Thrombocytopenia in the HELLP syndrome is not due to platelet-associated IgG (PAIgG)

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Accepted for publication 20 January 1992

Summary

The presence of membrane-bound and circulating platelet-associated IgG (PAIgG) in nine pregnant women with hemolysis, elevated liver enzymes, and low platelet count (HELLP syndrome) was investigated. The reference group consisted of 21 patients with chronic idiopathic thrombocytopenic purpura (ITP). In the majority of patients with ITP, thrombocytopenia results from the binding of PAIgG to the platelet membrane with subsequent platelet destruction. In none of the patients with HELLP syndrome membrane-bound or circulating PAIgG was found. By contrast, membrane-bound and circulating PAIgG was detected in 15 of the 21 cases of chronic ITP (71.4%). These findings suggest that platelet destruction in patients with HELLP syndrome does not result from the binding of PAIgG to the platelet membrane. Therefore, the treatment of thrombocytopenia in this syndrome with immunosuppressants (e.g., corticosteroids), as in chronic ITP, does not seem appropriate.

HELLP syndrome; Thrombocytopenia; Pre-eclampsia; Platelet-associated IgG

Introduction

Pre-eclampsia/eclampsia associated with hemolysis (H), elevated liver enzymes (EL), and low platelet count (LP) was first reported by Pritchard et al. in 1954 [1]. This variant of pre-eclampsia/eclampsia was designated ‘EPH gestosis type B’ by Goodlin et al. [2], and Weinstein [3] termed it the ‘HELLP syndrome’. In a recent study of 112 patients with well-defined HELLP syndrome, the perinatal mortality rate was found to be 367 per 1000 and neonatal morbidity was considerable [4]. In the same study there were two maternal deaths, two patients with ruptured liver hematoma, and nine with acute renal failure. Recommendations for the management of such pregnancies are conflicting. In view of the poor maternal and fetal outcome associated with the HELLP syndrome, most authors recommend expeditious delivery [4–6]; some advise a more conservative approach to prolong pregnancy in an attempt to achieve greater fetal maturity [2,7]. Neonatal thrombocytopenia has been observed in pre-eclampsia complicated by thrombocytopenia [9] and in the HELLP syndrome [5], suggesting that some immunologic component that crosses the placenta is

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TABLE I
Clinical data on admission of the patients with HELLP syndrome

<table>
<thead>
<tr>
<th>Data</th>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<th>6</th>
<th>7</th>
<th>8</th>
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<td>Age (years)</td>
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<td>26</td>
<td>29</td>
<td>26</td>
<td>26</td>
<td>25</td>
<td>25</td>
<td>32</td>
<td>26</td>
<td>33</td>
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<tr>
<td>Gravidity/parity</td>
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<td>1/0</td>
<td>1/0</td>
<td>1/0</td>
<td>1/0</td>
<td>1/0</td>
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<td>Gestational age (weeks)</td>
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<td>39</td>
<td>34</td>
<td>32</td>
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<td>35</td>
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<tr>
<td>Edema</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Significant proteinuria *</td>
<td></td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>+</td>
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<tr>
<td>Blood pressure (mmHg) systolic</td>
<td></td>
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<td>150</td>
<td>170</td>
<td>140</td>
<td>160</td>
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<tr>
<td>Blood pressure (mmHg) diastolic</td>
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<td>60</td>
<td>80</td>
<td>100</td>
<td>100</td>
<td>110</td>
<td>110</td>
<td>100</td>
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<tr>
<td>Epigastric pain</td>
<td></td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td></td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
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</tbody>
</table>

* Proteinuria of 2+ or more by dip stick, or 0.3 g/l or more in a 24-h urine collection was considered significant.

responsible for the thrombocytopenia [5]. An observation compatible with this hypothesis is found in the report of a patient with this syndrome treated with plasma exchange transfusion in the postpartum period: after the exchange, all laboratory parameters returned to normal [10]. By contrast, other authors have found no correlation between the degree of maternal thrombocytopenia and the development of neonatal thrombocytopenia [4,8].

In view of these conflicting observations, our investigations were undertaken to clarify the possible role of platelet-associated IgG (PAIgG) as a humoral immunologic factor in the pathogenesis of the HELLP syndrome. The reference group in this study consisted of patients with chronic idiopathic thrombocytopenic purpura (ITP). In the majority of patients with this disorder, thrombocytopenia is due to binding of PAIgG to the platelet membrane, resulting in phagocytosis by macrophages, primarily in the spleen. The consequences of our findings for the management of pregnancies affected by the HELLP syndrome are discussed.

TABLE II
Laboratory findings on admission of the patients with HELLP syndrome

<table>
<thead>
<tr>
<th>Findings</th>
<th>Patient</th>
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<th>7</th>
<th>8</th>
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<tr>
<td>LDH (U/l) 80–240 *</td>
<td></td>
<td>337</td>
<td>364</td>
<td>365</td>
<td>490</td>
<td>382</td>
<td>530</td>
<td>1308</td>
<td>456</td>
<td>567</td>
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<tr>
<td>Peripheral blood smear (schistocytes)</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
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<tr>
<td>GOT (U/l) 0–15 *</td>
<td></td>
<td>35</td>
<td>44</td>
<td>98</td>
<td>100</td>
<td>158</td>
<td>170</td>
<td>43</td>
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<td>97</td>
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<tr>
<td>GPT (U/l) 0–17 *</td>
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<td>73</td>
<td>163</td>
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<td>261</td>
<td>NA</td>
<td>34</td>
<td>53</td>
<td>104</td>
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<td>Platelet count (× 10^9/l)</td>
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<td>54</td>
<td>55</td>
<td>38</td>
<td>54</td>
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<td>APTT (s) 30–40 *</td>
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<td>34</td>
<td>40</td>
<td>36</td>
<td>31</td>
<td>33</td>
<td>38</td>
<td>35</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>PT (%) 80–120 *</td>
<td></td>
<td>111</td>
<td>95</td>
<td>95</td>
<td>105</td>
<td>108</td>
<td>110</td>
<td>100</td>
<td>115</td>
<td>98</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl) 250–450 *</td>
<td></td>
<td>350</td>
<td>280</td>
<td>460</td>
<td>260</td>
<td>290</td>
<td>310</td>
<td>340</td>
<td>410</td>
<td>290</td>
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<tr>
<td>FDP (semi-quantitative determination, negative &lt; 2.5 μg/ml)</td>
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<td>-</td>
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<td>-</td>
<td>-</td>
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</tbody>
</table>

* Normal range; NA, not available.
Patients and Methods

Patients with HELLP syndrome

The study group consisted of eight primigravidae and one multigravida with a mean age of 27.5 years (range: 25–33 years) and mean gestational age of 33.7 weeks (range: 26–39 weeks) on admission. These patients exhibited the criteria for the HELLP syndrome as described by Weinstein [3], namely hemolysis, elevated liver enzymes and thrombocytopenia. None of the patients studied had a previous history of hypertension or thrombocytopenia prior to or during pregnancy. Eight patients complained of epigastric pain and five had evidence of generalized edema with hyperreflexia. Five patients had proteinuria of 2+ or more by dip stick, or 0.3 g/l or more in a 24-h urine collection, which was judged to be significant. The blood pressure was normal on admission in two of the nine cases. Table I summarizes the clinical data of the patients at the time of admission to hospital. Initial blood tests included a routine blood chemistry test, coagulation profile with platelet count, and peripheral blood smear. Table II lists the laboratory findings. Treatment prior to and during delivery included strict bed rest with fetal heart rate monitoring and, where necessary, betamethasone (16 mg over a 2-day period) was given in an attempt to achieve greater fetal maturity. Atenolol or intravenous hydralazine was given when the diastolic blood pressure was greater than 110 mmHg. Two patients required anticonvulsant therapy with intravenous magnesium sulfate infusions. The coagulation profile, platelet count, and liver and renal function parameters were checked regularly. Platelet counts were determined in all infants after delivery.

Patients with chronic ITP

A reference group of 21 patients with chronic ITP (13 females, 8 males) was investigated. The mean age of the female patients was 32.5 years (range: 17–62 years) and that of the male patients 41.0 years (range: 28–75 years). The diagnosis of chronic ITP was established on the basis of the following criteria, as suggested by Lacey and Penner [11]: Persistence of thrombocytopenia for more than 6 months; absence of a plasmatic coagulation abnormality; normal or increased numbers of megakaryocytes in bone-marrow aspirates; absence of splenomegaly; exclusion of other conditions associated with thrombocytopenia (e.g., drug therapy, systemic lupus erythematosus, lymphoproliferative malignancies etc.). Platelet counts were evaluated with a Coulter counter of the T series and verified by examination of the peripheral blood smear. At the time of PAIgG determination, the mean platelet count in these patients was $31 \times 10^9/l$, with a range of $4–100 \times 10^9/l$. None of these patients showed signs of hemolysis, and serum glutamic-pyruvic transaminase (GPT) and glutamic-oxalo-acetic transaminase (GOT) levels were within the normal range.

Platelet serology

Platelet-rich plasma was prepared from 0.5% EDTA blood and washed three times with 0.3% EDTA-PBS solution (0.009 M Na$_2$HPO$_4 \cdot$2H$_2$O, 0.14 M NaCl, pH 7.1) in polystyrene tubes. The platelet adhesion immunofluorescence test (PAIFT) [12] was used to detect membrane-bound PAIgG on the patients' platelets. Circulating PAIgG in the patients' sera was sought with the PAIFT using platelets from 12 healthy blood donors. Sera from healthy male blood donors were used as negative controls. Sera from multiply transfused patients with multispecific HLA antibodies were employed as positive control specimens. Evaluation was performed semiquantitatively at 400-fold magnification with a fluorescence microscope. In both patient groups, PAIgG determination was performed upon admission to hospital before any specific therapy was initiated.

Results

All nine patients in the study group had evidence of hemolysis, elevated liver enzymes, and thrombocytopenia (HELLP syndrome) at the time of admission. The classic triad of high blood pressure, edema, and proteinuria of pre-eclampsia was not observed in all the women (Table I). Lactic dehydrogenase levels were elevated in all patients – a sign of hemolysis – with a mean of
533 IU/l (range: 337–1308 IU/l); the peripheral blood smear in the four patients in which it was examined showed burr cells and schistocytes. Serum GOT and GPT values were elevated in all cases. Initial platelet counts ranged from 28–58 × 10^9/l with a mean of 47 × 10^9/l. The coagulation profile upon admission revealed all patients to have normal levels of fibrin degradation products (FDP), a normal prothrombin time (PT) and activated partial thromboplastin time (APTT), and fibrinogen levels no lower than 250 mg/dl. These findings are summarized in Table II. Cesarean section had to be performed in eight patients within 72 h of admission due to evidence of deterioration in platelet count, blood pressure, or neurologic status; in one case where the cervix was favorable, delivery was expedited by induction of labor. Platelets, fresh frozen plasma, and packed red blood cells were transfused as necessary at the time of delivery. All infants had platelet counts above 150 × 10^9/l at delivery. One neonate delivered at 26 weeks of gestation died of pulmonary complications. There were no further complications or maternal deaths and laboratory findings normalized within 15 days postpartum in all patients. PAIgG was not detected on the platelets or in the serum of any of the patients with HELLP syndrome. By contrast, membrane bound and circulating PAIgG was detected in 15 of the 21 patients (71.4%) with chronic ITP.

Discussion

The patients presented in our study group fulfilled the criteria for the HELLP syndrome as described by Weinstein [3]. In contrast to the patients in most previous studies, however, the classic triad of pre-eclampsia was not present in all cases. In this respect, our patients were similar to those reported by Aarnoudse et al. [13] and Goodlin et al. [14]. Prior to delivery, none of our patients had signs of acute disseminated intravascular coagulation (DIC): FDP levels were not elevated, PT and APTT values were normal, and fibrinogen levels were no lower than 250 mg/dl. These observations are consistent with findings quoted in a recent report [15]. In five patients, generalized oozing was observed during cesarean section and signs of DIC appeared in the postpartum period; these patients were treated with low-dose heparin, AT III substitution, and platelet transfusion.

However, one of the most striking alterations in the hemostatic system of patients with the HELLP syndrome is progressive thrombocytopenia with potential bleeding complications. Furthermore, neonatal thrombocytopenia has been reported in the infants of women with hemolysis, elevated liver enzymes, and low platelet count [5,16], which is a cause for concern because of the potential for intracranial hemorrhage during labor in the thrombocytopenic infant. These observations have led to the suggestion that some immunologic component that crosses the placenta is responsible for the thrombocytopenia [5].

A report of a patient with this syndrome treated successfully with plasma exchange indirectly supports this hypothesis [10]. In a review of thrombocytopenia in pre-eclampsia and eclampsia Gibson et al. [17] found elevated levels of PAIgG in approximately one-half of their own pre-eclamptic patients with thrombocytopenia, suggesting that an antiplatelet factor may contribute to the thrombocytopenia in some patients with pre-eclampsia. Unfortunately, the patients in this study are not clearly described and, to our knowledge, these results have not been published in a more extensive report since. The patients discussed in our report are a well-defined group with well-documented evidence of hemolysis, elevated liver enzymes, and low platelet counts. In none of these patients was PAIgG detected on the platelets or in the serum. Even if elevated levels of PAIgG had been found in some of our patients with HELLP syndrome, further elaborate procedures would have been necessary to confirm an immunologic pathogenesis for the thrombocytopenia. The reason for this is that elevated levels of PAIgG have been found in various disorders with and without thrombocytopenia [18] and therefore do not always indicate immunologically mediated platelet destruction. However, it is generally accepted that in the majority of patients with ITP, thrombocytopenia is due to binding of PAIgG to the platelet mem-
brane, resulting in phagocytosis by macrophages, primarily in the spleen. Platelet survival studies in patients with ITP have shown a significant correlation between the amount of platelet-bound IgG and the rate of platelet destruction [19]. Evidence of membrane-bound and circulating PAIgG was found in 15 (71.4%) of our 21 patients with ITP. Similar results have been reported by other groups [20,21], so the failure to detect PAIgG in our patients with HELLP syndrome is unlikely to be due to lack of sensitivity of the detection method. However, in HELLP syndrome the situation appears to be different: Our findings do not indicate the involvement of PAIgG as a humoral immunologic factor in the pathogenesis of thrombocytopenia in this disorder. Furthermore, no association was found between the maternal and fetal platelet counts at delivery. A lack of association between maternal and fetal platelet counts in cases of HELLP syndrome has also been reported by others [4,8]. In view of the poor maternal and fetal outcome associated with this syndrome, most authors have recommended prompt delivery regardless of gestational age [4–6]. Others have suggested more conservative management to prolong pregnancy in cases of fetal immaturity [2,7]. Thiagarajah et al. reported improvements in liver function and platelet counts in five patients treated with prednisone or betamethasone [8]. Here one might speculate that corticosteroids have the same mode of action in improving platelet counts as in chronic ITP. In this disorder, corticosteroids are thought to reduce macrophage uptake of IgG-coated platelets and also to interfere with IgG binding to platelets, thus improving the platelet count. In another study, only three of 17 patients with HELLP syndrome treated with steroids for either suspected ITP or fetal lung immaturity demonstrated an improvement in the platelet count [4]. No improvement in platelet count or liver function was observed amongst our three patients with HELLP syndrome given betamethasone in an attempt to achieve fetal lung maturity.

In summary, our findings do not suggest the involvement of PAIgG as a humoral immunologic factor in the thrombocytopenia of HELLP syndrome. According to recent reports, it seems more likely that thrombocytopenia in pre-eclampsia is a result of altered platelet behavior [22]. Therefore, the treatment of low platelet counts in the HELLP syndrome with immunosuppressants (e.g., corticosteroids) or plasma exchange does not seem appropriate, and as long as the mechanisms underlying the thrombocytopenia remain unclear, expeditious delivery is the therapy of choice in this disorder.

Acknowledgment

We gratefully acknowledge the technical assistance of Herbert Klement.

References