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CASE REPORT

Successful Antenatal Management of Foeto-Maternal Alloimmune Thrombocytopenia

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Case Report

A 27-year-old second gravida with 16 weeks of gestation was referred to high-risk pregnancy unit in view of previous child having neurological deficit. Previous pregnancy records elicited the following details:

It was a booked pregnancy with otherwise uneventful antenatal course. At 37 weeks, mother was detected to have mild gestational hypertension (140/90 mm of Hg) without proteinuria. Emergency LSCS was performed for nonreactive pattern of foetal non-stress test and poor Bishop's score.

At LSCS, no abnormality of liquor, placenta, umbilical cord was noted. Male child 2.4 kg was delivered with a weak cry at birth. Neonate had repeated episodes of apnoea and refractory hypoglycaemia and thus shifted to NICU.

Platelet count of newborn at birth was 20,000/cu.mm. Ultrasonography of neonatal brain was suspicious of large extradural haemorrhage. MRI of the brain confirmed the same with thickness 4 cm in right temporo-parietal region, subarachnoid haemorrhage at right fronto-parietal region (Figs. 1, 2).

Neonate received platelet transfusion for thrombocytopenia. Subsequent CT scan brain showed no progression of haemorrhage and was managed conservatively. Baby was discharged on day 23 after explaining neurological deficit and poor prognosis to the parents.

Maternal platelet count was normal during pregnancy and delivery. It was a term neonate with inevident sepsis or severe thrombocytopenia leading to intracranial haemorrhage (ICH). Hence, possibility of foeto-maternal alloimmune thrombocytopenia (FMAIT) in previous child was suspected and present pregnancy was evaluated accordingly.

The couple was evaluated for human platelet antigen genotype by direct DNA sequencing. Patient's report documented: HPA-5a/5a. Husband's report showed: HPA-5a/5b (heterozygous) with 50% risk of foetus inheriting 5b genotype. Hence, amniocentesis was performed to assess foetal genotype. Foetal sample showed HPA-5a/5b genotype confirming HPA-5b incompatibility. The couple was counselled regarding the possibility of a worse outcome than previous pregnancy. Possible prevention by treating with intravenous immunoglobulin (IVIg) and high cost of therapy (total cost Rs. 13,72,000 for 8 weeks of treatment) was explained.

IVIg was given to mother 0.4 g/kg body weight/day every alternate day for 4 days every week starting from 24 weeks

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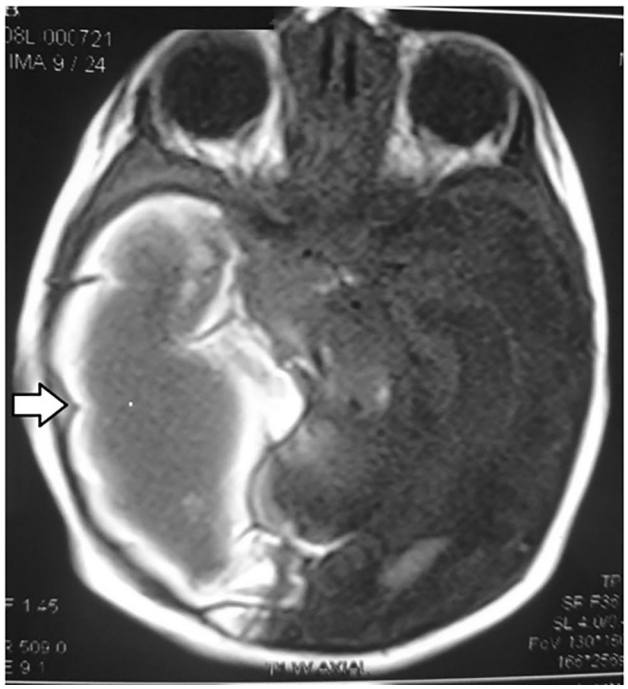

Fig. 1 MRI brain: large extra dural haemorrhage in right temporo-parietal region

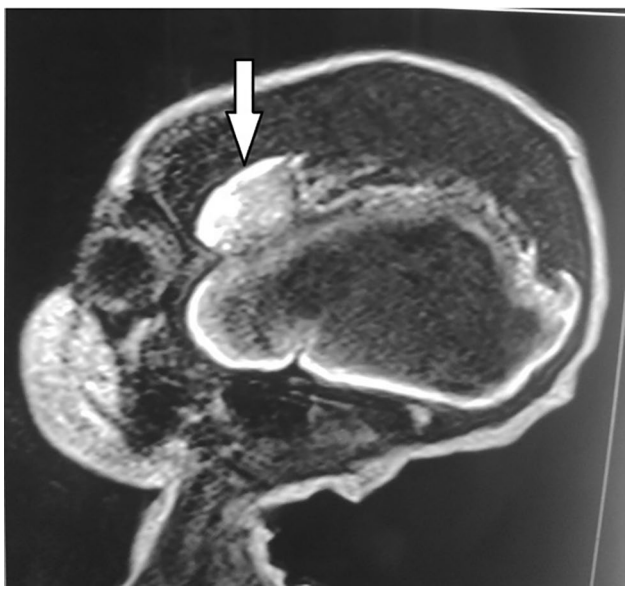

Fig. 2 MRI brain: subarachnoid haemorrhage right fronto-parietal region

till 32 weeks. Use of antiplatelet agent (aspirin) was avoided [2]. Serial foetal ultrasounds were performed every 2 weeks with focus on foetal brain to rule out ICH. Mother developed non-proteinuric severe gestational hypertension at 29 weeks. Hypertension was controlled with labetalol 200 mg orally 8 hourly. Prenatal steroids were given for advancing lung maturity. At 32 weeks, ultrasound documented borderline low liquor with absent end-diastolic flow in umbilical artery waveforms. Emergency LSCS was performed for the same. Male child 1.480 kg was delivered with 9/10 APGAR. Newborn had normal platelet count at birth and no evidence of ICH. Neonate was managed in NICU for 20 days in view of very low birth weight, prematurity and discharged with normal neurological findings. The child has normal milestones with good neurological outcome at 1-year follow-up.

Discussion

Foeto-maternal alloimmune thrombocytopenia (FMAIT) also known as foetal neonatal thrombocytopenia (FNAIT) or neonatal thrombocytopenia (NAIT) is the most common cause of severe foetal and neonatal thrombocytopenia and intracranial haemorrhage in otherwise healthy term neonates [1].

Incidence of FMAIT is 1 in 1000 pregnancies. In mild to moderate cases, FMAIT resolves within first seven days of life without any sequelae. Severe FMAIT (platelets $< 25 \times 10^9$/l) occurs in 1 in 10 000 live births in the UK [1]. 20% of these develop ICH, with 50% mortality, and 70% have neurodevelopmental impairment. 80% of ICH occurs during pregnancy (14% prior to 20 weeks and 30% before 30 weeks of gestation) [1].

History of sibling with antenatal ICH is the most useful clinical predictor of severe FMAIT. However, the disease that occurs in the first pregnancy may not be diagnosed until neonatal period, as in our case.

FMAIT results from formation of maternal antibodies against paternally derived foetal platelet alloantigen. Transplacental passage of maternal IgG causes destruction of foetal/neonatal platelets causing thrombocytopenia. GPIIIA, platelet glycoprotein carrying HPA polymorphism, is seen on surface of syncytiotrophoblastic villi in the first trimester and placentas. This explains formation of alloantibodies and clinical presentation during the first incompatible pregnancy in the absence of significant amount of foeto-maternal bleeding [2].

Most commonly detected antibodies in Caucasians are against human platelet antigen (HPA)-1a (80%) and HPA-5b (10–15%) [1]. In an Indian study, frequency distribution of HPA-1, HPA-2, HPA-4, HPA-5 and HPA-6 was found to be comparable with those reported in Caucasian population with no significant difference [3]. In our case, HPA-5b incompatibility was detected.

Diagnosis is based on documenting incompatibility of maternal/neonatal or maternal/paternal platelet antigen with maternal antibody to paternal antigen. Maternal HPA antibody titres do not correlate with severity of the disease and can alter with time, which limits its clinical value [2].

If the HPA genotype of father is heterozygous, then foetus has 50% possibility of inheriting the marker and foetal HPA status is confirmed by amniocentesis at 16 weeks of gestation. Procedure being invasive has related risk of miscarriage (0.5–1%) and chance of stimulating anti-HPA formation [1]. Although non-invasive technique of foetal platelet antigen genotyping for HPA-1a by cell-free DNA (cfDNA) testing can be performed, it is not established widely in clinical practice [1].

Antenatal management of FMAIT has changed over past few years. Invasive therapy by weekly foetal blood sampling and intra-uterine transfusion of platelets is associated with risks to foetus. Hence, non-invasive maternal IVIg therapy, which is safe and effective, is recommended by RCOG guidelines 2019, as the first line of treatment in management of FMAIT [1]. Steroids do not reliably raise foetal platelet counts and therefore cannot be used as a mainstay therapy, as an alternative to maternal IVIg [1]. The mechanism of IVIg treatment involves Fc receptor saturation in placenta, thereby preventing antibody transfer to foetus and foetal platelet destruction [4].

Recommended dose of IVIg is 1 gm/kg/week, transfused over 4–5 h in divided doses.

Side effects include headache, fatigue, flushing, myalgia, nausea, fever/chills and hypotension. Rarely aseptic meningitis, acute renal injury, thrombosis, haemolytic anaemia, stroke can occur. Anaphylactic reactions are uncommon. Our patient reported mild headache at 3 occasions which responded to oral acetaminophen (500 mg).

There is hardly any evidence of IVIg treatment early between 12 and 16 weeks and/or addition of steroids [1]. As foetal platelet antigens are completely expressed by 16–18 weeks of gestation, in mothers with previous baby with ICH, IVIg should be started by 16–18 weeks of gestation [1]. In our case, as couple was referred late, therapy was started by 24 weeks after confirmation of diagnosis and monetary arrangements as weekly IVIg is expensive.

Serial foetal ultrasounds are recommended every 2–4 weeks with a focus on foetal brain to rule out ICH after 18–20 weeks of gestation. If ICH is detected at early gestation, IVIg therapy and prolongation of pregnancy should be considered [1].

Termination of pregnancy by elective caesarean section at 37 weeks of gestation as precautionary measure is recommended for such cases with prior steroids for lung maturity. In multiparae, labour induction at 38 weeks avoiding rotational/vacuum and foetal scalp blood sampling is reasonable option [1].

Although severe FMAIT with ICH has very high morbidity and mortality, a reliable test for prediction is not available [1]. Anti-HPA-1a immunoglobulin and recombinant anti-HPA-1a are potential preventive approaches to reduce incidence of FMAIT in future [1].

Clinical vigilance, prompt diagnosis and multidisciplinary antenatal management are the mantra for successful outcome in FMAIT.

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Author Contributions SRP took part in clinical suspicion of FMAIT, obtained the second opinion from Dr. Purnima Satoskar, Jaslok (Panel Hospital), gave IVIg therapy at BARC Hospital on Indoor basis, provided complete antenatal care with strict maternal and foetal monitoring till delivery. NM obtained administrative permission for high-cost maternal IVIg therapy and procurement of IVIg on high priority basis and guided in antenatal management at BARC Hospital. PRS coordinated with ICMR, immunohaematology for confirmation of diagnosis and planned out antenatal management. RHS patient was referred to Nanavati (Panel Hospital) for supportive NICU and haematology backup. Dr. Rajkumar Shah performed emergency LSCS and provided immediate post-operative care. BPK evaluated the couple and subsequently the foetus to confirm diagnosis of FMAIT at National Institute of Immunohaematology.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from the patient for publication of the case along with figures.

References

1. Regan F, Lees CC, Jones B, Nicolaides KH, Wimalasundera RC, Mijovic A. On behalf of the Royal College of Obstetricians and Gynaecologists. Prenatal management of pregnancies at risk of fetal neonatal alloimmune thrombocytopenia (FNAIT). Scientific impact paper no.61. BJOG. 2019; https://doi.org/10.1111/147-0528.15642.
2. Espinoza JP, Caradeux J, Norwitz ER, Illanes SE. Fetal and neonatal alloimmune thrombocytopenia. Rev Obstet Gynecol. 2013;6(1):e15–21.
3. Kulkarni B, Mohanty D, Ghosh K. Frequency distribution of human platelet antigens in the Indian population. Transfus Med. 2005;15:119–24. https://doi.org/10.1111/j.0958-7578.2005.00561.x.
4. Branch DW, Silver RM, et al. Immunologic disorders in pregnancy. In: Gibbs RS, Karlan BY, Haney AF, Nygaard IE, editors. Danforth's obstetrics and gynecology. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 674–5.

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