filipino couple with two previous normal pregnancies 14 and 12 years back. The mother presented in her third pregnancy at 9 weeks gestation due to recurrent vaginal bleeding. Early viability scan was performed and showed normal appearance of fetus and gestational sac. Her routine booking blood results showed a Hb of 12.8g/dl, Red blood cells (RBC) 5.64x10^9/L, mean corpuscular volume (MCV) 68.8fl, mean corpuscular haemoglobin (MCH) 22.7pg, Hb A_2 2.5% and Hb F 0.8%, suggestive of iron deficiency anaemia or α^0-thalassaemia trait). There was no evidence of common haemoglobin variants or beta thalassaemia. Given the high risk ethnic background for α^0-thalassaemia the partner was screened. Routine investigations showed Hb 14.9g/dl, MCV 75.4fl, MCH 25.0pg.

Although these results are more suggestive of α+-thalassaemia trait, DNA analysis of the α-globin gene cluster was requested and performed for the couple. Gap-PCR analysis showed the patient to have α^0-thalassaemia trait, heterozygous for the Filipino α^0-thalassaemia mutation--FIL (genotype $^{--FIL}/\alpha\alpha$). Gap-PCR analysis for her partner gave negative results for alpha thalassaemia deletions. DNA sequencing showed heterozygosity for the mutation α2 codon 59 GCC>GAC. (Genotype $\alpha\alpha^{Adana}/\alpha\alpha$). This results in a highly unstable alpha-chain variant Hb Adana leading to α^+ thalassaemia phenotype. In combination with alpha-zero thalassaemia deletion this has been reported to result in hydrops fetalis.

The couple was referred to the fetal medicine clinic at 17 weeks of gestation. Ultrasound scan showed no evidence of hydrops at that point; however fetal size was below the 5th centile of the growth scale. The couple was counselled regarding the 1 in 4 risk of having a child with fetal α-thalassaemia hydrops and the option of prenatal genetic diagnosis. They opted to have amniocentesis. The fetal chromosomes were normal. DNA analysis from amniocytes showed the fetus to be compound heterozygous for the α^0-thalassaemia deletion and the Hb Adana mutation (genotype$^{--FIL}/\alpha\alpha^{Adana}$). The couple was counselled about fatal hydrops fetalis, intrauterine blood transfusions and the option of termination of pregnancy. They however decided to continue the pregnancy without any interventions.

Subsequent follow up scans identified signs of hydrops fetalis (skin oedema, pleural effusion, pericardial effusion and ascites) from about 22 weeks. The couple decided to wait for natural outcomes rather than any further invasive procedure being fully aware of unfavourable outcomes without any fetal therapy. Intrauterine fetal death was diagnosed on ultrasound scan at 28 weeks of gestation. Labour was induced and a still born baby weighing 750 grams was delivered showing skin oedema but no other external structural abnormalities. Post mortem studies confirmed the diagnosis of hydrops by confirming the findings on the scan in addition to increased placental nucleated red blood cells which is consistent with the diagnosis of thalassaemia.

Discussion

To our knowledge, only two cases in the literature were reported where the fetus was compound heterozygous for Hb Adana and α^0 thalassaemia, genotype $--^{FIL}/\alpha^{Adana}\alpha$. In both cases it resulted in the phenotype Hb H hydrops fetalis. In the first case the fetus was given an intrauterine transfusion at 29 weeks, delivered by caesarean section at 34 weeks and remains transfusion dependent.[2] There were two affected fetuses in the same family in the second case, both developed hydrops fetalis and both pregnancies were terminated following counselling with the parents.[3] In our case the fetus was also compound heterozygote for the same Filipino α^0-thalassaemia deletion and severe α+-thalassaemia Hb Adana mutation (genotype $--^{FIL}/\alpha\alpha^{Adana}$) and subsequently developed severe hydrops fetalis resulting in intrauterine fetal death.

α+-Thalassaemia results either from gene deletions which is the most frequent form or from single point mutations or insertions.[4] The two most clinically relevant deletions are the 3.7kb deletion found in individuals from Africa, the Mediterranean area, the Middle East, the Indian subcontinent and Oceania, and the 4.2kb deletion commonly in Southeast Asia and the Pacific islands.[5] Non-deletion mutations are mostly found in populations from the Mediterranean area, Africa and Southeast Asia. Hb H disease results from the compound heterozygous state for α+- and α^0-thalassaemia. It may be deletional or secondary to non deletional mutations. The majority of cases of Hb H disease have a relatively mild deletional form with moderate hypochromic microcytic anaemia; they lead a relatively normal life and rarely require hospitalization. The non deletional form of Hb H disease is potentially more severe, and may lead to a thalassaemia intermedia phenotype with more severe symptoms in surviving patients who may become blood transfusion dependent and possibly require splenectomy, or even Hb H fetal hydrops.

α-thalassaemia should be acknowledged by health professionals as a possible cause when fetal hydrops is diagnosed. The national sickle cell and thalassaemia screening programme in the UK is mainly targeting couples at risk for sickle cell anaemia and β-thalassaemia. The screening algorithm, based on family origin and MCH, aims to identify couples at risk of Hb Barts hydrops fetalis due to homozygous α^0-thalassaemia but does not screen for deletional Hb H disease as it usually has a benign course. Couples at risk for non deletional (the severe form) Hb H disease, or hydrops due to compound heterozygosity for non-deletional α+-thalassaemia and α^0-thalassaemia in England may not be identified by routine screening. As it is prevalent in South-east Asia, the Mediterranean and the Middle East, family origin and mean cell haemoglobin (MCH) can be used as a first line screen to identify couples who need further DNA testing, prenatal diagnosis and counselling about the risks in the current or future pregnancies.[6] The national screening algorithm specifies a threshold below MCH 25 for further testing and if this had been applied strictly in the present case the diagnosis of Hb Adana would have been missed. This was also the situation for the cases described by Henderson et al.[3] and emphasises the fact that not all couples at risk of clinically significant haemoglobinopathies can be reliably identified by the screening programme.

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None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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