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Revisiting HELLP syndrome

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ABSTRACT

HELLP syndrome was first described in 1982 by Weinstein et al. and the term HELLP refers to an acronym used to describe the clinical condition that leads to hemolysis, elevated liver enzymes and low platelets. The syndrome frequency varies from 0.5 to 0.9% pregnancies and manifests preferentially between the 27th and 37th week of gestation. Approximately 30% of cases occur after delivery. Although the etiopathogenesis of this syndrome remains unclear, histopathologic findings in the liver include intravascular fibrin deposits that presumably may lead to hepatic sinusoidal obstruction, intrahepatic vascular congestion, and increased intrahepatic pressure with ensuing hepatic necrosis, intraparenchymal and subcapsular hemorrhage, and eventually capsular rupture. Typical clinical symptoms of HELLP syndrome are pain in the right upper quadrant abdomen or epigastric pain, nausea and vomiting. However, this syndrome can present nonspecific symptoms and the diagnosis may be difficult to be established. Laboratory tests and imaging exams are essential for differential diagnosis with other clinical conditions. Treatment of HELLP syndrome with corticosteroids, targeting both lung maturation of the fetus is still an uncertain clinical value. In conclusion, three decades after the tireless efforts of Dr. Weinstein to characterize HELLP syndrome, it remains a challenge to the scientific community and several questions need to be answered for the benefit of pregnant women.

Contents

1. Introduction

HELLP syndrome was first described in 1982 by Weinstein et al. and the term HELLP refers to an acronym used to describe the clinical condition that leads to hemolysis, elevated liver enzymes and low platelets [1]. Weinstein was undoubtedly the researcher with the greatest importance to advance the recognition of HELLP syndrome. He studied in detail 29 cases that were published in 1982 [1] and other 57 cases, published in 1985 [2].

The etiology of HELLP syndrome is not yet fully elucidated. Such syndrome is associated with severe clinical complications which may lead to both mother and fetus death, thus it is necessary to have a faster diagnosis and appropriate clinical intervention [3,4].

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1.1. Etiopathogenesis

HELLP syndrome is typically seen in patients with severe preeclampsia, although it can occur in the absence of this disease. This variant sometimes does not present hypertension, proteinuria and edema. Patients may have a general malaise or viral-like symptoms, which makes the HELLP syndrome clinical diagnosis a challenge [3].

Evaluating the natural progression of the syndrome, Dr. Weinstein concluded that thrombocytopenia occurred first. After, there is an increase in liver enzymes and finally hemolysis. In 25% of cases, the syndrome was manifested in the postpartum period [1].

Pain in the right upper quadrant around a week before admission was emphasized by Weinstein. A rare life-threatening complication of HELLP syndrome is hepatic hemorrhage and rupture, which occurs in approximately 0.5% of cases [4].

Although the etiopathogenesis of this condition remains unclear, histopathologic findings in the liver include intravascular fibrin deposits that presumably may lead to hepatic sinusoidal obstruction, intrahepatic vascular congestion, and increased intrahepatic pressure with ensuing hepatic necrosis, intraparenchymal and subcapsular hemorrhage, and eventually capsular rupture [1,5,6].

1.2. Frequency

HELLP syndrome's frequency varies from 0.5 to 0.9% pregnancies. It manifests before the delivery in 70% of cases and occurs preferentially between the 27th and 37th week of gestation [4]. Approximately 10% of cases manifest before the 27th week and 20% after the 37th [7]. The syndrome affects primarily pregnant women with higher white ethnicity [9].

Approximately 30% of HELLP syndrome cases occur after delivery, usually up to 48 h, even though some take up to 7 days. In these cases, the prognosis is worse, the presenting risk of renal failure and pulmonary edema significantly increased compared to the syndrome occurrence prior to labor [10,11].

In general, postpartum syndrome occurs in women who had proteinuria and hypertension in pregnancy. However, in about 10 to 20% of cases they are not associated with these previous symptoms [4,12]. Although variable, the manifestation of HELLP syndrome is fast. In more than 50% of cases, excessive weight gain and the presence of generalized edema are signs of HELLP development [13].

1.3. Diagnostic criteria

The diagnosis of the complete form of HELLP syndrome requires the presence of symptomatic triad, hemolysis, hepatic changes with increased enzymes and thrombocytopenia, as well as severe symptoms, as general malaise, with or without vomiting, pain in the right upper quadrant of the abdomen, excessive weight gain and the presence of generalized edema [1,2,13,14].

Laboratory tests are important for HELLP syndrome diagnosis and should always be requested in cases of preeclampsia, eclampsia and in pregnant women with pain in the right upper quadrant of the abdomen. Hemolysis is a major feature of this syndrome and results from microangiopathic hemolytic anemia. The fragmentation of erythrocytes is secondary to endothelial damage and fibrin deposition in vascular walls. These fragments identification in blood film (schizocytes) suggest microangiopathic anemia [15,16].

The hemolytic process is associated with decreased hematocrit and hemoglobin values [17,18]. Hemoglobinemia or hemoglobinuria can be macroscopically identified in about 10% of pregnant women with HELLP syndrome [19].

The free plasma hemoglobin binds to haptoglobin and hemoglobin–haptoglobin complex is rapidly sequestered by the liver. It avoids hemoglobin loss or accumulation in the kidneys and iron excretion, which keeps away the iron deleterious actions. This process leads to a pronounced decrease of haptoglobin plasma levels, sometimes reaching to undetectable levels, since this protein is not produced in response to its consumption [17,18]. Although haptoglobin plasma decrease is an important parameter for the diagnosis of acute hemolysis, its determination is not usually used for HELLP syndrome diagnosis [18].

The elevated liver enzymes reflect injury to the liver microcirculation and consequent impairment of its function. An increase in plasma asparate aminotransferase (AST) and alanine aminotransferase (ALT) reflects hepatic injury. The elevation of glutathione S-transferase-A1 (GST-A1) is a more sensitive and earlier indicator of acute injury [20]. However, GST-a1 assessment is not routinely performed, and it is thus not used for the diagnosis of HELLP syndrome [19].

Endothelial injury is associated with activation and aggregation of platelets and the increased peripheral consumption of these, resulting in thrombocytopenia. Other clinical conditions associated with pregnancy can also determine thrombocytopenia, such as gestational thrombocytopenia in immune thrombocytopenic purpura (ITP) and PE [21]. Platelets count less than 100×10^9/L are relatively rare in PE and gestational thrombocytopenia, but frequent in ITP and mandatory in HELLP syndrome [12,22].

Currently there are two major definitions for diagnosing the HELLP syndrome. In the Tennessee Classification System, Sibai has proposed strict criteria for true HELLP syndrome, platelet count $< 100 \times 10^9$/L, AST ≥ 70 UI/L and LDH ≥ 600 UI/L, besides the data of intravascular hemolysis (observed in the peripheral blood analysis of the microscopic film abnormal), increased serum bilirubin (≥20.5 μmol/L or ≥1.2 mg/100 mL) and elevated LDH levels (>600 U/L) [12,13]. The Mississippi-Triple Class is based on the nadir of platelets count any time during the course of the disease. Class 1 and class 2 are associated with hemolysis (LDH > 600 U/L) and elevated AST levels (≥70 U/L), while class 3 requires only LDH > 600 U/L and AST ≥ 40 U/L in addition to the specific count (platelet count in class 1: $<50 \times 10^9$/L, class 2: 50×10^9/L — 100×10^9/L and class 3: $>100 \times 10^9$/L). Class 3 is considered as a clinical significant transition stage or a phase of the HELLP syndrome which has the ability of progression [23–25].

Incomplete or partial form of HELLP syndrome occurs and it is defined by only one or two elements of the triad (hemolysis, hepatic changes with increased enzymes and thrombocytopenia) [7,13,23,26]. It can progress to complete form [23,26]. A partial or full reversal of the syndrome can rarely occur [27,28].

1.4. Clinical Symptoms

Typical clinical symptoms of HELLP syndrome are pain in the right upper quadrant abdomen or epigastric pain, nausea and vomiting. Pregnant women often report discomfort a few days before the presentation of abdominal pain [12,27]. Approximately 30–60% of pregnant women have headache and about 20%, visual symptoms. The intensity of symptoms is exacerbated at night. However, this syndrome can present nonspecific symptoms, which could lead to a misinterpretation of viruses [12].

The spontaneous rupture of a liver subcapsular hematoma is more frequent in the liver's right lobus [4,12,29]. This process is accompanied by symptoms such as a sudden beginning, epigastric pain, backache and pain in the right shoulder, anemia and hypotension [30,31]. A low index of suspicion is warranted in patients with such symptoms to prompt emergent imaging and to allow rapid diagnosis, since it is associated with a significant increase in maternal and perinatal morbidity and mortality. Hepatic rupture can also occur in postpartum [32].

1.5. Differential Diagnosis

HELLP syndrome symptoms can be confused with other clinical conditions and a differential diagnosis can be a challenge. The obstetrician should pay attention to the nuances of the clinical history (pyelonephritis with septicemia, cholecystolithiasis, pancreatic, cocaine intoxication) and