Frequency of Immune Thrombocytopenia in Newborns: A Prospective Study

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Thrombocytopenia is a common condition in distressed newborns, but little is known about thrombocytopenia in an unselected cohort of neonates. In an attempt to address this issue, a multicenter prospective study was conducted in three obstetrical wards of AP-HP in Paris. We found the frequency of neonatal thrombocytopenia ($<150 \times 10^9$ /L) to approximate 0.9% (48 of 5,632 appropriate samples). An immune mechanism was likely to be the cause of thrombocytopenia in 10 of the 33 cases studied, implying an incidence of 0.3% of immune neonatal thrombocytopenia in the general population. The frequency of alloimmune thrombocytopenia was 1.5/1,000 liveborn neonates, and 1/1,000 when consid-

THROMBOCYTOPENIA is a common condition in dis-THROMBOCY I OPENIA IS a common cert tressed newborns¹ and is reported to affect 20% to 40% of infants in intensive care units.^{2,3} However, the frequency of neonatal thrombocytopenia in a normal cohort of newborns is not defined because platelet count is not routinely performed, except in cases of neonatal bleeding or purpura or when a previously recognized immune maternal disorder is prone to induce fetal thrombocytopenia. In an attempt to address the issue of neonatal thrombocytopenia in an unselected population of newborns and for defining the contribution of immune etiologies in this condition, a multicenter prospective study was conducted in three large obstetrical centers in Paris, France. We found the frequency of neonatal thrombocytopenia to be approximately 0.9% and the frequency of ascertained immune thrombocytopenia to be approximately 0.3%. This finding raises important issues concerning the monitoring of thrombocytopenic newborns, the management of their mothers and their future siblings.

MATERIALS AND METHODS

Population studied. The study was examined by the Committee of Protection of Persons for Biomedical Research (CPPRB) of University Hospital Saint Antoine, Paris VI. It was found in agreement with the Helsinky convention, and we were allowed to proceed.

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ering anti-HPA-1a allo-immunization. Because thrombocytopenia, whatever its cause, was often silent and delayed, it appears that the only way to detect neonatal thrombocytopenia in time to prevent its potential disastrous complications would be to perform a systematic neonatal blood sampling for platelet count. All cases of ascertained thrombocytopenia should then be screened for an immune mechanism to enable early detection of autoimmune diseases in mothers and careful monitoring of subsequent pregnancies and deliveries, leading to appropriate prevention of potential severe deleterious effects in the offspring. © 1997 by The American Society of Hematology.

During a 16-month period, we attempted to obtain umbilical cord blood samples from all neonates born in three different obstetrical departments in Paris, France. We did not exclude premature newborns or children born to women who previously had been characterized to have platelet allo or autoantibodies. During the 16-month study, a total of 6,081 of 8,836 newborns were sampled. Lack of sampling in 2,755 (31%) newborns was mostly due to the unability of nurses in the obstetrical ward to perform the sampling because of other responsibilities and overwork. Because only 69% of the newborns were actually sampled, we were concerned about a possible bias in the selection of sampled newborns. To address this issue, 100 of the 6,081 sampled babies and 100 of the 2,755 not sampled babies, taken at random in our study group, were compared for sex, ethnic origin, birthweight, gestational age, mode of delivery, Apgar score, resuscitation in a neonatal intensive care unit, parity, and maternal age. Comparison of these two groups (screened and unscreened), showed no significant difference for the variables tested, except for birthweight, which was significantly lower (P = .0054) and maternal age significantly higher (P = .011) in the unscreened group.⁴ As such, some of the babies may have not been sampled because of their low birthweight. Of the 6,081 blood samples obtained, 449 (7%) were not analyzed for various technical problems, such as presence of platelet aggregates, blood clotting, unmarked, or broken test tubes. The percentage of excluded samples was the same in each of the three centers. Ultimately, platelet counts were obtained on 5,632 neonatal blood samples representing 64% of all the liveborn infants in the three centers.

Methods. Platelet count was performed on EDTA anticoagulated blood using a standard automatic blood cell counter. Diagnosis of thrombocytopenia was based on the finding of a platelet count <150 \times 10⁹/L. This diagnosis was systematically confirmed by determining platelet count on a second venous or capillary blood sample. When neonatal thrombocytopenia was established and informed consent obtained, platelet typing of the parents and identification of maternal allo or autoantiplatelet antibody was performed using radioimmunoassays and monoclonal antibody specific immobilization of platelet antigen (MAIPA).⁵ Maternal serum was systematically screened with a panel of phenotyped donors and the fathers's platelets. Diagnosis of antiplatelet alloimmunization requires both parental human platelet antigen (HPA) incompatibility and detection in the maternal serum of an alloantibody, directed against the offending HPA. A parental HPA-1 mismatch is the likely cause of neonatal alloimmune thrombocytopenia (NAIT), even when there is no detectable anti-HPA-1a antibody in the serum of the mother.6 In contrast, in the other HPA systems when parental HPA incompatibility is not associated with the corresponding anti-HPA antibody in the maternal serum, the diagnosis of NAIT is equivocal. In our study, we define these cases as "potential alloimmune thrombocytopenia." Maternal

			Neonatal Platelet Count $ imes$ 10 ⁹ /L					Neonatal Clinical Status	
Case	Parental Mismatch	Maternal Status	UC	Nadir	(day)	RD	Treatment	Bleeding	Associated Illness
1	HPA-1	Anti-HPA-1a	46	28	(0)	3	IVIgG (day 1)	Absence	IUGR
2	HPA-1	Anti-HPA-1a	50	38	(1)	5	None	Absence	Absence
3	HPA-1	Anti-HPA-1a	2	2	(0)	6	IVIgG (day 0)	Extensive purpura	Absence
4	HPA-1	Anti-HPA-1a	20	20	(0)	0	IVIgG, platelets (day 0)	Hemorrhage after PUBS	Porencephaly
5	HPA-1	No anti-HPA-1a	135	17	(5)	7	IVIgG (day 5)	Absence	Acute fetal distress
6	None	Thrombocytopenia, HIV infection	74	66	(1)	?	None	Absence	Absence
7	None	AITP, anti-GPIbIX	143	106	(5)	8	None	Absence	Absence
8	HPA-5	AITP, anti-HPA-5a	49	30	(9)	15	IVIgG, (days 1, 3, 4)	Absence	Absence
9	HPA-5	AITP, anti-GPIbIX, anti-HPA-5b	113	55	(2)	5	None	Meningeal hemorrhage	Transient respiratory distress
10	HPA-5	Compensated thrombocytolysis, anti-GPIbIX	8	2	(0)	60	Corticosteroids (1 mg/d)	Purpura	Absence

Table 1. Clinical and Biological Data of the 10 Newborns Displaying an Immune Neonatal Thrombocytopenia

Abbreviations: UC, umbilical cord sampling; IUGR, intrauterine growth retardation; (day), day when the nadir of platelet count was reached; IVIgG, intravenous immunoglobulins; RD, recovery day; PUBS, percutaneous umbilical blood sampling.

platelet-associated IgG (PAIgG) was determined by radioimmunoassay.⁷ To confirm the specificity of circulating antiplatelet autoantibodies, maternal serum was preincubated with mouse IgG-agarose beads, centrifuged, and the supernatant, devoid of human antibodies cross-reacting with mouse IgG, was then tested by the MAIPA test.⁸⁹

RESULTS

Frequency of the thrombocytopenia. In 48 of the 5,632 newborns evaluated, the platelet count was $<150 \times 10^9/L$, indicating an incidence of 0.9% thrombocytopenia at birth. Severe thrombocytopenia ($\leq 50 \times 10^9/L$) was either present at birth in nine of the 48 newborns diagnosed or developed after birth in nine additional cases. The natural history of thrombocytopenia was a postnatal decrease in platelet count in 28 of 39 (72%) neonates who underwent sequential platelet counts. The average nadir of 68 $\times 10^9/L$ (range, 21 to 124), was reached at day 3 (range, 1 to 9). Complete resolution of the thrombocytopenia spontaneously occurred within 4 to 60 days (median, 8 days).

Hemorrhagic symptoms were observed in four cases (Table 1). Two neonates displayed an extensive purpura at birth (cases 3 and 10). In one case (case 4), bleeding was secondary to a traumatic percutaneous umbilical fetal sampling: an emergency Cesarean section resulted in the birth of a severely anemic and thrombocytopenic girl (hemoglobin, 7.1 g/dL; platelet count, 20×10^{9} /L). She was resuscitated, infused with red blood cells, 3 U of frozen, irradiated, cytomegalovirus (CMV) negative, HPA-1a negative platelets, and intravenous immunoglobulin (IVIgG). This treatment resulted in a complete correction of the platelet count within a few hours. A left subependymal hemorrhage and porencephaly was seen, whose mechanism is controversial (anoxia due to the severe acute anemia or alloimmune thrombocytopenia), and which resolved without sequelae. Meningeal hemorrhage was observed in a unique infant (case 9), born to a gravida 4, para 3 woman who had previously undergone one spontaneous abortion and two uneventful deliveries. During the fourth pregnancy, she developed thrombocytopenia, anti-GPIbIX autoantibodies, as well as anti–HPA-5b alloantibodies. Antenatal fetal platelet count performed at 37 weeks gestation was 138×10^9 /L, allowing vaginal delivery. Neonatal platelet count was 135×10^9 /L at birth, and constantly over 50×10^9 /L during the postnatal course. Meningeal hemorrhage resolved without sequelae.

A specific treatment was initiated before day 5 in 6 of 48 newborns (Table 1) because of hemorrhagic symptoms (three cases) and/or severity of thrombocytopenia (three cases). Treatment included corticosteroid 1 mg/day (case 10), platelet concentrate infusion (case 4), IVIgG (cases 1, 3, 4, 5, and 8).

Of these 48 newborns, 15 were symptom-free, apparently healthy, and born to mothers with uncomplicated pregnancies, whereas nine were born to mothers affected by a previously characterized immune abnormality (n = 6) or severe hypertension (n = 3) and 24 exhibited fetal distress (n = 15), extensive neonatal purpura (n = 1), infection (n = 4), or other various diseases (n = 4).

Immunological studies. To determine the respective frequency of either allo or autoimmune thrombocytopenia in these newborns, we performed immunological studies. Adequate samples could be obtained from the parents in 33 of the 48 cases with thrombocytopenia: 11 of the 15 symptomfree cases, in all of the six cases associated with a previously recognized maternal immune disorder, in the only case of neonatal hemorrhagic expression, and in 15 of the other 27 cases with associated maternal or fetal pathology.

In 10 of these 33 cases, the presence of maternal antiplatelet allo or autoantibodies was evident (Table 1). Neonatal thrombocytopenia was assigned to anti–HPA-1a fetomaternal alloimmunization in four cases where there was both

Table 2. Clinical and Biological Data of the 13 Newborns Displaying a Potential Immune Thrombocytopenia

	D	Maternal Status	Neonata	I Platelet RD Co	unt ×10 ⁹ /L		Neonatal-Associated Disease	
Case	Mismatch		UC	Nadir	(day)	RD		
11	HPA-5	Hypertension	105	105	(0)	11	Premature, respiratory distress	
12	HPA-5	Healthy	137	43	(5)	>8	IUGR, septicemia (D4)	
13	HPA-5	Healthy	137	90	(6)	60	Microcephaly, IUGR	
14	HPA-5	Healthy	115	79	(0)	1	Premature, IUGR	
15	HPA-5	Healthy	134	90	(4)	5	Absence	
16	?	Anti-GPIbIX	148	110	(9)	11	Absence	
		Anti-HPA-5b						
17	HPA-5	Sepsis	103	65	(3)	5	Sepsis	
18	HPA-5	Healthy	144	119	(2)	5	Absence	
19	HPA-3	Healthy	139	193	(0)	1	IUGR	
20	HPA-3	Anti-GPIbIX	70	27	(6)	36	Down syndrome, right-hand agenesia	
21	HPA-3	Anti-GPIbIX	138	124	(0)	1	Absence	
22	HPA-3	Healthy	113	65	(0)	13	Absence	
23	None	Anti GPIbIX	85	50	(1)	4	Absence	

None of these newborns exhibited any hemorrhagic symptom. Therefore, none of them received any specific therapy aimed at increasing their platelet count.

parental HPA-1 incompatibility and maternal anti-HPA-1a antibodies, and in one case of isolated HPA-1 parental mismatch without anti-HPA-1a alloantibody in the maternal serum. In five cases, neonatal thrombocytopenia was related to maternal autoimmunity, which was overt in four cases and hidden in one case: One woman displayed thrombocytopenia with elevated PAIgG, related to a human immunodeficiency virus (HIV) infection, detected because of thrombocytopenia; retrovir 750 mg/day was prescribed from week 20 of gestation on. The baby was HIV-infected and subsequently developed acquired immune deficiency syndrome (AIDS), whereas thrombocytopenia was only transient, with a normal platelet count at 1 month of age. Three women had an already diagnosed autoimmune thrombocytopenic purpura (AITP) with elevated PAIgG, two of whom disclosed associated alloantibodies against HPA-5b or HPA-5a. In the last case, already described,¹⁰ the mother displayed a decreased platelet lifespan despite a normal platelet count, together with anti-GPIbIX autoantibody, leading to the diagnosis of compensated thrombocytolysis and hidden maternal autoimmunity. In this case, there was also a parental incompatibility for HPA-5, without circulating maternal alloantibodies.

In 13 of the 23 remaining cases, immune biological abnormalities were found, which cannot be assigned with certainty to neonatal thrombocytopenia (Table 2). In 11 of 13 cases, the parents were found to be incompatible in HPA-3 or HPA-5 systems, without detection of circulating specific maternal alloantibodies (HPA-5, seven cases; HPA-3, four cases). In one case, HPA-5b alloantibody was found in the plasma of an HPA-5a mother, but platelet phenotyping of both the father and the newborn could not be performed. In three of these 12 cases of suspected of alloimmunization, an anti-GPIbIX autoantibody was also seen in the mothers sera. Finally, in one case, anti-GPIbIX autoantibody was the only abnormality found in the serum of the mother.

In the remaining 10 newborns, immune study was negative, showing neither parental HPA incompatibility nor specific maternal antiplatelet antibody.

DISCUSSION

In a detection prospective study involving 5,632 unselected newborns, we find the overall frequency of neonatal thrombocytopenia, as defined as a platelet count $<150 \times$ 10^{9} /L, to approximate 0.9%. This frequency may have been underestimated for the following reasons: (1) Intrauterine growth retardation is often associated with neonatal thrombocytopenia.^{2,3} It is most likely that small for gestational age prone to thrombocytopenia were more numerous among the nonscreened newborns, as the mean birthweight in this population of 2,755 neonates was significantly lower than in the population of 5,632 screened newborns, whereas gestational age was comparable in both groups; and (2) Platelet count in thrombocytopenic newborns was found to decrease after birth, suggesting that infants in whom the platelet count was in the low normal range at birth may develop thrombocytopenia during the first week of life. Moreover, in our study, the incidence of severe neonatal thrombocytopenia, defined as a platelet count $\leq 50 \times 10^{9}$ /L, is either 0.14% (9 of 5,632 newborns) at birth, which is consistent with the 0.12% reported by Burrows and Kelton,¹¹ or 0.28% when including the 9 newborns whose platelet count decreased below this threshold during the first days of life.

The most important finding of our prospective study, aimed at defining not only the frequency, but also the causes of neonatal thrombocytopenia, is the frequent involvement of an immune mechanism. Neonatal immune thrombocytopenia is due to the transplacental transfer of circulating maternal antiplatelet antibodies. Autoimmune antibodies present in cases of maternal AITP recognize maternal, as well as fetal, platelet antigens and thus generally induce both maternal and fetal thrombocytopenia. The risk of neonatal hemorrhage is reported to occur mainly during delivery. In contrast, maternal alloantibodies developed against a fetal platelet alloantigen inherited from the father and absent on the maternal platelets, may induce a severe fetal thrombocytopenia; it may occur as early as the eighteenth week of gestation and carries the risk of severe antenatal cerebral hemorrhage and/or porencephaly, warranting specific antenatal management.¹²⁻¹⁶

In the present study, an immune mechanism was shown to account for thrombocytopenia in 10 of the 33 cases studied, implying the incidence of immune neonatal thrombocytopenia to approximate 0.3% of live births. This suggests that this condition is not that uncommon in newborns. Our study shows that it may be clinically silent, even in case of HPA-1a alloimmunization, and therefore, pass unnoticed: In 15 of 48 neonates in our series, thrombocytopenia (related to HPA-1a alloimmunization in two cases) would not have been detected at birth, because the newborns were symptom-free and apparently healthy. We observed only one case of spontaneous severe bleeding: a meningeal hemorrhage that occurred in a newborn whose thrombocytopenia, due to the association of circulating maternal allo and autoantiplatelet antibodies, was moderate. This severe accident may be related to an impairment of platelet function induced by antiplatelet antibodies, as already reported.¹⁷ The low frequency of clinically severe neonatal alloimmunization is in contrast with previous retrospective studies reporting only symptomatic cases. In these studies, intracerebral hemorrhages due to NAIT have been reported to be frequent, resulting in 10% to 20% of neurological sequelae and 10% of deaths.^{18,19} Such a dramatic outcome has probably been prevented in our series by systematic detection of thrombocytopenia, leading to a specific treatment aimed at improving the platelet count in case of prolonged, severe neonatal thrombocytopenia.

The frequency of NAIT ascertained on the presence of maternal alloantibodies against specific platelet antigens was 1.5 of 1,000 liveborn neonates and one of 1,000 when considering anti-HPA-1a alloimmunization. These results are consistent with the one of 1,000 incidence of anti-HPA-1a-related NAIT found when systematically screening primiparous women⁴ or women of various parities.²⁰ The same incidence of one of 1,000 was found for anti-HPA-1a alloimmunization in a population of women regardless of parity.²¹ However, alloimmunization does not always result in NAIT²¹⁻²³ and conversely, maternal circulating antibodies were undetectable in up to 29% of neonatal thrombocytopenia associated with parental mismatch for platelet antigens and in six of 19 (32%) cases in our series. Those cases address the question as to whether neonatal thrombocytopenia is related to fetomaternal alloimmunization in the absence of detectable alloantibodies in the maternal serum. Systematic follow-up of subsequent pregnancies should help to answer this question.

In conclusion, our findings, when systematically screening an unselected population of newborns, imply that the incidence of neonatal thrombocytopenia is generally significantly underestimated, as this disorder is frequently both silent and delayed. Therefore, a systematic sampling for platelet count, within the first days of life, appears to be the only way to detect neonatal thrombocytopenia in time to prevent its potential complications. Similarly, immune neonatal thrombocytopenia is not a rare event, and comprehensive immunological studies should be performed in all cases of neonatal thrombocytopenia, including when a neonatal

APPENDIX

of potential severe deleterious effects in their offspring.

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