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SHORT COMMUNICATION

# SEVERE FETOMATERNAL ALLOIMMUNE THROMBOCYTOPENIA PRESENTING WITH FETAL HYDROCEPHALUS

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## SUMMARY

We report two patients where the finding of isolated fetal hydrocephalus led to the detection of severe fetal thrombocytopenia, using fetal blood sampling. Serological investigation led to the diagnosis of fetomaternal alloimmune thrombocytopenia (FMAIT) due to anti-HPA-1a. Both women had had previous unsuccessful pregnancies probably due to FMAIT; one had had four miscarriages at 17–18 weeks' gestation. The other had had one previous pregnancy complicated by severe fetal anaemia, and eventually hydrocephalus developed and the fetus died without the diagnosis of FMAIT being considered. Subsequent pregnancies in the two women were also affected by FMAIT, but prenatal treatment, predominantly with serial fetal platelet transfusions, resulted in a successful outcome in both cases. These observations suggest that FMAIT should be suspected if there is isolated fetal hydrocephalus, unexplained fetal anaemia, or recurrent miscarriages. The accurate diagnosis of FMAIT is important because recent advances in prenatal management can improve the outcome of subsequently affected pregnancies.

KEY WORDS: neonatal alloimmune thrombocytopenia; intrauterine haemorrhage; hydrocephalus

## INTRODUCTION

Fetomaternal incompatibility for human platelet antigens (HPAs) may cause maternal alloimmunization and fetal and neonatal thrombocytopenia (Kaplan *et al.*, 1991; Waters *et al.*, 1991; Goldman *et al.*, 1994). The term neonatal alloimmune thrombocytopenia is commonly used to describe the condition, as most cases are diagnosed after birth. However, thrombocytopenia occurs *in utero* occasionally with serious consequences for the fetus, and a better general term for the condition as a whole is fetomaternal alloimmune thrombocytopenia (FMAIT). Antibodies against HPA-1a are responsible for 80–90 per cent of cases.

In FMAIT due to anti-HPA-1a, the first-born child is affected in about 50 per cent of cases (Mueller-Eckhardt *et al.*, 1989; Kaplan *et al.*, 1991). In these studies, 10–15 per cent of infants had no bleeding manifestations but the remainder had purpura, bruising, and/or more severe haemorrhage. Intracranial haemorrhage (ICH), which is the major cause of mortality and long-term morbidity, occurred in 15–20 per cent of cases. In the study of Kaplan *et al.* (1991) of 127 cases, death due to severe haemorrhage occurred in 7 per cent and there were neurological sequelae in 21 per cent. Although there is a serious risk of severe haemorrhage at the time of delivery, nearly 50 per cent of ICH cases occur *in utero* (Mueller-Eckhardt *et al.*, 1989), usually between 30 and 35 weeks of gestation but sometimes even before 20 weeks (Waters *et al.*, 1991).

The appearance of ICH on ultrasound and other scans depends on the age of the haemorrhage, and over a period of about a month the haematomas break down to form porencephalic cysts (Lam and

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Shulman, 1985; De Vries *et al.*, 1988). Hydrocephalus may occur after ICH, due to occlusion of the cerebrospinal fluid pathways. In the absence of obvious haemorrhage, hydrocephalus may be attributed to a genetic, infective, or other cause, and FMAIT not considered.

Montemagno *et al.* (1994) briefly described two pregnancies where the finding of isolated fetal hydrocephalus led to the detection of fetal thrombocytopenia using fetal blood sampling (FBS) and the subsequent diagnosis of FMAIT due to anti-HPA-1a. In this paper, we report two women where isolated fetal hydrocephalus similarly pointed to the diagnosis of FMAIT, and where intensive prenatal management of subsequent pregnancies was successful. Furthermore, FMAIT might have been suspected earlier in both women as they both had had previous unsuccessful pregnancies.

## MATERIALS AND METHODS

### *Platelet serology*

The platelet immunofluorescence test (PIFT) (Von dem Borne *et al.*, 1978) and monoclonal antibody immobilization of platelet antigens (MAIPA) assay (Kiefel *et al.*, 1987) were used for platelet typing and the detection of HPA-1a antibodies.

### *Fetal blood sampling*

Fetal blood sampling and platelet transfusions were performed using ultrasound-guided cordocentesis, as previously described (Nicolaides *et al.*, 1987).

### *Platelet concentrates*

Platelet concentrates for fetal transfusions were prepared by apheresis of the mother or HPA-1a-negative donors, as previously described (Murphy *et al.*, 1993, 1994). All platelet donors were seronegative for cytomegalovirus (CMV). The platelet concentrates were gamma-irradiated and transfused within 24 h of collection.

## CASE REPORTS

### *Patient L.M.*

*First five pregnancies.*—She had had five miscarriages at 17–18 weeks' gestation. The last of these was shown to have hydrops and hydrocephalus; the haemoglobin was 2·9 g/dl and the platelet count was $17 \times 10^9$/l. The mother was found to be HPA-1a-negative and to have anti-HPA-1a in her serum. The father's platelet type was HPA-1a/1a.

*Sixth pregnancy.*—Prednisolone (20 mg/day) was started at 16 weeks. FBS was carried out at 25 weeks. There was severe thrombocytopenia (platelet count $<10 \times 10^9$/l) and platelets were transfused, raising the count to $300 \times 10^9$/l. Unfortunately, there was a cord haematoma compressing the umbilical artery, resulting in fetal death.

*Seventh pregnancy.*—Prednisolone 20 mg/day and IVIgG 1 g/kg per week was administered to the mother from 16 weeks until delivery. FBS was carried out at 26 weeks and the fetal platelet count was again less than $10 \times 10^9$/l. Weekly fetal platelet transfusions were given to maintain the fetal platelet count above $30 \times 10^9$/l by raising the platelet count to $300–500 \times 10^9$/l immediately after each transfusion. Transfusions were given weekly until 33 weeks, when a normal infant was delivered by Caesarean section 2 days after the last platelet transfusion.

### *Patient S.R.*

The *first pregnancy* was complicated by severe fetal anaemia. There was no evidence of haemolytic disease and the fetus was transfused with red cells on ten occasions. Eventually hydrocephalus developed and the fetus died at 28 weeks; the diagnosis of FMAIT was not considered.

*Second pregnancy.*—Hydrocephalus was detected at 19 weeks. FBS was carried out and the fetal platelet count was less than $10 \times 10^9$/l. The mother was found to be HPA-1a-negative and to have weak to moderate strength anti-HPA-1a in her serum. The father's platelet type was HPA-1a/1a.

*Third pregnancy.*—Prednisolone 20 mg/day and IVIgG 1 g/kg per week were given from 14 weeks' gestation but an ultrasound scan showed that ICH had already occurred at 16 weeks and the pregnancy was terminated.

In her *fourth pregnancy*, ultrasound-guided intraperitoneal injections of immunoglobulin were given to the fetus from 12 to 18 weeks. FBS was carried out at 18 weeks and the fetal platelet count

was $12 \times 10^9$/l. A fetal platelet transfusion was given and maternal red cells were also transfused as there was some bleeding from the cord. Serial platelet transfusions were started but there were poor responses because of immune destruction of the transfused platelets by maternal HLA antibodies (Murphy *et al.*, 1993). There were improved responses to transfusions prepared from the mother and from HLA-compatible HPA-1a-negative donors. A normal infant was delivered by Caesarean section at 35 weeks after 20 fetal platelet transfusions.

## DISCUSSION

The recurrence of FMAIT in subsequent pregnancies is very common (>85 per cent) and the condition tends to become more severe (Shulman *et al.*, 1964; Reznikoff-Etievant, 1988; Kaplan *et al.*, 1991). If a previous sibling has had ICH, the risk of prenatal ICH in subsequent pregnancies is high. The use of FBS to measure the fetal platelet count (Daffos *et al.*, 1984) has made it possible to diagnose FMAIT *in utero* and to assess its severity, and the technique provides a means for transfusing compatible platelets. Management of affected pregnancies has concentrated on protecting the fetus from thrombocytopenic bleeding, particularly ICH. Maternal administration of IVIgG and/or steroids may be effective in some mildly affected cases, but serial fetal platelet transfusions are the preferred therapy for severely affected cases (Lynch *et al.*, 1992; Murphy *et al.*, 1994; Kaplan *et al.*, 1995).

The recent advances in prenatal management of FMAIT emphasize the importance of making an accurate diagnosis of FMAIT. At the present time, a diagnosis of FMAIT will be considered if there is minor or major haemorrhage in the fetus or neonate, or if thrombocytopenia is found on a routine blood count. Confirmation of the diagnosis depends on exclusion of other causes of fetal/neonatal thrombocytopenia and laboratory investigations (Kaplan *et al.*, 1991; Waters *et al.*, 1991; McFarland, 1993; Goldman *et al.*, 1994). However, Montemagno *et al.* (1994) reported two pregnancies with severe isolated fetal hydrocephalus, in one of which ICH was seen sonographically; FBS revealed severe fetal thrombocytopenia and laboratory investigations confirmed the diagnosis of FMAIT. They suggested that FMAIT should be suspected in cases of hydrocephalus, especially when it recurs, or when there are ultrasound or necropsy findings that suggest ICH. FBS allows investigations to be carried out for FMAIT, infection, and abnormal karyotype, in contrast to amniocentesis, which only allows karyotyping.

The case histories of the two patients presented in this report support the need to consider the diagnosis of FMAIT in patients with isolated hydrocephalus, and suggest that the diagnosis should also be considered in women with recurrent late miscarriages, and in pregnancies complicated by severe fetal anaemia. In these circumstances, laboratory investigations for FMAIT should be carried out. Confirmation of the diagnosis will allow counselling of the parents and advance planning of the prenatal management of any subsequent pregnancies.

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