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Intracranial hemorrhage
and neonatal autoimmune
thrombocytopenia: a rare and
unpredictable event

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Title figure:

Human blood (source: https://www.nigms.nih.gov/education/life-magnified/Pages/1b4_kunkel-human-blood.aspx)

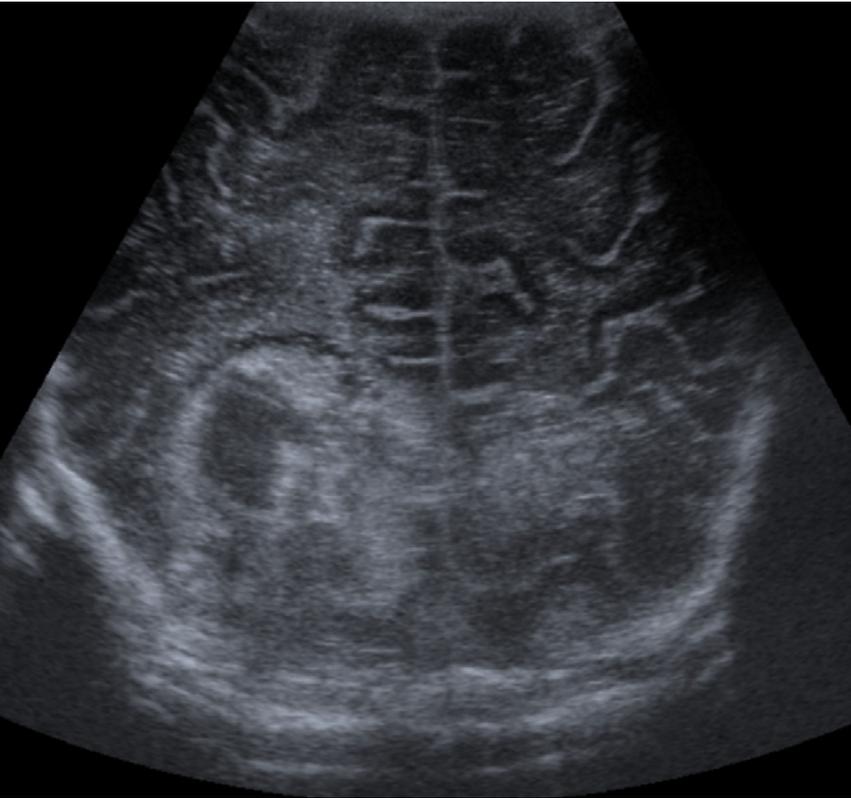
Fetal and neonatal immune thrombocytopenia are caused by maternal IgG crossing the placenta and destroying fetal platelets. Two main forms are described. The autoimmune condition is related to maternal immune thrombocytopenia (ITP), while the alloimmune form, commonly named fetal and neonatal alloimmune thrombocytopenia (FNAIT), is due to transplacental passage of specific antibodies against fetal platelets exhibiting antigens inherited from the father. The incidence of fetal and neonatal intracranial hemorrhage in those two conditions differs widely, with 10–30% in FNAIT and 0–2.9% in the autoimmune form (1, 2–4). We here describe the case of a male newborn infant with early onset of severe autoimmune thrombocytopenia complicated by symptomatic neonatal intracranial hemorrhage.

CASE REPORT

This Caucasian boy was born by spontaneous vaginal delivery to a 29-year-old G1/P1 at 39 1/7 weeks of gestation. The mother had been affected by ITP since the age of 7 years, requiring treatment with oral steroids and intravenous immunoglobulin (IVIG) administration during adolescence.

Pregnancy had been uneventful and no anomalies had been found on prenatal ultrasounds. The mother's platelet counts were between 30 and 60 G/L during the first trimester of pregnancy. At 18 weeks of gestation, she received a short course of oral prednisone therapy before amniocentesis because of a platelet count of 35 G/L. Her platelet count progressively increased during pregnancy and no further treatment was required. At the time of delivery, her platelet count was 135 G/L.

Labor and spontaneous vaginal delivery were uneventful. Birth weight was 3050 g (P10–25), length 48 cm (P5) and head circumference 35 cm (P25–50). The neonate adapted well to extrauterine life (Apgar scores 9, 10 and 10 at 1, 5 and 10 minutes, respectively) and clinical examination at birth was normal. There was no risk of infection. A complete cord blood count revealed severe thrombocytopenia (5 G/L) that was confirmed on a venous blood sample. The baby was promptly admitted to the neonatology unit and received an immunoglobulin infusion (400 mg/kg) and

**Fig. 1**

Coronal brain ultrasound shows hyperechoic lesions in the occipital lobes: on the right, the lesion is larger and heterogeneous with a central hypoechoic and a peripheral hyperechoic zone, suggesting hemorrhage.

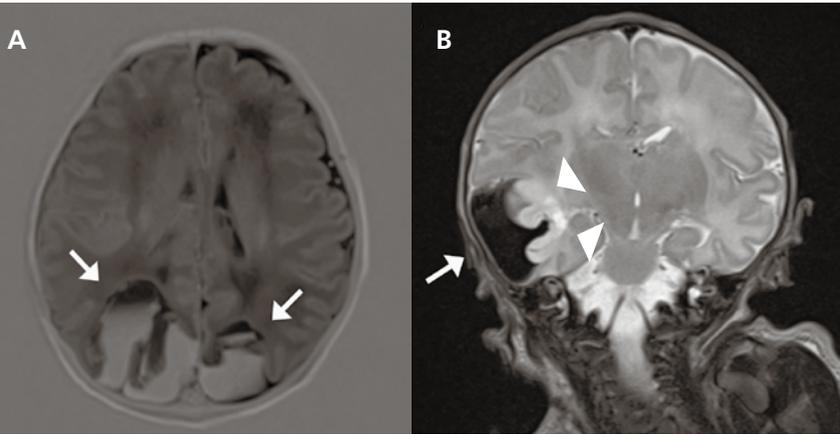


Fig. 2

Brain MRI: Subpial hemorrhage (white arrows) is depicted as a high intensity signal on axial T1-weighted sequences (A) and a low intensity signal on coronal T2-weighted sequences (B); on the T2-weighted sequence, the leptomeningeal localization of the bleeding is clearly visible and is associated with high intensity signal cortical edema (white arrowheads).

a platelet transfusion (15 ml/kg) from donor apheresis. The platelet count was at 10 G/l and 35 G/l 12 and 24 hours after the platelet transfusion, respectively.

At 24 hours of life, he developed apnea and periodic breathing requiring low-flow oxygen therapy and short bag-mask ventilation. There was no clinical or laboratory evidence of infection. Brain ultrasound performed on the 2nd day of life showed a large heterogeneous right-sided temporo-parieto-occipital lesion and a small left-sided occipital echogenic lesion, suspicious of intracranial hemorrhages predominantly within the right hemisphere (Fig. 1). Brain CT scan confirmed the hemorrhagic nature of the lesions and brain MRI was able to better depict the hemorrhagic site, which was mainly extraparenchymal and within the leptomeningeal space, suggestive therefore of a subpial hematoma. The T2-weighted sequences showed swelling in the adjacent cortex (Fig. 2). There were no anomalies in the basal nuclei.

Bedside EEG monitoring revealed multifocal electrical seizures starting from the left occipital lobe and oral phenobarbital treatment was started. Other possible causes of neonatal thrombocytopenia (e.g. infections, hemangioma or renal vein thrombosis) were excluded.

Given the severity of the intracranial hemorrhage and the mild maternal thrombocytopenia during pregnancy, evaluation for possible alloimmune thrombo-

cytopenia was also performed. A search for maternal antibodies (autoantibodies and alloantibodies with a cross-match between maternal serum and paternal platelets) was performed and completed by platelet genotyping of the baby and both parents. There was only one antigenic incompatibility between maternal and baby platelets in the HPA-15 antigenic system without anti-HPA-15b antibodies detectable in maternal serum. This finding reasonably excluded the diagnosis of alloimmune thrombocytopenia.

During the first 10 days of life, the patient received a total 6 of platelet transfusions and 6 intravenous infusions of immunoglobulins. The child was discharged on day of life 17 with a normal neurological examination and a platelet count of 70 G/l. Phenobarbital was stopped before discharge. Platelet counts progressively increased and were within the normal range 8 weeks after birth (above 150 G/l). At the last follow-up at 12 months of life, the child exhibited normal psychomotor development and an unremarkable neurological status.

Neonatal thrombocytopenia can be classified based on several different aspects: platelet size, mode of acquisition (congenital or acquired), age of onset (early: < 72 hours or late: ≥ 72 hours), gestational age, or by pathological mechanisms (allo- and autoimmune platelet destruction are two of the most important mechanisms).

FNAIT occurs when the mother forms antiplatelet IgG-class antibodies against paternal platelet antigens expressed either on fetal platelets that have entered the maternal circulation or on the fetal trophoblast. These antibodies can cross the placenta and destroy fetal platelets that express a paternal antigen on their surface. In Caucasians, the most frequently involved antigen in severe FNAIT is the human platelet antigen (HPA)-1a (75 – 80%) (5); in this situation, mothers with HPA-1bb genotype develop anti-HPA-1a antibodies. Other commonly involved antigens are HPA-5b, HPA-15b and HPA-3a (accounting for 15% of cases) but other rare antigens can also be involved (< 5% of cases). The incidence of FNAIT has been estimated at 1/800 to 1/1000 live births (6). Clinical findings in affected newborns are dependent on the severity of thrombocytopenia: petechiae, bruising and intracerebral bleeding are the most frequent manifestations. The presence of antiplatelet alloantibodies in maternal serum is required to confirm the diagnosis.

ITP occurs in approximately 1/1000 pregnant women

and accounts for 3 to 5% of pregnancy-associated thrombocytopenias. Maternal IgG autoantibodies react with both maternal and fetal platelets leading to fetal or neonatal autoimmune thrombocytopenia. Large prospective studies have shown that the incidence of severe neonatal autoimmune thrombocytopenia (defined as a platelet count < 50 G/L) varies from 5% to 20% and the incidence of thrombocytopenia less than 20 G/L varies from 1% to 5% (1, 7). About 1% of neonates born from mothers with ITP will have significant bleeding complications (7).

The major risk in case of severe neonatal thrombocytopenia is intracranial hemorrhage (ICH). This risk is greater in alloimmune disease where an ICH incidence of 10–30% has been reported. The incidence of ICH in autoimmune thrombocytopenia is much less common (0–2.9 %) (1, 2–4).

Not only the incidence of ICH differs between the two forms, but also the timing and the hemorrhagic pattern. According to Govaert et al. (8), the typical cerebral lesion in alloimmune thrombocytopenia is more often a superficial hemorrhage usually affecting the temporal lobe. It is typically a subpial hemorrhage becoming a subarachnoid hematoma by extending towards the surface. If the hemorrhage enlarges towards deeper structures, reaching the ventricle, an intraventricular hemorrhage may occur. A significant proportion of these ICHs take place in utero,

often associated with permanent sequelae (1–3). In contrast, fetal diagnosis of ICH in the setting of auto-immune thrombocytopenia is unusual and the majority of cases of ICH occur after birth (9). Intraventricular hemorrhage is frequent (10). In the majority of reported cases, the prognosis is poor: in 22 cases, Koyoma et al. identified five stillbirths, six deaths after live birth, four children with psychomotor impairments, and only four children without sequelae. For three children, the prognosis was unknown (9).

CONCLUSION

Severe neonatal thrombocytopenia is a rare complication of maternal autoimmune thrombocytopenia and is unfortunately not reliably predicted by maternal characteristics such as platelet count during pregnancy or delivery, presence of detectable antiplatelet antibodies, past medical history of autoimmune thrombocytopenia or corticosteroid therapy (9, 11). Neonatal cerebral hemorrhage due to autoimmune thrombocytopenia is much less common than in the alloimmune form, but potentially more serious. It also tends to occur after birth and clinicians must be aware of its timing.

From the experience with the presented case and the literature review, platelet count should be tested at birth in all babies born from mothers with thrombocytopenia during pregnancy, especially in case of a known history of autoimmune thrombocytopenia, independent of the maternal platelet counts during pregnancy or at delivery. If below the normal range at birth, it should be closely monitored, as the platelet count may fall during the first 3–5 days of life. Following current recommendations, IVIG and platelet transfusion should be administered if the platelet count is below 30 G/L. In case of bleeding, the treatment should be administered regardless of the platelet count, accompanied by platelet transfusion (12–16). Because of the high rate of intracranial hemorrhage in newborns affected by thrombocytopenia (platelet count < 50 G/L), radiological investigations should be

done as soon as possible after delivery, even if the index of suspicion is low (ultrasound, and MRI in case of abnormal ultrasound findings) (16). Prompt diagnosis, followed by timely and correct treatment, as well as close multidisciplinary follow-up are essential to ensure the best possible outcome.

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