Frequency of Immune Thrombocytopenia in Newborns: A Prospective Study

By Marie Dreyfus, Cécile Kaplan, Elizabeth Verdy, Nicole Schlegel, Isabelle Durand-Zaleski, Gil Tchernia, and the Immune Thrombocytopenia Working Group

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 x 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 considering 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.

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platelet-associated IgG (PAIgG) was determined by radioimmunoassay. 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, was then tested by the MAIPA test.

RESULTS

Frequency of the thrombocytopenia. In 48 of the 5,632 newborns evaluated, the platelet count was <150 × 10^9/L, indicating an incidence of 0.9% thrombocytopenia at birth. Severe thrombocytopenia (≤50 × 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 × 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 (IVlgG). 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), IVlgG (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 symptom-free 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 fetomatern al alloimmunization in four cases where there was both
Table 2. Clinical and Biological Data of the 13 Newborns Displaying a Potential Immune Thrombocytopenia

<table>
<thead>
<tr>
<th>Case</th>
<th>Parental Mismatch</th>
<th>Maternal Status</th>
<th>Neonatal Platelet RD Count x 10^9/L</th>
<th>Neonatal-Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>HPA-5</td>
<td>Hypertension</td>
<td>105 105 (0)</td>
<td>Premature, respiratory distress</td>
</tr>
<tr>
<td>12</td>
<td>HPA-5</td>
<td>Healthy</td>
<td>137 43 (5)</td>
<td>IUGR, septicemia (D4)</td>
</tr>
<tr>
<td>13</td>
<td>HPA-5</td>
<td>Healthy</td>
<td>137 90 (6)</td>
<td>Microcephaly, IUGR</td>
</tr>
<tr>
<td>14</td>
<td>HPA-5</td>
<td>Healthy</td>
<td>115 79 (0)</td>
<td>Premature, IUGR</td>
</tr>
<tr>
<td>15</td>
<td>HPA-5</td>
<td>Healthy</td>
<td>134 90 (4)</td>
<td>Absence</td>
</tr>
<tr>
<td>16</td>
<td>HPA-5</td>
<td>Anti-GPIIbIX</td>
<td>148 110 (9)</td>
<td>Absence</td>
</tr>
<tr>
<td>17</td>
<td>HPA-5</td>
<td>Sepsis</td>
<td>103 65 (3)</td>
<td>Sepsis</td>
</tr>
<tr>
<td>18</td>
<td>HPA-5</td>
<td>Healthy</td>
<td>144 119 (2)</td>
<td>Absence</td>
</tr>
<tr>
<td>19</td>
<td>HPA-3</td>
<td>Healthy</td>
<td>139 193 (0)</td>
<td>IUGR</td>
</tr>
<tr>
<td>20</td>
<td>HPA-3</td>
<td>Anti-GPIIbIX</td>
<td>70 27 (6)</td>
<td>Down syndrome, right-hand agenesia</td>
</tr>
<tr>
<td>21</td>
<td>HPA-3</td>
<td>Anti-GPIIbIX</td>
<td>138 124 (0)</td>
<td>Absence</td>
</tr>
<tr>
<td>22</td>
<td>HPA-3</td>
<td>Healthy</td>
<td>113 65 (0)</td>
<td>Absence</td>
</tr>
<tr>
<td>23</td>
<td>None</td>
<td>Anti GPIIbIX</td>
<td>65 50 (1)</td>
<td>Absence</td>
</tr>
</tbody>
</table>

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

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 x 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. It is most likely that small for gestational age thrombocytopenia were more numerous among the unscreened 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 <50 x 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, 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.\textsuperscript{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 anti-platelet antibodies, as already reported.\textsuperscript{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.\textsuperscript{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 women\textsuperscript{4} or women of various parities.\textsuperscript{20} The same incidence of one of 1,000 was found for anti--HPA-1a alloimmunization in a population of women regardless of parity.\textsuperscript{21} However, alloimmunization does not always result in NAIT\textsuperscript{21-23} 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 fetomaternial 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 pathology likely to be associated with thrombocytopenia is present. Identification of immune neonatal thrombocytopenia should enable early detection of autoimmune diseases in mothers and also enable a careful monitoring of subsequent pregnancies and deliveries, leading to appropriate prevention of potential severe deleterious effects in their offspring.

**APPENDIX**

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**REFERENCES**

12. Kaplan C, Daffos F, Forestier F, Cox WL, Lyon-Caen D,
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