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CASE REPORT

α-Thalassemia with Haemoglobin Adana mutation: prenatal diagnosis

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Abstract

Thalassaemia carriers are common in the Asian region including Malaysia. Asymptomatic patients can be undiagnosed until they present for their antenatal visits. Devastating obstetric outcome may further complicate the pregnancy if both parents are thalassaemia carriers leading to hydrophic fetus due to haemoglobin Bart's disease. However in certain cases where unexplained hydrops fetalis occur in parents with heterozygous thalassaemia carrier,mutated α genes should be suspected. We report a twenty-nine year old woman in her third pregnancy with two previous pregnancies complicated by early neonatal death at 21 and 28 weeks of gestation due to hydrops fetalis. DNA analysis revealed the patient to have heterozygous (--SEA) α-gene deletion, while her husband has a compound heterozygosity for $\alpha^{3.7}$ deletion and codon 59 (GGC → GAC) mutation of the α-gene. This mutation, also known as hemoglobin Adana, can explain hydrops fetalis resulting from two alpha gene deletions from the patient (mother) and a single alpha gene deletion with mutation from the father. The third pregnancy resulted in a grossly normal baby boy with 3 α-gene deletions (HbH disease). We postulate that, in view of heterogenisity of the α-thalassaemia in this patient with severely unstable haemoglobin Adana chains from her husband, there will be a 25% possibility of fetal hydrops in every pregnancy.

Keywords: haemoglobin adana, α-thalassaemia, hydrop fetalis in pregnancy

INTRODUCTION

α-Thalassemia is a common health problem, especially among Malaysian Chinese and Malay carriers of the α-thalassemia-1 or α^0 -thalassemia gene (--SEA/αα).[1] The risk of developing hydrops fetalis increases if a couple has similar α-thalasaemia traits which complicate the pregnancy. In the advanced fetomaternal setting, early screening of couples with thalassaemia trait for fetal anemia may further predict the outcome of pregnancy and early intervention can be done. This will further alleviates parents' anxiety and prepare them for the pregnancy outcome.

CASE REPORT

We report a twenty-nine year old woman with a previous caesarean section currently in her third pregnancy. Her two previous pregnancies were complicated by early neonatal death at 21 and 28 weeks of gestation due to hydrops fetalis. She was diagnosed to have thalassaemia with a double α-gene deletion since her first pregnancy. The husband was diagnosed to have a single α gene deletion, yet the two previous babies were found to have hydrops fetalis by ultrasound and postmortem. The mother's blood group was AB-Rh positive. Screening for infectious causes of non-immune hydrops such as parvovirus and syphilis were negative. Unfortunately fetal karyotyping was not performed. Cordocenthesis was attempted in the second pregnancy but had failed.

The husband's mother had a consanguineous marriage with four children. The husband's father had died due to unknown illness at the age of 81 years old. The husband was the eldest with a sister and two younger brothers. Her husband had previous multiple admissions during his childhood due to anaemia but was only told to

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have a single α gene deletion and had never required any blood transfusion. Clinically, her husband had a tinge of jaundice with palpable liver and spleen. His youngest brother also had similar symptoms. His wife, which is the patient, was healthy and was able to keep her hemoglobin level at more than 10 g/dL throughout this pregnancy.

DNA analysis

Both the patient and her husband had DNA analysis to determine if there were additional gene mutations causing the two previous hydrops fetalis. It was found that the patient had heterozygous (--SEA) α-gene deletion. The husband's blood was sent for further DNA study to detect other types of uncommon α-thalassaemia mutations in the haematology unit, Hospital Kuala Lumpur (HKL). Multiplex Polymerase Chain Reaction (PCR) revealed a compound heterozygosity for $\alpha^{3.7}$ deletion and codon 59 (GGC → GAC) mutation of the α-gene. This mutation is also known as hemoglobin Adana (Hb Adana) which can cause hydrops in a fetus who has two α gene deletion from the patient (mother) and a single alpha gene deletion with mutation from the father.

Obstetrics management

In this pregnancy, she came early for booking at ten weeks period of amenorrhea (POA). Her pregnancy was dated and nuchal translucency (NT) scan done at 12 weeks POA was normal (NT 1.3 mm). She was seen bi-weekly by the feto-maternal specialist for fetal surveillance. Fetal middle cerebral artery peak systolic velocity (MCA-PSV) was closely monitored every week and later two weekly to look for any evidence of fetal anaemia before presenting with hydropic features (Table 1 and Fig. 1)

Regular two-weekly follow-up revealed that the fetus was growing well along the 50th centile without any evidence of fetal anaemia from the MCA-PSV monitoring to suggest early hydrophic changes. Upon further discussion, she was keen for a trial of normal vaginal delivery for this pregnancy and further assessment of the baby will be done post-delivery.

Clinical outcome

She presented again at 38 weeks and 5 days with leaking liquor of less than 18 hours. The labour was induced with intravenous oxytocin in view of pre-labour rupture of membranes and intravenous ampicillin was administered during the intra-partum period. The labour did not progress after 8 hours despite good contraction. She then underwent an emergency caesarean section for failed induction of labour. Intraoperative findings were uncomplicated. She delivered a grossly normal baby boy, weighing 2.7 kg with good Apgar score. The baby's cord blood was sent for DNA analysis. She was discharged home well with her son at postoperative day 2.

In view of its rare presentation, sparse literature and inadequate information for further

Table 1: Serial middle cerebral artery (MCA) velocity measurements according to gestation

Week of gestation	MCA	MCA PSV
14 weeks + 6 days	25.7 cm/s	< 1.5 MoM
16 + 6	22.2 cm/s	
18 + 4	22.38 cm/s	
20 + 6	32.2 cm/s	
21 + 6	32.33 cm/s	
22 + 6	32.55 cm/s	
23 + 6	35.56 cm/s	
24 + 6	49.40 cm/s	
26 + 0	39.19 cm/s	
26 + 6	44.10 cm/s	
28 + 0	44.95 cm/s	
29 + 6	45.5 cm/s	
34 + 0	49.81 cm/s	
38 + 1	63.3 cm/s	

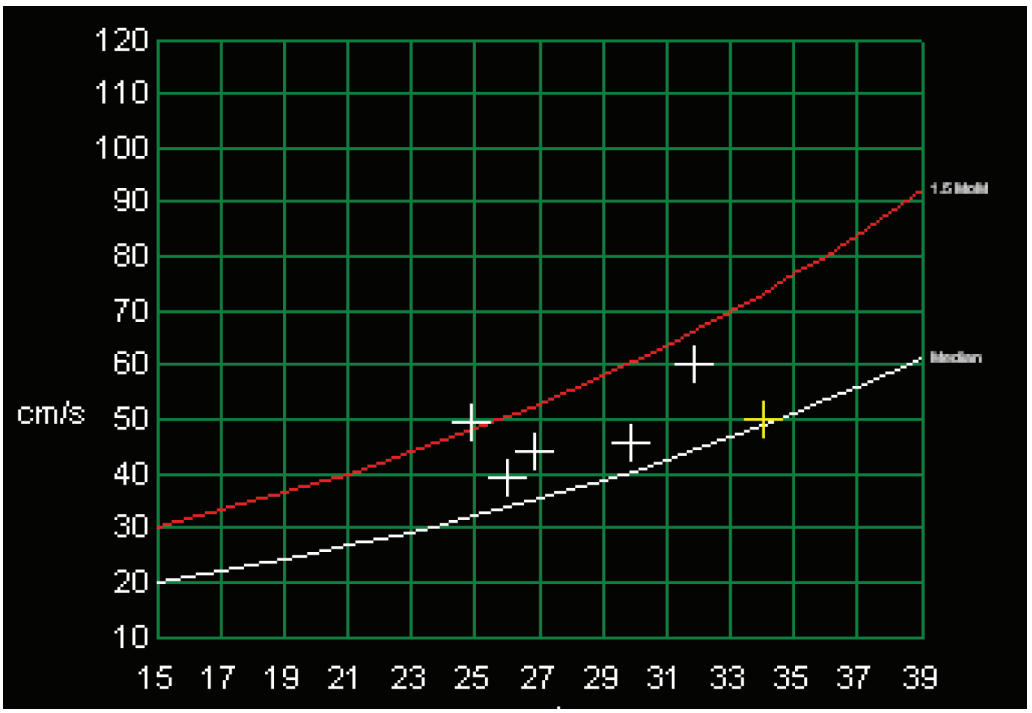

FIG. 1: Graph showing serials of fetal Middle Cerebral Artery (MCA) velocity (+) according to patient's gestation

offspring prediction, the family members agreed to genetic screening. A family screening was arranged a year later in collaboration with the hematologist in tracing the mutated codon 59 (GGC → GAC) of the α2 gene (haemoglobin Adana). The result revealed that the baby boy has 3 α-gene deletions also known as HbH disease. The baby's uncle has similar mutated gene as his father (heterozygous α-thalassemia 3.7 deletion with codon 59 (GGC → GAC) mutation), the haemoglobin Adana. His aunty has a single α-gene deletion. However, another uncle has normal α gene genotype. This is represented in the family genogram. (Fig. 2)

DISCUSSION

Antenatal screening programmes have been established in many places throughout the world[2] including Malaysia. Thalassaemias are commonly diagnosed during antenatal screening as many patients have their full blood count

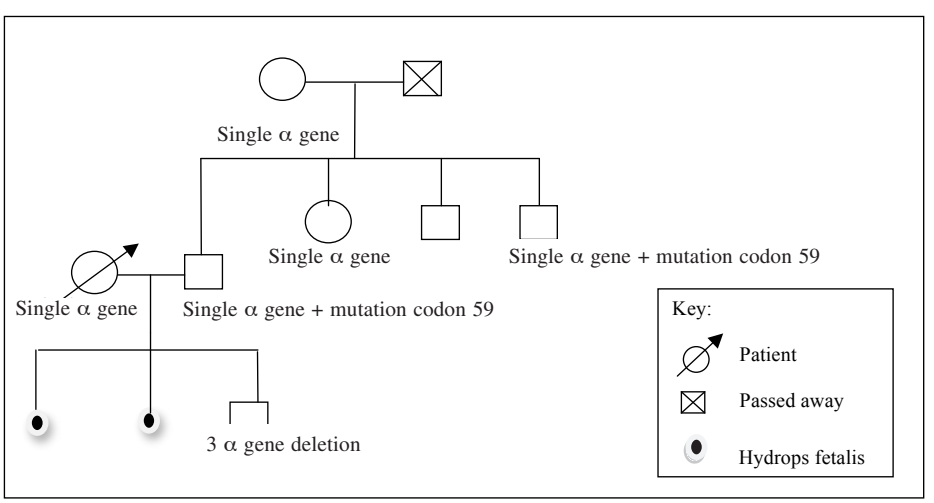

FIG. 2: Family genogram

done. It can be detected by the full blood count screening programmes with the initial identification of at-risk couples by microcytosis (MCV < 82 fl), in the absence of iron deficiency.[3] It is important to detect thalassaemia early as couples with alpha^0-thalassaemia traits have a 25% risk of having a fetus affected by homozygous alpha-thalassaemia or haemoglobin Bart's disease, with severe fetal anaemia *in utero*, hydrops fetalis, stillbirth or early neonatal death, as well as causing various maternal morbidities.[4] Furthermore, for couples with thalasaemia traits and the pregnancies complicated with hydrops fetalis, it would be necessary to investigate for compound heterogenosity for non-deletional mutations of the alpha genes are known to give rise to HbH hydrops fetalis.[5-7]

As for this patient, she was diagnosed with double α-gene deletions earlier prior to her first pregnancy. Her husband was diagnosed with a single α-gene deletion. The worst probability of the fetal outcome would be a three gene deletions or also known as haemoglobin-H disease (thalassaemia intermedia). However with the two consecutive pregnancies complicated with hydrops fetalis, we postulated that there could possibly be another gene mutation in the α-gene that had not been discovered before. Thus, a non deletional α-thalassaemia was suspected. Hb constant spring mutation turned out to be negative. Instead, compound heterozygosity for (-α3.7) deletion and codon 59 (GGC → GAC) mutation (haemoglobin Adana) was detected.

Haemoglobin Adana is among the severe non-deletional α-thalassaemia gene mutations known. There is little documentation regarding this disease due to its rarity. However, it was known as a cause of fetal hydrops if the fetus already has a 3 α -gene problem with non-deletional mutation giving rise to unstable chains.[5-8] Eng *et al* in 2001 reported three cases of severe non deletional α2-globin gene mutation detected using single tube multiplex PCR assay, among the α-thalsaaemia traits in the southeast Asian population associated with Hb-H hydrop fetalis syndrome.[9] These include the codon 59 GGC → GAC mutations and two uncommon mutations which were codon 30 ΔGAC and codon 35 TCC→CCC.[10] We postulate that, in view of heterogenisity of the α-thalassaemia in our patient with severely unstable haemoglobin Adana chains from her husband, there will be a 25% possibility of fetal hydrops in every pregnancy (Fig. 3).

A case report in Indonesia described three different families with homozygosity of Hb Adana ($\alpha^{cd\,59}\,\alpha/\,\alpha^{cd\,59}\,\alpha$) presented with hydrops fetalis fetuses despite having two functional α-globin genes. The clinical manifestations of these hydrops fetalis fetuses were noted to be more severe than those of fetuses with the – –SEA/– –SEA or ($\alpha^{cd\,59}\,\alpha$ /– –) genotype with miscarriages in early gestation. In the study, it was noted that the compound heterozygote for Hb Adana on the α1-globin gene and α^0-thal did not manifest as hydrops fetalis, but severe haemolytic

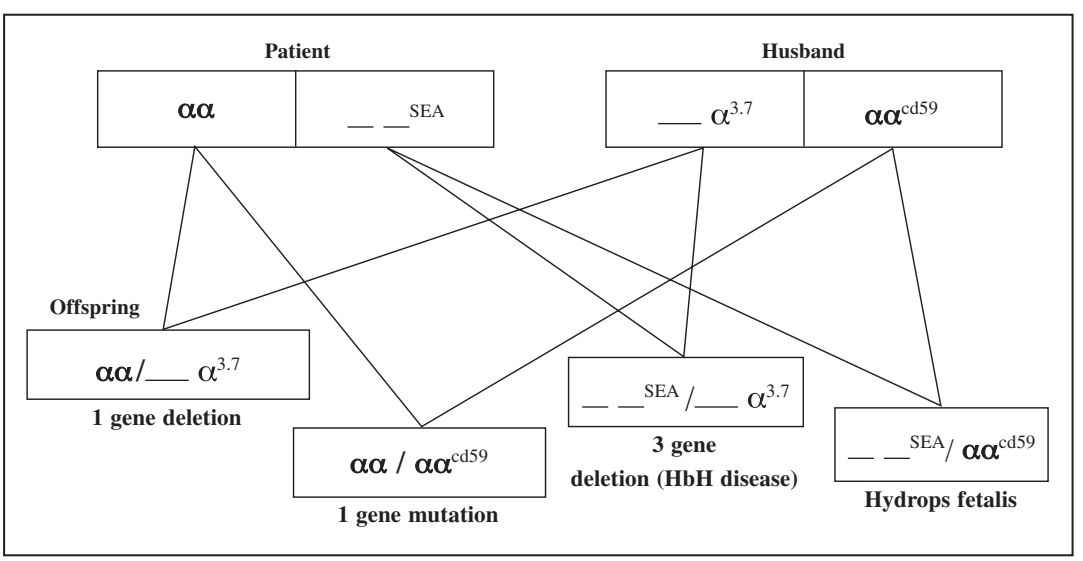

FIG. 3: Postulated inheritance pattern of offspring: Mendelian inheritance pattern for double α-gene deletion and single α-gene deletion with codon 59 mutation. Possible α-genotype of the couple's offspring.

anemia which required regular blood transfusion from a young age.[10,11] It was postulated that it could be possibly due to the higher rate of the α2-globin gene being transcripted than the α1-globin gene, resulted in the higher amount of variant α-globin chain or unstable variant Hb. Thus, this further contributes to unstable presentation of the Hb Adana genotype, causing the patient to present with more anaemia symptoms.[12]

Although the exact mechanism of hydrops fetalis in a fetus with the codon 59 GGC → GAC homozygosity is still unknown due to the two intact α -globin genes on chromosome 16, it appears that the severity of the phenotype might be due to the variant α-globin chains which interfere with normal tetramer formation or possible damaged erythrocytes or decreased α-globin chains synthesis. Moreover, most Hb Adana carriers are asymptomatic or exhibit only mild anemia, with red cell indices quite similar to those of α^+-thal carriers due to one α -globin gene deletion.[12] Although there is little information about Hb Adana, the carrier is known to develop severe anaemia, further complicating the pregnancy due to its instability.

Thalassaemia screening from as early as 16 years old has been promoted in Malaysia since 2008 and the awareness of this disorder is on the rise. Couples with known thalassaemia traits are encouraged to undergo early pregnancy screening for prenatal diagnosis. In the current fetomaternal advance, preconception counseling and early diagnosis of possible hydrops fetalis can be made. A strict and close monitoring of fetal well-being for high risk cases is possible as seen in our patient. It would provide couples with thalassaemia carrier status hope for future pregnancies.

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