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Intracranial Hemorrhage and Autoimmune Thrombocytopenia in a Neonate: A Rare "Unpredictable" Event

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Abstract

Neonatal thrombocytopenia is a rare complication of maternal autoimmune thrombocytopenia, and no maternal predictors of its gravity and potential complications have been identified. Neonatal cerebral hemorrhage, a feared event in the setting of autoimmune thrombocytopenia, is fortunately uncommon, but it can occur in utero or in the perinatal period, with potentially serious consequences. The authors report the case of a boy born to a mother affected by autoimmune thrombocytopenia, who presented with severe thrombocytopenia at birth and developed intracranial hemorrhage despite mild maternal thrombocytopenia at delivery and a prompt preventive treatment of the newborn. Platelet count should be tested at birth in all babies born from mothers with autoimmune thrombocytopenia, irrespective of maternal platelets counts during pregnancy or at delivery, and should be closely monitored during the first days of life. Systematic early and serial cranial ultrasound might be advocated in the setting of neonatal thrombocytopenia.

Keywords

autoimmune, brain, magnetic resonance imaging, neonatal seizures, neonate, neuroimaging, seizures

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Fetal and neonatal immune thrombocytopenia is caused by maternal immunoglobulin G crossing the placenta and destroying fetal platelets. Two main forms are described. The autoimmune condition is related to maternal immune thrombocytopenia, while the alloimmune form, commonly named fetal and neonatal alloimmune thrombocytopenia, 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 these 2 conditions differs widely, of 10% to 30% in fetal and neonatal alloimmune thrombocytopenia and 0% to 2.9% in the autoimmune form, respectively.[1–4] The authors describe here the case of a male newborn 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 gravida 1, para 1 mother at 39 1/7 weeks of gestation. The mother had been affected by immune thrombocytopenia (ITP since the age of 7 years, which was treated by oral steroids and intravenous immunoglobulin administration during adolescence).

Pregnancy was uneventful, and no anomalies were found on prenatal ultrasounds at 14, 16, 20, 27, and 32 weeks of gestation. The mother's platelet count was between 30 and 60 G/L

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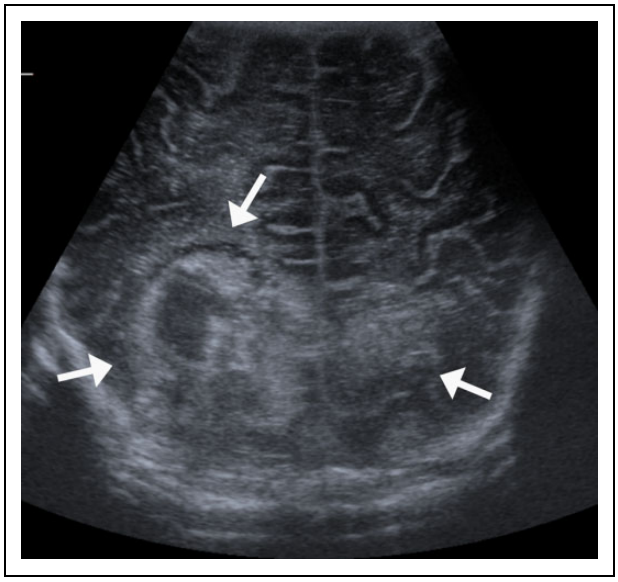

Figure 1. Coronal brain ultrasound shows hyperechoic lesions in the occipital lobes. On the right, the lesion is larger and heterogeneous, with a central hypoechoic zone and a hyperechoic peripheral zone suggesting hemorrhage (white arrowheads).

during the first trimester of pregnancy. At 18 weeks' 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 initiated. At the time of delivery, her platelet count was 135 G/L. No anomalies were found on repeated fetal ultrasounds. The labor and the spontaneous vaginal delivery were uneventful. Birth weight was 3050 g (10th-25th percentile), length 48 cm (5th percentile), and the head circumference 35 cm (25th-50th percentile). The neonate displayed a good adaptation to extrauterine life (Apgar score 9/10/10), and clinical examination at birth was normal. There were no risk factors for feto-maternal infection. A complete cord blood count revealed a severe thrombocytopenia (5 G/L), which was confirmed by a venous blood sample. The baby was promptly admitted to the neonatology unit and received an immunoglobulin infusion (400 mg/kg) and a platelet transfusion (15 mL/kg) from donor apheresis. The platelet count was at 10 and 35 G/L 12 ant 24 hours after the platelet transfusion, respectively.

At 24 hours of life, he developed apneas and periodic breathing requiring oxygen flow and short bag-mask ventilation. There was neither clinical nor biological evidence of infection. Brain ultrasound performed on the second day of life showed large heterogeneous right temporo-parieto-occipital and small left occipital echogenic lesions, suggestive of intracranial hemorrhage predominant within the right hemisphere (Figure 1). Brain computed tomography scan confirmed the hemorrhagic nature of the lesions, and brain magnetic resonance imaging (MRI) was able to better depict the hemorrhagic site, which was mainly extraparenchymal and within the leptomeningeal space, therefore compatible with a subpial hematoma. The T2-weighted sequences showed swelling in the adjacent cortex (Figure 2). There were no anomalies in the basal nuclei.

Bedside electroencephalography monitoring revealed multifocal electrical seizures starting from the left occipital lobe, and an oral phenobarbital treatment was started. Other possible causes of neonatal thrombocytopenia were investigated. There were neither clinical nor biological signs of infection or necrotizing enterocolitis. Hypersplenism or renal vein thrombosis was excluded by abdominal ultrasound; no clinical sign of Kasabach-Merritt phenomenon was found. Coagulation studies were normal, excluding a disseminated intravascular coagulation. The mother and the baby did not receive any drug potentially causing thrombocytopenia. There was no preeclampsia during pregnancy. Other rare causes of thrombocytopenia such as Fanconi anemia, congenital amegakaryocytic thrombocytopenia, thrombocytopenia-absent radius syndrome, Alport syndrome, Bernard-Soulier syndrome, and Wiskott-Aldrich syndrome were not investigated in the absence of suggestive features.

Given the severity of the intracranial hemorrhage and the mild maternal thrombocytopenia during pregnancy, an evaluation for a possible alloimmune thrombocytopenia was also performed. A search for maternal antibodies (autoantibodies and alloantibodies with a crossmatch between maternal serum and paternal platelets) was done and completed by a platelet genotyping of the baby and both parents. There was only one antigenic incompatibility between maternal and baby platelets in the human platelet antigen-15 antigenic system without anti-HPA-15b antibodies detectable in maternal serum. This finding clearly excluded the diagnosis of alloimmune thrombocytopenia.

During the first 17 days of life, the patient received 6 platelet transfusions and 6 intravenous injections of immunoglobulins. The child was discharged at 17 days of life with a normal neurological status, and his last platelet count was 70 G/L. Phenobarbital was stopped before discharge. Platelet count progressively increased at ambulatory follow-up and was in normal range 8 weeks after birth (above 150 G/L; Figure 3). At the last follow-up at 12 months of life, the child exhibited normal psychomotor development and unremarkable neurological status.

Discussion

Thrombocytopenia can be classified according to several different methods: platelet size, mode of acquisition (congenital or acquired), early (<72 hours of age) or late ($\geq$72 hours of age) onset, gestational age, or by pathological mechanisms: allo- and autoimmune platelet destructions are two of the most important mechanisms.

Fetal and neonatal alloimmune thrombocytopenia occurs when the mother forms antiplatelet immunoglobulin G class antibodies against paternal platelet antigens. These antibodies can cross the placenta and destroy fetal platelets expressing a paternal antigen on their surface. In Caucasians, the most frequently involved antigen in severe fetal and neonatal

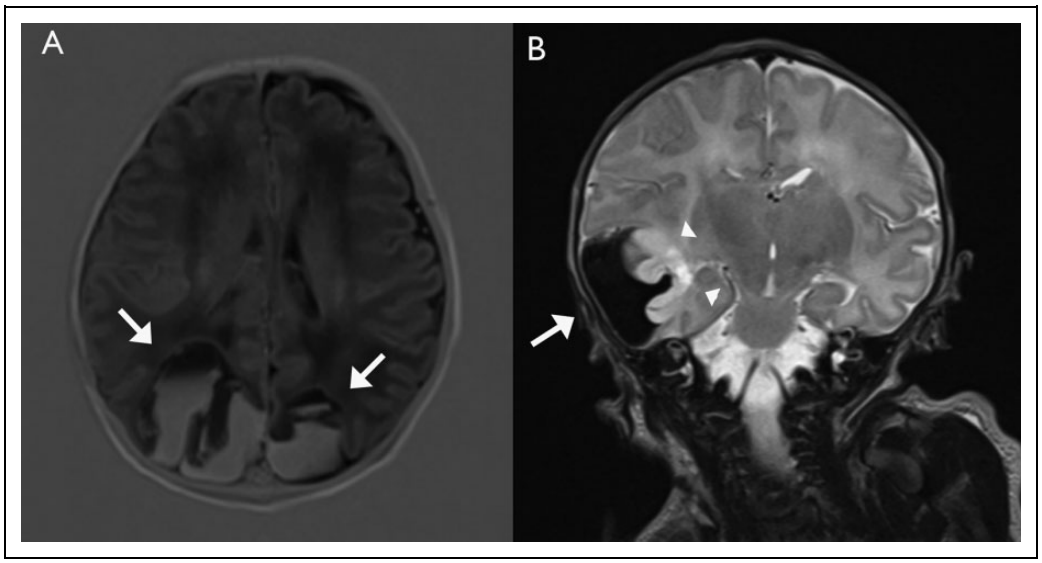

Figure 2. Brain MRI: Subpial hemorrhage (white arrows) is depicted as a high-intensity signal on axial T1-weighted sequence (A) and low-intensity signal on coronal T2-weighted sequence (B). On the T2-weighted sequence, the leptomeningeal localization of the bleeding is clearly visible and is associated with high-intensity signal cortical edema (white arrowheads).

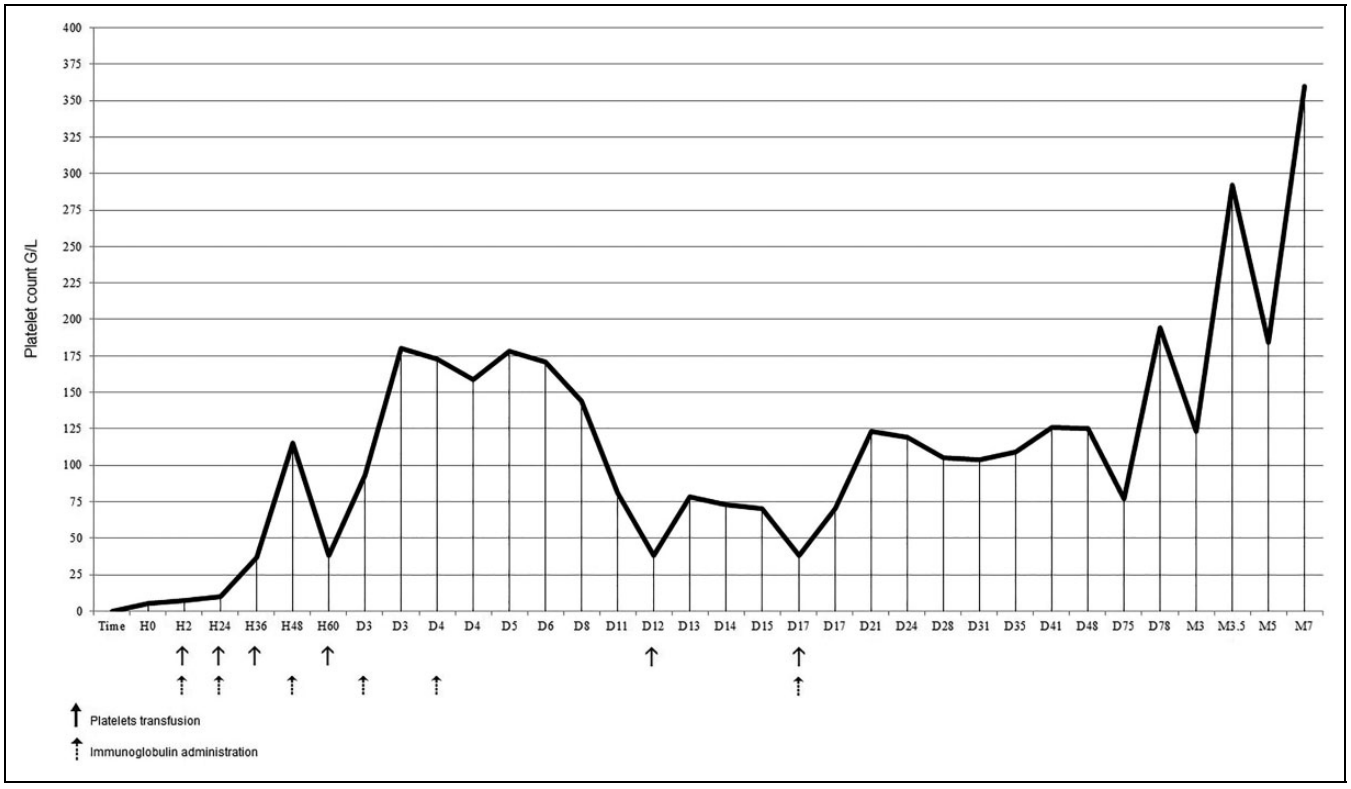

Figure 3. Platelet count trend and timing of treatment. H indicates hours of life; D, days of life; M, month of life; ↑, platelet transfusion; ↟, immunoglobulin administration.

alloimmune thrombocytopenia is the human platelet antigen -1a (75%-80%)[5]; in this situation, mothers with human platelet antigen-1bb genotype develop anti-human platelet antigen-1a antibodies. Other commonly involved antigens are human platelet antigen-5b, anti-human platelet antigen-15b, and human platelet antigen-3a (15%), but other rare antigens can also be involved (<5%). The incidence of fetal and neonatal alloimmune thrombocytopenia 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 the mother's serum is required to confirm the diagnosis.

Immune thrombocytopenia occurs in approximately 1/1000 pregnant women and accounts for 3% to 5% of pregnancy-associated thrombocytopenia. Maternal IgG autoantibodies react with both maternal and fetal platelets, leading to a fetal or neonatal autoimmune thrombocytopenia. Large prospective studies have shown that the incidence of severe autoimmune neonatal thrombocytopenia (defined as a platelet count <50 G/L) varies from 5% to 20% and the incidence of thrombocytopenia lower than 20 G/L varies from 1% to 5%.[1,7] About 1% of neonates born from mothers with immune thrombocytopenia will have significant bleeding complications.[7]

The major risk in case of severe neonatal thrombocytopenia is intracranial hemorrhage . This risk is greater in alloimmune disease where a 10% to 30% incidence of ICH has been found. The incidence of intracranial hemorrhage in autoimmune thrombocytopenia is much less common (0%-2.9%).[1–4]

Not only is the incidence of intracranial hemorrhage distinct between the 2 forms but also the timing and the hemorrhagic pattern. Indeed, the typical cerebral lesion in alloimmune thrombocytopenia, according to Govaert et al,[8] is more often a superficial hemorrhage usually affecting the temporal lobe. It is typically a subpial hemorrhage becoming a subarachnoid hematoma by growing toward the surface. If the hemorrhage grows deeper and reaches the ventricle, an intraventricular hemorrhage may occur. A significant proportion of these intracranial hemorrhages take place in utero, often associated with permanent sequelae.[1–3] In contrast, fetal diagnosis of intracranial hemorrhage in the setting of autoimmune thrombocytopenia is unusual and the majority of cases of intracranial hemorrhage occur after birth and are frequently intraventricular.[9,10] In the majority of reported cases, the prognosis is poor: In 22 cases, Koyama[9] identified 5 stillbirths, 6 deaths after live birth, 4 children with psychomotor impairments, and only 4 children without sequelae. For 3 children, the prognosis was unknown.

Conclusions

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, medical history of autoimmune thrombocytopenia, and corticosteroid therapy.[9,11] Neonatal cerebral hemorrhage due to autoimmune thrombocytopenia is much less common than in the alloimmune form, but potentially serious. It also tends to occur after birth and clinicians must be aware of this timing.

From this experience 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 known history of autoimmune thrombocytopenia, independently of their platelet count 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 to 5 days of life. Following current recommendations, intravenous immunoglobulin and platelet transfusion should be administered if the platelet count is lower than 30 G/L. In case of hemorrhagic diathesis, 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 (cranial ultrasound and brain MRI in case of pathological findings at ultrasound) should be done as soon as possible after delivery, even if the suspicion index is low.[16] A prompt diagnosis, a correct treatment, and a close multidisciplinary follow-up are essential to ensure the best outcome.

Established Facts

Severe neonatal thrombocytopenia with subsequent intracranial hemorrhage is a rare complication of maternal autoimmune thrombocytopenia with potential serious morbidity.

Novel Insights

Neonates born to mothers with maternal immune thrombocytopenia should be closely monitored after birth independently of maternal platelets count, even at delivery. Prompt diagnosis and treatment are essential to reduce the risk of neurological disabilities.

Author Contributions

AB, CFC, RDL and JF have been involved in the clinical care of the patient and have drafted the manuscript. FB has interpreted the hematological findings and critically revised the manuscript. ML was involved in US and MRI interpretation. All authors reviewed and accepted the final version.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Ethics approval is not requested in our Institution for single-case reports but the parents have been informed and have given their oral consent for publication.

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