

CASE REPORT

A rare manifestation of neonatal alloimmune thrombocytopenia

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SUMMARY

Neonatal alloimmune thrombocytopenia (NAIT) results from a fetomaternal incompatibility with maternal sensitisation against a fetal human platelet antigen (HPA) and antibodies transfer to the fetal circulation, leading to platelet destruction. The clinical presentation is variable and isolated intraocular haemorrhage is rare. We present the case of a male newborn, with intrauterine growth restriction, born at 29 weeks due to pre-eclampsia. He presented proptosis of the left eye, hyphaema and elevated intraocular pressure, with no other signs of haemorrhage. Severe thrombocytopenia was found ($27 \times 10^9/L$). Perinatal infection and maternal thrombocytopenia were excluded. Positive anti-HPA-1a and antihuman leucocyte antigen class I alloantibodies were found in the mother. Platelet crossmatch between the father's platelets and mother's plasma was positive. Platelet transfusions and intravenous immunoglobulin were given with favourable response. This case highlights an unusual presentation of NAIT, which should be suspected in the presence of severe thrombocytopenia in the first 24–72 h of life.

BACKGROUND

Neonatal thrombocytopenia (NT) is defined as a platelet count below $150 \times 10^9/L$. It is found in 1–5% of newborns at birth and in 22–35% of all newborns admitted to neonatal intensive care units.^{1–3} The risk of severe thrombocytopenia ($<50 \times 10^9/L$) is higher in the more premature infants.³ NT is usually present in one of two clinical patterns which reflect the most common causes: early (within 72 h after birth) and late (after 72 h of life). Causes of early onset NT include placental insufficiency, perinatal asphyxia, infections, autoimmune and alloimmune NT. Late onset NT is caused by late onset sepsis and necrotising enterocolitis, among others.^{1,2}

Neonatal alloimmune thrombocytopenia (NAIT) is the main cause of severe early NT, occurring in 1/1000–5000 births.^{1,2} It is the platelet equivalent of haemolytic disease of the newborn and results from transplacental passage of maternal alloantibodies directed against the fetal platelet antigens inherited from the father and absent on maternal platelets. These alloantibodies bind to fetal platelets and cause their destruction, resulting in severe fetal thrombocytopenia and NT.^{1,4} In Caucasians, about 80% of cases are due to antihuman platelet antigen (HPA) 1a. Unlike haemolytic disease of the newborn, NAIT often develops in the first pregnancy.^{2–5}

The clinical presentation of NAIT is variable. While signs of skin bleeding (petechiae or bruising)

are the most common symptoms, NAIT can also lead to lung or gastrointestinal bleeding as well as intraocular and retinal haemorrhage (7%).^{6,7} However, isolated intraocular haemorrhage is rare. The most serious complication of NAIT is an intracranial haemorrhage (ICH), which can be fatal or lead to severe sequels.^{3,7}

Diagnostic testing includes the determination of maternal–paternal platelet antigen incompatibility, the detection of maternal platelet alloantibodies and the parent's platelet HPA genotype.⁶

The treatment of choice for NAIT is platelet transfusion from an HPA-compatible donor or washed maternal platelets. However, frequently these options are not promptly available and these newborns are submitted to random donor platelet transfusion.^{2,3} In addition, intravenous immunoglobulin (IVIg) can also be used as an adjuvant therapy and intravenous methylprednisolone has also been used.³

All newborns with a suspicion of NAIT should be submitted to a cranial ultrasound in order to detect an eventual ICH. Additionally, adequate platelet counts should be maintained during the first 72–96 h because the risk of ICH is higher during this period.^{3,5}

CASE PRESENTATION

We describe the case of a male newborn from the first pregnancy of a non-consanguineous healthy couple, complicated by intrauterine growth restriction (IUGR). Serological maternal investigation was irrelevant. Family medical history was normal. There was no history of maternal thrombocytopenia or haemorrhage. At 29 weeks and 6 days the pregnancy became complicated by the occurrence of pre-eclampsia and obstetric ultrasounds revealed anamnios and signs of acute fetal distress. Antibiotics were administered to the mother, lung maturation with betamethasone was carried out and it was decided to perform a caesarean section. The infant was born with an Apgar score of 3/9/9, requiring intubation and mechanical ventilation. Birth weight was 965 g. Physical examination revealed the presence of left eye proptosis and haemorrhage in the anterior chamber of the eye (hyphaema; figures 1 and 2). Ophthalmic evaluation confirmed the presence of hyphaema of the left eye as well as retinal haemorrhage and elevated intraocular pressure (16 mm Hg). There were no signs of skin bleeding, active mucosal bleeding or hepatosplenomegaly.



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Figure 1 Clinical presentation: left eye proptosis and haemorrhage in the anterior chamber of the eye (hyphaema).

INVESTIGATIONS

Complete blood count performed after birth revealed thrombocytopenia ($27 \times 10^9/L$) without anaemia or altered white cell count. Peripheral blood smear excluded platelet aggregation. An infectious cause was also excluded (negative C reactive protein and blood culture). Since NAIT was suspected, parental blood testing was performed. Maternal platelet HPA phenotype was 1b1b and paternal phenotype was 1a1a. Positive anti-HPA-1a and antihuman leucocyte antigen class I alloantibodies were found in the mother. Platelet crossmatch between the father's platelets and mother's plasma was found to be strongly positive. Cranial ultrasound performed on the 1st, 4th and 10th days of life showed no evidence of haemorrhage. At day 18, cranial ultrasound showed a bilateral grade II peri-intraventricular haemorrhage (PIVH) (Papile's classification).

TREATMENT

The newborn was submitted to platelet transfusion from a random donor (15 mL/kg) in his first hours of life and presented a favourable response ($113 \times 10^9/L$). However, he needed another transfusion in the 5th and 10th days of life (thrombocytopenia of $27 \times 10^9/L$). Owing to previous unavailability, only the last transfusion was from a compatible donor (HPA-1a negative), where a single dose of IVIg (1 g/kg) was also administered (figure 3).

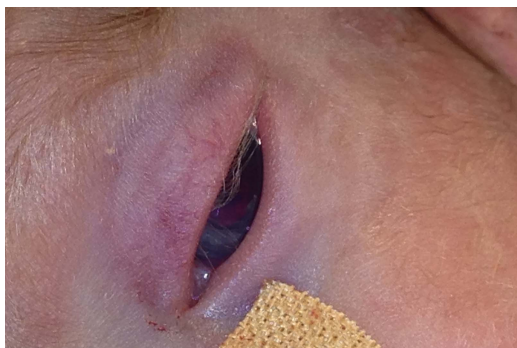


Figure 2 Clinical presentation: left eye proptosis and haemorrhage in the anterior chamber of the eye (hyphaema).

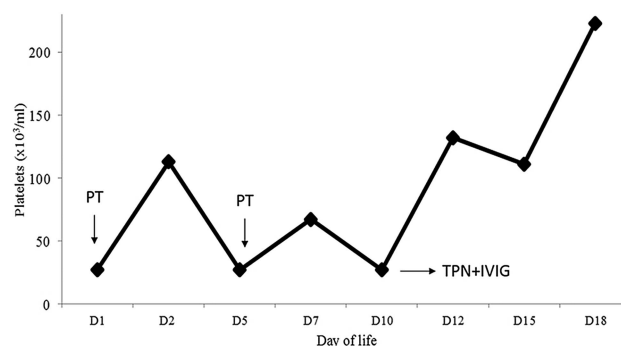


Figure 3 Treatment and platelet count response. PT, random donor platelet transfusion; TPN, platelet transfusion from a compatible donor (HPA-1a negative); IVIg, intravenous immunoglobulin.

Intraocular elevated pressure was treated with latanoprost from the 4th to the 23 days of life.

OUTCOME AND FOLLOW-UP

After the third platelet transfusion and IVIg a gradual platelet increase occurred, with normalisation at day 18 ($223 \times 10^9/L$).

The newborn never had signs of skin bleeding or mucosal haemorrhage.

There was a gradual decrease of intraocular haemorrhage and intraocular pressure with normalisation at day 18.

He had a late onset sepsis at day 10 with a positive blood culture to *Staphylococcus epidermidis*, with a good clinical response after 8 days of antibiotic treatment (vancomycin and cefotaxime).

At day 51 he was discharged home with a normal physical examination and adequate growth.

Ophthalmic reevaluation performed at 2 months old included a cranioencephalic and orbits MRI, which excluded the presence of lesions or haemorrhage. Retinal imaging with Retcam showed only a small perifoveal haemorrhage and no hyphaema. Retinopathy of prematurity was never observed.

Cranial ultrasound at 2 months old also showed PIVH reabsorption.

Given the increased risk of NAIT recurrence, counselling was offered to the couple in case of another pregnancy.

DISCUSSION

NAIT is a rare and severe condition which should be suspected in case of a severe thrombocytopenia in the first 72 h of life.^{2 6} A careful clinical history including maternal and familial background as well as investigation of other causes of neonatal thrombocytopenia is absolutely essential,⁷ since although the mother can be asymptomatic, she or a sister may have a history of previous affected newborns.⁸

NAIT's clinical presentation and severity are variable. Presentation varies from an incidentally detected thrombocytopenia in a well newborn to life threatening in utero or post-natal ICH.⁶

In the case described NAIT was not the first diagnostic hypothesis, because the newborn had other risk factors for thrombocytopenia, such as IUGR and pre-eclampsia. Also, NAIT is infrequent in premature newborns. It is usually present in an otherwise healthy term newborn.^{6 7} Nevertheless, this newborn had a very low platelet count and, despite a favourable initial response to random donor platelet transfusion at days 5 and 10, he needed to repeat it, thus presenting a favourable and

lasting response only from the second week of life and after compatible-donor platelet transfusion and IVIg. These clinical aspects are consistent with NAIT, which is usually resolved after 1 week.^{1 2 5} Initial diagnosis of NAIT was also difficult due to the absence of skin haemorrhage (the most common clinical manifestation of NAIT). To our knowledge, this is the first described case of NAIT with only intraocular haemorrhage as clinical presentation and without any other sign of haemorrhage.

Alloimmune thrombocytopenia probably also affected the unborn child, justifying in part the IUGR, considering that the association between fetal alloimmune thrombocytopenia and reduced birth weight in boys has also been described.⁹

This newborn had a PIVH at day 18 when the platelet count was already normal ($223 \times 10^9/L$). Probably, the factors contributing to this PIVH were the prematurity (although it usually occurs earlier) and the late onset sepsis.

In case of suspicion of NAIT, every newborn must be submitted to a cranial ultrasound in order to diagnose a possible ICH since this is the most feared and serious complication of NAIT.^{3 7}

NAIT's prognosis is usually favourable when ICH is absent, with recovery of platelet count in 8–10 days of life.⁵

NAIT's treatment is platelet transfusion, ideally from an HPA-compatible donor or washed maternal platelets. The threshold for transfusion is still in debate; however, transfusion is accepted when platelet's count is less than $50 \times 10^9/L$ in premature newborns and less than $30 \times 10^9/L$ in term newborns otherwise healthy and without signs of bleeding.³

IVIg is an adjunctive therapy that can be used but it takes longer than platelet transfusions to act. Intravenous methylprednisolone has also been used, though with a lack of proven efficacy in studies.³

NAIT tends to be more severe in subsequent pregnancies. Platelet antigen typing (maternal and paternal) and screening

the maternal serum for platelet antibodies should be performed if there is a personal or familial history of a newborn affected with NAIT. Preventive antenatal strategies should be based on the risk of NAIT's severity, which is higher if there is a history of a previous infant with an early onset ICH. However, antenatal management remains controversial. Treatment options include maternal weekly IVIg from 20 weeks of gestation (with or without prednisone). It can be started earlier (from 12 weeks) if there is a higher risk of severity.¹⁰ Intrauterine platelet transfusions are another treatment option that should be reserved to severe or refractory cases given the risk of fetal haemorrhage and intrauterine death.⁵ HPA-matched donor platelets or washed maternal platelets have been proven to be equally effective.¹¹ Optimal approach is still a matter of debate since there is a lack of non-invasive diagnostic methods to measure fetal platelet counts.^{12 13} Nevertheless counselling is fundamental, since later pregnancies should be managed by physicians with experience in NAIT's diagnosis and management.¹⁴

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Competing interests None.

Patient consent Obtained.

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Learning points

- Neonatal alloimmune thrombocytopenia (NAIT) should be considered in case of severe thrombocytopenia in the first 72 h of life (after exclusion of other possible causes of neonatal thrombocytopenia).
- Clinical presentation is variable; isolated intraocular haemorrhage without other signs of haemorrhage is possible.
- All newborns with suspicion of NAIT must be submitted to a cranial ultrasound to diagnose a possible intracranial haemorrhage.
- NAIT treatment includes a compatible donor platelet transfusion and IVIg as soon as possible. If adequate platelet transfusion is not available, random donor platelets should be used.
- Given the high risk of recurrence, counselling should be offered to couples with an affected newborn in case of subsequent pregnancies.

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