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

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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 P1A, P1B, or B. 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.

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 macrosomia. The infant was a female whose weight was 3,160 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/μL. By 24 hours of age, the platelet count fell to 6,000/μL.

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 2 years of age, all of her developmental milestones were below the one year norm. On physical examination at age 2 years, the weight, length, and head circumference were all well below the third percentile. She had cranial asymmetry, frontal bossing, searching nystagmus, optic atrophy, generalized hypotonicity, and severe mental retardation.

Case 2

The younger brother of Case 1 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 macrocephaly 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 1,200/μL 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

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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 PI" and Bak4 antigens using the PSIFT test. Anti-PI" typing reagents were from cases of neonatal alloimmune thrombocytopenic purpura (NATP) and posttransfusion purpura studied by us previously. Anti-Bak4 was obtained from Dr A.E.G. von dem Borne of Amsterdam. A second anti-Bak4 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. PI11 typing was done with the 51Cr-release test using a complement-activating, anti-PI11 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 PI11 negative, and two were Bak4 negative, but all were PI11 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 PI11 negative, and in four cases, they were Bak4 negative. On repeated testing, serum Pen failed to give detectable reactions with platelets from a patient with type I Glanzmann’s thrombasthenia (GT). Platelets
from this same GT patient have been shown previously to contain no detectable quantities of membrane glycoproteins Ib or IIa. The same GT platelets gave strong positive reactions with HLA-specific antisera. Pen serum, tested in cytotoxicity against a panel of lymphocytes from 100 normal subjects, gave weak positive reactions with only 12%. No definite specificity 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 PlA1 and PlE1, but the mother is Bak negative. Bak-specific reagents were not available when typing was done on the other family members. However, absorption of serum Pen with platelets from a Bak-negative donor removed all reactivity in PSIFT against a panel of platelets from nine normal subjects who were Bak positive.

### DISCUSSION

It seems likely that the porencephaly and severe neurologic impairment of these two children is attributable to intracerebral hemorrhage resulting from severe alloimmune thrombocytopenia. In Case 2, porencephaly 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 al9 and by Naidu et al.10 Thus, operative delivery, which has been recommended for infants at risk of NATP,11,12 will not prevent all cases of intracerebral hemorrhage because catastrophic bleeding may occur in utero.

Most cases of NATP are associated with maternal–fetal incompatibility for the high-frequency platelet-specific antigen PlA1. The PlA1 antigen appears to be carried on a normal platelet membrane glycoprotein, GPIIbα. A recent report has implicated a second platelet-specific antigen, Bak, which is present on platelets from 90% of a Caucasian population, as the provocative antigen in two siblings with NATP born to a PlA1-positive mother.4 Alloantisers specific for the antigen Bak, like those reactive with PlA1, fail to bind to platelets that lack surface glycoproteins Ib or IIa.4 In one other case of NATP, the low-frequency platelet antigen PlE2 was implicated as the immunogen.7

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 possibility that a platelet autoantibody might have caused thrombocytopenia in her children. An antibody reactive 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.14 The absence of bleeding symptoms in Mrs Pen even after cesarean section argues strongly against the possibility that she has GT. Her PlA1-positive platelet phenotype is also in conflict with this possibility because PlA1 is absent or only weakly expressed on platelets of patients with this disorder.8,15,16 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 PlA1 or PlE2. Although she is Bak negative, the reaction pattern of her serum with the platelet panel and the total absorption of her antibody by Bak-negative platelets indicate that it is not specific for Bak. 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 1 GT. These findings are consistent with the possibility that serum Pen recognizes a high-frequency, platelet-specific alloantigen other than PlA1 and Bak, which is carried on glycoprotein Ib or IIa. Studies of the reaction of serum Pen against platelets from a Hispanic population have not yet been performed but are necessary to determine whether the Pen-negative phenotype is more common in that group than among midwestern Caucasians.

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