short report
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IS THE HELLP SYNDROME DUE TO INHERITED FACTORS? REPORT OF TWO CASES

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ABSTRACT

The etiology and pathogenesis of the HELLP syndrome, a multisystem disease occurring only in pregnancy, are still unclear. Curiously, very few authors have investigated whether inherited factors may be involved. We report two cases of HELLP syndrome in two unrelated women whose fetuses were relatives (first cousins).

The first case concerned a woman aged 32 with a normal course pregnancy who was admitted to the hospital for fever, nausea and vomiting, low platelets, hemolysis and increased liver enzymes. Abruptio placentae with fetal death and severe disseminated intravascular coagulation with hemorrhages ensued within a few hours. Hysterectomy was then performed. After treatment with transfusions and drugs the patient slowly improved; 28 days later she left the hospital in good condition. The second case involved a woman aged 31 with a normal course pregnancy who was admitted to the hospital for epigastric pain, nausea, low platelets, hemolysis and increased liver enzymes. The patient underwent an immediate cesarean section and delivered a live infant; no bleeding occurred during or after delivery. The patient's condition rapidly improved and she left the hospital after 13 days.

Until now, no author has proved that inherited fetal factors are at work in the HELLP syndrome. Our observations suggest a role for genetic factors, and this needs to be investigated in prospective studies.

Key words: HELLP syndrome, hemolysis, thrombocytopenia, preeclampsia-eclampsia

In 1954 Pritchard[1] described hemolysis and thrombocytopenia associated with severe toxemia of pregnancy. Weinstein[2] considered this syndrome as unique variant of severe preeclampsia and named it the HELLP syndrome, with H standing for hemolysis, EL for elevated liver function tests, and LP for low platelet counts. Indeed some cases of the HELLP syndrome are diagnosed in previously normal, non hypertensive pregnant women.[3]

The HELLP syndrome is a severe disease: in a review of 442 pregnancies with this condition,[4] 35 suffered eclampsia and 407 severe preeclampsia; there were 5 (1.1%) maternal deaths, 4 subcapsular liver hematomas and 4 retinal detachments. Maternal morbidity included disseminated intravascular coagulation (21%), abruptio placentae (16%), acute renal failure (7.7%) and pulmonary edema (6%). There were 38 overall perinatal deaths in a series of 114 births (33.3%).[5]

Since the HELLP syndrome occurs in pregnant women only and immediate delivery is the most important therapy for ensuring both maternal and neonatal survival,[2] it is reasonable to assume that factors derived from the fetus play a crucial role in its etiology and pathogenesis. Curiously, very few authors have investi-

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gated whether inherited factors and/or consanguinity are involved in this syndrome. We report two cases of the HELLP syndrome in two unrelated women whose fetuses were relatives (first cousins).

Case report

Case 1. Woman aged 32, primigravid (39 weeks gestation, normotensive, with a normal course of pregnancy), was admitted to the hospital for fever, nausea and vomiting. The platelet count was 29×10^9/L, aspartate aminotransferase = 343 IU/L, alanine aminotransferase = 153 IU/L, lactate dehydrogenase = 720 IU/L. Abruptio placentae with fetal death (female, g 3000) ensued within a few hours. Severe disseminated intravascular coagulation (prothrombin activity = 45%, partial thromboplastin time = 45", fibrinogen = 128 mg/dL, D-Dimer >16000 ng/mL, antithrombin III = 37%, platelets = 19×10^9/L, schistocytes on the peripheral blood smear) and severe vaginal hemorrhaging required treatment with red cells concentrates, fresh frozen plasma, antithrombin III concentrates. Hemorrhage persisted and multiple hematomas of the abdominal wall and oligohematuria with a progressive increase of creatinine values suddenly occurred. Total hysterectomy was performed. In the days that followed transfusions and drugs (diuretics etc.) were administered, and the patient slowly improved; after 28 days she left the hospital in good condition.

Case 2. Woman aged 31, primigravid (38 weeks gestation, normotensive, with a normal course pregnancy), was admitted to the hospital for epigastric pain and nausea lasting three days. The platelet count was 33×10^9/L, aspartate aminotransferase = 279 IU/L, alanine aminotransferase = 258 IU/L, lactate dehydrogenase = 702 IU/L, haptoglobin = 2.6 mg/dL with schistocytes on the peripheral blood smear. Prothrombin time, partial thromboplastin time, and fibrinogen were normal; antithrombin III was slightly decreased (62%). The patient underwent an immediate cesarean section, and gave birth a full-term live female (2500 g). The mother was treated with fresh frozen plasma and antithrombin III concentrates; no bleeding occurred during or after delivery. The patient's condition rapidly improved, and she left the hospital after 13 days.

Discussion

Both these cases met Weinstein's criteria for a diagnosis of the HELLP syndrome.[1] The etiology and pathogenesis of this disease are still poorly understood. Some authors emphasize the oxidative damage to the endothelium, an impaired thromboxane A2/prostacyclin balance and alteration of the von Willebrand factor multimer composition, whose interaction with the platelet membrane is mediated not only by the glycoprotein Ib but also by glycoprotein IIb/IIIa.[3,6-9] This mechanism is similar to the one described for thrombotic thrombocytopenic purpura occurring during pregnancy.[10]

Other authors believe that maternal responses (auto-antibodies?) to self-components derived from the fetus result in autoimmune phenomena, with consumption of the complement component C4.[11,12] Weistein's observations that 95% of newborn infants from mothers with the HELLP syndrome demonstrated schistocytes on the peripheral blood smear, and that 52% showed hyperbilirubinemia without blood group incompatibility are interesting. These findings support the hypothesis of a substance able to cross the placenta and produce some typical aspects of the HELLP syndrome in the fetus. Recently, Halim et al.[13] observed that bolus injections and infusion of endothelin-1 (a 21-aminoacid peptide synthesized by endothelial cells that exers an extremely potent vasoconstrictive action)[14] in female rabbits causes vasospasms and liver ischemia producing HELLP syndrome-like blood parameters (increased liver enzymes, indirect bilirubin and thrombin-antithrombin complexes; decreased antithrombin III and platelet counts).

Wilcken et al.[15] reported the HELLP syndrome in mothers whose babies had a 3-hydroxyacyl coenzyme A dehydrogenase deficiency, a recessively inherited condition, and conclude that there may be adverse effects on maternal

liver function from a fetus with the above mentioned deficiency, since heterozygosity in the mother alone cannot account for such damage.

In conclusion, the pathogenesis of the HELLP syndrome is probably multi-factorial, involving at different stages the mechanisms described, most of which could be mediated by inheritance. Until now, no author except Wilcken et al. has reported evidence of inherited fetal factors in this syndrome. However, most of these studies are retrospective and therefore it is impossible to evaluate the occurrence of the syndrome in relatives of the patients. Our observations suggest a role for genetic factors, but this have to be proven in prospective studies.

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