Neonatal Alloimmune Thrombocytopenic Purpura and Congenital Porencephaly in Two Siblings Associated With a "New" Maternal Antiplatelet Antibody

By J.M. Friedman and R.H. Aster

We report a brother and sister, both of whom have porencephaly, hydrocephalus, optic atrophy, severe mental retardation, and spastic quadraparesis. In the younger child, abnormal intracranial structure was demonstrated by sonography at 32 weeks' gestation and was suspected earlier. Both children had transient severe thrombocytopenia as newborns. The mother is healthy and has never had purpura or other bleeding symptoms. However, her serum was found to react strongly with platelets from the father and from both children. The antibody in the mother's serum is platelet-specific but does not appear to be directed against any of the known antigens associated with neonatal alloimmune thrombocytopenic purpura (NATP) in other families, including Pf$^1$, Pf$^2$, or Bak$. Although the mother's serum reacts with platelets from all 47 unrelated normal donors tested and from both the mothers and the fathers of 17 other children with suspected NATP, it does not react with her own platelets or with platelets from a patient with Glanzmann's thrombasthenia. These observations suggest that the serum from this woman identifies a previously undescribed high-frequency platelet-specific alloantigen and that sensitization to this determinant caused severe immune thrombocytopenia in both her children. It is likely that this led to intracranial hemorrhage in utero in these cases.

IN 1980, Jesurun et al briefly described two siblings with congenital porencephaly and severe neonatal thrombocytopenia. We have found that the serum from the mother of these children contains an unusual antibody that is strongly cytotoxic for their platelets and for those of her husband. This antibody does not appear to react with any previously recognized antigen and may define a new platelet-specific alloantigen.

CASE REPORTS

Case 1

The patient was the product of a term pregnancy that was normal except that fetal activity was noted to be poor throughout. The delivery was vaginal with cephalic presentation and was complicated by fetal macrocrania. The infant was 9.160 g (50th percentile); length, 46 cm (10th percentile); and head circumference, 40.6 cm (~97th percentile). She was noted at birth to have multiple petechiae and ecchymoses and a large subcutaneous hematoma of the scalp. CBC at a few hours of age revealed a hemoglobin of 8.7 g/dL and a platelet count of 24,000/$\mu$L. By 24 hours of age, the platelet count fell to 6,000/$\mu$L.

Computed tomography (CT) brain scan on the first day of life is shown in Fig 1. The presence of blood within the cerebral ventricles was documented by ventricular tap. The baby was treated with phenobarbital for seizures and with random platelet transfusions and steroids. Platelet counts rose transiently after the transfusions but fell again within 12 to 18 hours. The platelet count returned to normal by day 3 of life and remained so after steroids were withdrawn. The baby was discharged from the nursery at 22 days of age.

The child has subsequently been healthy except for one hospitalization for pneumonia and one for dehydration. However, her growth and especially her development have been extremely slow. At 2½ years of age, all of her developmental milestones were below the one year norm. On physical examination at age 2½ years of age, the weight, length, and head circumference were all well below the third percentile. She had cranial asymmetry, frontal bossing, searching nystagmus, optic atrophy, generalized hypertonicity, and severe mental retardation.

Case 2

The younger brother of Case 1, the patient was the product of an uncomplicated term pregnancy. Growth and intracranial structure of the fetal head were monitored repeatedly by sonography from the 18th week of gestation, and abnormal intracranial sonolucent areas were clearly evident during the third trimester (Fig 2). The baby was delivered by cesarean section because of macrocrania and double-footling breech presentation. The birth weight was 3,120 g (50th percentile); the length, 50.5 cm (75th percentile); and the head circumference, 37.5 cm (97th percentile). The infant was noted to have petechiae and ecchymoses all over his body. His platelet count fell during the immediate newborn period to a nadir of 12,000/$\mu$L at 36 hours of age. A CT brain scan on the day of birth showed markedly dilated lateral and third ventricles and a large porencephalic cyst replacing much of the left cerebrum. The baby was treated by double-volume exchange transfusion twice without significant effect on the platelet count, but the count did increase transiently after transfusion of random-donor platelets. He was also treated with prednisone beginning on the fourth day of life. By 1 week of age, the thrombocytopenia had resolved. He was discharged at age 2 weeks.

A ventriculoperitoneal shunt was inserted at age 1 month for treatment of the hydrocephalus. His health has generally been good since, although his psychomotor development is markedly delayed. On physical examination at age 16 months, his height was in the 90th percentile, his weight in the tenth to 25th percentile, and his...
NATP DUE TO A "NEW" MATERNAL ANTIBODY

stillbirth of a male infant whose external appearance was normal. The fifth and sixth pregnancies produced children with severe neurologic impairment (Cases 1 and 2). All of the pregnancies, except the first, were by the same father.

The mother has never had purpura or bleeding problems. Her platelet count the day after she gave birth to Case 2 was 269,000/μL. There is no other family history of birth defects or mental retardation and no consanguinity.

SEROLOGIC STUDIES

The clinical course of these children and the lack of evidence for autoimmune thrombocytopenia in their mother led to serologic studies to investigate the possibility that their neonatal thrombocytopenia was of alloimmune origin. Maternal serum was assayed for antiplatelet antibodies by two standard techniques: complement-mediated platelet cytotoxicity using 51Cr release and the platelet suspension immunofluorescence test (PSIFT) using fluorescein-labeled anti-IgG. Platelets were typed for P1<sup>+</sup> and Bak<sup>+</sup> antigens using the PSIFT test. Anti-P1<sup>+</sup> typing reagents were from cases of neonatal alloimmune thrombocytopenic purpura (NATP) and posttransfusion purpura studied by us previously. Anti-Bak<sup>+</sup> was obtained from Dr A.E.G. von dem Borne of Amsterdam. A second anti-Bak<sup>+</sup> antibody from our collection, which gave reactions identical to those of the Amsterdam serum against a panel of platelets from 90 normal subjects, was also used. P1<sup>+</sup> typing was done with the 51Cr-release test using a complement-activating, anti-P1<sup>+</sup> antibody obtained from Dr N.R. Shulman of the National Institutes of Health.

The Pen serum, tested about one month after it was drawn, gave strong positive reactions in both 51Cr release and indirect immunofluorescence testing against platelets from the father and from both children obtained when their platelet levels were normal. It failed to react with autologous platelets on repeated occasions. After about six months of storage at -30 °C, the serum gave much weaker reactions in the 51Cr test. Strength of the reactions in PSIFT was unchanged, however, and all subsequent studies were done with the latter technique.

Serum Pen, used undiluted or at dilution 1:10, gave strongly positive reactions in PSIFT with platelets from 47 unrelated normal subjects. Two of these were P1<sup>+</sup> negative, and two were Bak<sup>+</sup> negative, but all were P1<sup>+</sup> positive. The serum gave equally strong reactions against platelets from both the mothers and the fathers of 17 other children with suspected NATP studied serially. In eight of these cases, the mother’s platelets were P1<sup>+</sup> negative, and in four cases, they were Bak<sup>+</sup> negative. On repeated testing, serum Pen failed to give detectable reactions with platelets from a patient with type I Glanzmann’s thrombasthenia (GT). Platelets...
GPIIIa.  
A recent report has implicated a second  
carried on a normal platelet membrane glycoprotein,  
catastrophic bleeding may occur in utero.  

et al.\' Thus, operative delivery, which has been recom-  

specific antigen  
who were Baka positive.  
against a panel of platelets from nine normal subjects  
absorption of serum Pen with platelets from 90% of a Caucasian population, as the  
provocative antigen in two siblings with NATP born to  

from this same GT patient have been shown previously  
to contain no detectable quantities of membrane glyco-  
proteins IIb or IIIa.\' The same GT platelets gave  
strong positive reactions with HLA-specific antisem-  
s. Pen serum, tested in cytotoxicity against a panel  
of lymphocytes from 100 normal subjects, gave weak  
positive reactions with only 12%. No definite specific-  
ity could be assigned to these reactions.  

Platelet and lymphocyte typings in the Pen family  
are summarized in Table 1. The entire family is  
positive for PI^{A1} and PI^{E1}, but the mother is Bak^a  
negative. Bak^a-specific reagents were not available  
when typing was done on the other family members.  
However, absorption of serum Pen with platelets from  
a Bak^a-negative donor removed all reactivity in PSIFT  
against a panel of platelets from nine normal subjects  
who were Bak^a positive.  

**DISCUSSION**  

It seems likely that the porencephaly and severe  
neurologic impairment of these two children is attrib-  
utable to intracerebral hemorrhage resulting from  
severe alloimmune thrombocytopenia. In Case 2, por-  
encephaly was clearly demonstrated sonographically  
before the cesarean section delivery. Intracerebral  
hemorrhage probably also occurred before delivery  
in Case 1, in which the infant's head was large at birth.  
Congenital porencephaly in infants with NATP has  
also been reported by Zalneraitus et al.\' and by Naidu  
et al.\' Thus, operative delivery, which has been recom-  

The P1^2 antigen appears to be  
but the mother is Bak^a  
negative. Bak^a-specific reagents were not available  
when typing was done on the other family members.  
However, absorption of serum Pen with platelets from  
a Bak^a-negative donor removed all reactivity in PSIFT  
against a panel of platelets from nine normal subjects  
who were Bak^a positive.  

**Table 1. Platelet and Lymphocyte Phenotypes in the Pen Family**  

<table>
<thead>
<tr>
<th>Subject</th>
<th>PI^{A1}</th>
<th>Bak^a</th>
<th>PI^{E1}</th>
<th>HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>A2;B35,w6;Cw4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A24;B44,w4:-</td>
</tr>
<tr>
<td>Case 1</td>
<td>+</td>
<td>NT</td>
<td>+</td>
<td>A2;B35,w6;Cw4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A24;B60,w6;Cw3</td>
</tr>
<tr>
<td>Case 2</td>
<td>+</td>
<td>NT</td>
<td>+</td>
<td>A2;B35,w6;Cw4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A24;B44,w4:-</td>
</tr>
<tr>
<td>Father</td>
<td>+</td>
<td>NT</td>
<td>+</td>
<td>A2;B44,w6;Cw4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A24;B60,w6;Cw3</td>
</tr>
</tbody>
</table>

When Bak^a typing serum became available, only platelets from the mother could be obtained for study. NT, not tested.  

Most cases of NATP are associated with maternal–fetal incompatibility for the high-frequency platelet-specific antigen PI^{A1}.\' The PI^{A1} antigen appears to be  
carried on a normal platelet membrane glycoprotein, GPIIIa.\' A recent report has implicated a second  
platelet-specific antigen, Bak^a, which is present on  
platelets from 90% of a Caucasian population, as the  
provocative antigen in two siblings with NATP born to  
a PI^{A1}-positive mother.\' Alloantiserums specific for the  
antigen Bak^a, like those reactive with PI^{A1}, fail to bind  
to platelets that lack surface glycoproteins IIb or IIIa.\' In one other case of NATP, the low-frequency  
platelet antigen PI^{E2} was implicated as the immuno-  
gen.\'  

Normal platelet levels in the blood of Mrs Pen, the  
absence of a history suggestive of thrombocytopenia,  
and failure of the antibody in her serum to react with  
autologous platelets argue strongly against the possi-  
bility that a platelet autoantibody might have caused  
thrombocytopenia in her children. An antibody reac-  
tive with platelets from all normal subjects but not  
autologous platelets or platelets from patients with  
Glanzmann's thrombasthenia has been described in a  
multiply transfused patient with Glanzmann's disease.\' The absence of bleeding symptoms in Mrs Pen  
even after cesarean section argues strongly against the  
possibility that she has GT. Her PI^{A1}-positive platelet  
phenotype is also in conflict with this possibility  
because PI^{A1} is absent or only weakly expressed on  
platelets of patients with this disorder.\'\'\'\'\'\'\' Weak  
antilymphocyte activity was found in her serum, but  
anti-HLA antibodies have not been shown conclusively  
to be capable of causing NATP. Moreover, all the  
HLA antigens of Case 2 are shared with his mother  
except for a “blank” at the HLA-C locus. The weak  
lymphocytotoxic reactions seen with serum Pen  
appear, therefore, to be an incidental finding.  

The mother's platelet phenotype and the reaction  
pattern of her serum with the normal platelet panel  
make it unlikely that her antibody is specific for PI^{A1} or  
PI^{E2}. Although she is Bak^a negative, the reaction pattern  
of her serum with the platelet panel and the total  
absorption of her antibody by Bak^a-negative platelets  
indicate that it is not specific for Bak^a. Serum Pen  
reacted with platelets from each of 81 subjects tested  
and failed to react only with the mother's own platelets  
and platelets of a patient with type I GT. These  
findings are consistent with the possibility that serum  
Pen recognizes a high-frequency, platelet-specific  
alloantigen other than PI^{A1} and Bak^a, which is carried  
on glycoprotein IIb or IIIa. Studies of the reaction  
serum Pen against platelets from a Hispanic popula-  
tion have not yet been performed but are necessary to  
determine whether the Pen-negative phenotype is more  
common in that group than among midwestern Cauca-  
sians.  

**ACKNOWLEDGMENT**  

We are grateful to the El Paso Rehabilitation Center and to  
Cecilia Sada for facilitating our study, to Janice Collins for her  
outstanding technical assistance, and to the Pen family for their  
cooperation.
REFERENCES


Neonatal alloimmune thrombocytopenic purpura and congenital porencephaly in two siblings associated with a "new" maternal antiplatelet antibody

JM Friedman and RH Aster

Updated information and services can be found at:
http://www.bloodjournal.org/content/65/6/1412.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml