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HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome

HELLP (hemoliz, yükselmiş karaciğer enzimleri ve düşük trombosit) sendromu

Gonca İmir Yenicesu, İclal Özdemir Kol, Cem Yenicesu, Ali Çetin

Departments of Obstetrics and Gynecology (Prof. A. Çetin, MD, Assist. Prof. A. G. İ. Yenicesu, MD) and Anesthesiology and Reanimation (Assist. Prof. İ. Özdemir Kol, MD), Cumhuriyet University School of Medicine, TR-58140 Sivas; Department of Family Medicine (Cem Yenicesu, MD, Specialist in Family Medicine), Cayiralan State Hospital, Yozgat

Abstract

The HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome is a severe and life-threatening complication of preeclampsia with typical laboratory findings. The frequency of the disease is 1 to 150-300 live births in perinatal centers. The course of the HELLP syndrome is unpredictable. On the one hand, complete reversal of symptoms under conservative treatment have been reported in individual cases, on the other hand, rapid, therapy-resistant deterioration of the disease had been observed in the majority of patients accompanied by severe complications as liver rupture. As a consequence; the mother and the newborn need intensive care and these women should be delivered in an obstetric intensive care unit. The maternal mortality reported from the international literature is 3.3% and the perinatal mortality 22.6%. This review will emphasize the controversies surrounding the diagnosis and management of HELLP syndrome.

Keywords: HELLP, diagnosis, classification, complications, management

Özet

HELLP (hemoliz, yükselmiş karaciğer enzimleri ve düşük trombosit) sendromu tipik laboratuar bulguları olan, şiddetli ve hayatı tehdit eden bir preeklampsi komplikasyonudur. Perinatal merkezlerde hastalığın sıklığı 150-300 canlı doğumda 1'dir. HELLP sendromunun seyri tahmin edilemez. Bir tarafta tedavi ile semptomların tam olarak geri döndüğü az sayıdaki vakalar bildirilirken, diğer tarafta hastaların çoğunda karaciğer rüptürü gibi şiddetli komplikasyonların eşlik ettiği, hızlı ve tedaviye dirençli bir kötüye gidiş gözlenmiştir. Sonuç olarak anne ve yenidoğanın yoğun bakıma ihtiyacı vardır ve bu kadınlar bir obstetrik yoğun bakım ünitesinde doğum yapmalıdır. Uluslararası literatürde maternal mortalite %3,3 ve perinatal mortalite %22,6 olarak bildirilmiştir. Bu derleme HELLP sendromunun tanı ve tedavisi ile ilgili tarışmaların üzerinde duracaktır.

Anahtar sözcükler: HELLP, tanı, sınıflandırma, komplikasyonlar, tedavi

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Corresponding author:

Dr. Gonca İmir Yenicesu, Kadın Hastalıkları ve Doğum Anabilim Dalı, Cumhuriyet Üniversitesi Tıp Fakültesi, TR-58140 Sivas. Email: imirgonca@yahoo.com

Definition, history, and incidence

The syndrome was originally described as EPH (edema, proteinuria, hypertension) gestosis type B by Goodlin et al. [1] who stated that it had been reported in the obstetric literature for about 100 years. Weinstein first considered this condition to be a unique variant of severe preeclampsia and called it "the HELLP syndrome" in reference to the laboratory abnormalities [2].

Investigations into the pathophysiology of HELLP syndrome, have revealed a disorder characterized by hepatic endothelial disruption followed by platelet activation, aggregation, and consumption resulting in distal ischemia and hepatocyte death [3]. This vasculopathy can be limited to a hepatic segment or might be throughout the liver. Most commonly, HELLP syndrome involves smaller terminal arterioles yielding a process with characteristic histologic features. The classic hepatic lesion in HELLP syndrome is periportal or focal parenchymal necrosis which is associated with hyaline deposits of fibrin-like material [4].

The incidence of the HELLP syndrome has been suggested at approximately 20% of severe preeclampsia [5] but the exact incidence may be different as the diagnosis is often missed because of the varying presentation. There appears to be no difference in severity and occurrence of the HELLP syndrome between twin pregnancy and singleton gestation [6]. Regardless of whether the HELLP syndrome exists as a distinct entity or a spectrum of pregnancy complications, it generally presents before term and is associated with significant adverse maternal and perinatal outcome [7].

Sibai and associates [5] revealed that 70% had evidence of the syndrome antepartum and 30% developed in postpartum. Patients in the postpartum group are at increased risk for the development of pulmonary edema with acute renal failure [5].

Diagnosis: clinical symptoms and laboratory findings

There are two major definitions in the diagnosis of the HELLP syndrome [8]. In the Tennessee Classification System, strict criteria for "true" or "complete" HELLP syndrome has been proposed [9]. Intravascular hemolysis is diagnosed by abnormal peripheral blood smear, increased serum bilirubin (≥ 20.5 μmol/L or ≥ 1.2 mg/100 mL) and elevated LDH levels (> 600 units/L (U/L) [10].

In The Mississippi-Triple Class System, a further classification of the disorder is based on the nadir PLT count any time during the course of the disease [11]. Class 1 and class 2 are associated with hemolysis (LDH > 600 U/L) and elevated AST (≥ 70 U/L) concentration, while class 3 requires only LDH > 600 U/L and AST≥ 40 U/L in addition to the specific PLT count [11, 12]. Class 3 HELLP syndrome is considered as a clinical significant transition stage or a phase of the HELLP syndrome which has the ability of progression [12].

The diagnosis of HELLP syndrome is made by laboratory parameters alone, although supporting typical findings of preeclampsia, help rule out other potential imitators [13]. Laboratory evaluation should include a complete blood count with platelet count, a peripheral smear, coagulation studies, serum aspartate aminotransferase (AST), creatinine, glucose, bilirubin, and LDH levels. Of the laboratory studies routinely obtained for diagnostic purposes, platelet count and liver function tests are the best standardized and can fulfill these criteria [13].

Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome has been recognized as a complication of preeclampsia-eclampsia. The diagnosis of HELLP syndrome requires the presence of hemolysis based on examination of the peripheral smear, elevated indirect bilirubin levels, or low serum haptoglobin levels in association with significant elevation in liver enzymes and a platelet count below 100.000/mm3 after differential diagnosis of hemolysis and thrombocytopenia. The presence of this syndrome is associated with increased risk of adverse outcome for both mother and fetus [13]. During the past 15 years, several retrospective and randomized trials have been published in an attempt to refine the diagnostic criteria, to identify risk factors for adverse pregnancy outcome, and to treat women with HELLP syndrome [2, 3, 7]. Despite the rich literature, the diagnosis and management of this syndrome remain controversial.

Most patients with HELLP syndrome present with hypertension, and proteinuria, and report epigastric or right upper quadrant pain [14]. Other patients, however, present with

only nausea or vomiting, and still others may have nonspecific symptoms. Hypertension and proteinuria may be absent or only slight. It has been suggested that all pregnant women having any of the above symptoms should have a full blood count with platelet and liver enzyme determinations irrespective of the blood pressure.

Severe hypertension (systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥110 mm Hg) is not a constant finding in HELLP syndrome [13]. Hypertension is not obligatory to diagnose HELLP syndrome [13].

Classifications

The terminology and diagnostic criteria used to describe the syndrome have been confusing and inconsistent in the past. Sibai et al., [7] established laboratory criteria for the diagnosis and provided standards for subsequent discussions in the literature. In that classification, Sibai [9] defined laboratory abnormalities: hemolysis by an abnormal peripheral smear, elevated bilirubin >1.2 mg/dL, or elevated lactate dehydrogenase (LDH) >600 U/L; elevated liver enzymes by an AST >70 IU/L and LDH >600 U/L; and low platelets (defined as <100.000/mm3). Martin et al. [12] also attempted to classify the disease noting an increase in untoward outcomes, including cardiopulmonary, central nervous system, and renal dysfunction, as the degree of thrombocytopenia worsened. The authors defined class 1 HELLP syndrome as a platelet below 50.000/mm3, whereas those with platelet between 51.000 and 100.000/mm3 were defined as class 2. Class 3 HELLP syndrome represented a newly classified group of patients with hepatocyte death but a higher platelet count, 101.000 to 150.000/mm3. Still others have offered differing criteria for the diagnosis of HELLP syndrome to Sibai's and Martin's, each assessing varying degrees of hepatic involvement as evidenced by liver function test abnormalities to represent thresholds for diagnosis [15, 16]. In the classification of van Pampus, the cut off value of AST was 50 IU/L, and the other parameters of the diagnosis were similar to Sibai's classification. Visser et al. [16], classified the patients of HELLP syndrome with the platelet level of <100.000/mm3 and AST>30 IU/L. These differing depictions of HELLP syndrome with differing criteria for platelet count and liver function test abnormalities have likely confused clinicians.

Complications: maternal and neonatal

The most dramatic sequelae of hepatic involvement by preeclampsia are the development of segmental hepatic infarction, extensive parenchymal hemorrhage, or subcapsular hematoma [13]. In a review of 442 cases of HELLP syndrome managed at the University of Tennessee, 0.9% of patients with HELLP syndrome were complicated by a ruptured subcapsular hematoma [5]. The most common complications are: Disseminated intravascular coagulopathy 21%, abruptio placentae 16%, acute renal failure 8%, severe ascites 8%, pulmonary edema 6%, pleural effusions 6%, cerebral edema 1%, retinal detachment 1%, laryngeal edema 1%, subcapsular liver hematoma 1%, acute respiratory distress syndrome 1%, and maternal death 1% [5]. In a study by Van Pampus et al [15], 10% of women with HELLP syndrome were identified as having serious complications, including eclampsia, cerebral ischemia, and abruptio placentae compared with a 24% rate for women with true HELLP. It appears once severe preeclampsia has manifested remarkable end-organ involvement, adverse renal, central nervous system, and pulmonary complications can arise and should be evaluated [13].

Conventional management: management of complications, supplement therapy, prophylaxis, and delivery

When the HELLP syndrome is diagnosed, the main priority is to assess and stabilize the woman's condition, especially coagulation dysfunction [17]. Then, fetal wellbeing should be evaluated by ultrasound biophysical profile, umbilical artery Doppler and cardiotocography. A decision needs to be made as to whether immediate delivery is indicated [17]. The consensus of opinion for severe cases (eg. class I HELLP syndrome)

is that the control of hypertension and immediate delivery, generally by caesarean section, is the treatment of choice. A woman with moderate HELLP syndrome at a gestational age greater than 34 weeks should also be delivered immediately. The pregnancies with HELLP syndrome who are remote from term should be transferred to a tertiary referral centre when the maternal condition is stable [18]. Before 34 weeks, the woman should be delivered if the condition cannot be controlled rapidly. Where delivery is not indicated immediately, antenatal corticosteroids should be administered for 48 hours to promote fetal lung maturity. When a course of steroids has been completed in the setting of the HELLP syndrome, neonatal outcome is significantly improved in cases compared with controls [19]. The patient and the baby must be assessed continually during this period and she should be delivered if her condition worsens.

In milder cases of the HELLP syndrome occurring near term induction of labour is appropriate; however at very early gestational ages where the cervix is very unfavourable, elective caesarean section is preferred [20]. Milder cases such as class III may even be allowed to proceed to term and to undergo a spontaneous vaginal delivery, and in certain cases temporising management may improve fetal and neonatal as well as maternal outcome [16]. However, the woman's condition must be monitored very closely during this time, and the condition of the baby assessed regularly, as intrauterine growth retardation is common [21]. The use of epidural analgesia and/or anesthesia in the presence of thrombocytopenia is controversial. A platelet count of greater than 100.000/µL is regarded as a safe cutoff point for insertion of a Tuohy needle, but where the platelet count is less than 100.000/µL, most anesthetists are against epidural block. When other elements in the coagulation screen are abnormal, epidural block is contraindicated [22]. Although bleeding in the gravid patient is related to more factors than platelet count alone, women with the HELLP syndrome in whom an intrapartum platelet count above 40.000/µL is maintained are unlikely to have clinically significant postpartum bleeding. Before caesarean section correction of thrombocytopenia is particularly important. Platelet consumption occurs rapidly and the effect of platelet transfusion is transient. Repeated platelet transfusions are not advocated in the absence of haemorrhage as delivery itself will usually lead to a reversal of the thrombocytopenia. In cases of coagulation dysfunction, the defective plasma components may be replaced by administration of fresh frozen plasma, packed red cells and anti-thrombin III. Women with the HELLP syndrome should be monitored very carefully, for at least 48 hours after delivery, ideally in an intensive care facility. The use of a central venous pressure catheter may prove invaluable for fluid balance. The syndrome will resolve within 48 hours of delivery in most women, and an upward trend in platelet count and a downward trend in lactate dehydrogenase concentrations should be apparent in women without complications by the fourth postpartum day [23]. A more protracted postpartum recovery period should be expected for progressively severe expressions of the HELLP syndrome [24]. Regular assessment of liver, renal and coagulation function is essential during this critical period. Those women who develop disseminated intravascular coagulation may show delayed resolution or even deterioration. In resistant cases or clinical deterioration, plasma exchange should be considered as a therapeutic option as it has been shown to be successful [25].

Steroid treatment in the management of HELLP syndrome

The results of these studies demonstrate improved laboratory values and urine output in patients receiving dexamethasone, but provide limited evidence of reduced maternal morbidity [9, 26-28]. However, because most of these trials were performed postpartum, the true extent glucocorticoids can influence outcomes has yet to be determined. Glucocorticoids are the only known drugs to improve the maternal laboratory findings in cases of severe preeclampsia. The medication is directed not only to improve neonatal outcomes by lowering the incidence of such complications as respiratory distress syndrome and intraventricular hemorrhage, but also to attempt to reduce maternal morbidity [13]. The dose, route of administration, and duration of treatment of

glucocorticoids is important and has varied between studies [26-28]. Glucocorticoids improve the maternal condition in a dose-dependent manner. Maternal platelet count increased more dramatically before delivery with a high-dose protocol of glucocorticoids versus standard regimens used for enhancing lung maturity [29]. High-dose glucocorticoid therapy is recommended to improve laboratory abnormalities in patients with HELLP syndrome. For most patients with HELLP syndrome, the dosage is as follows: 10 mg intravenous dexamethasone every 6 hours for 2 doses followed by 6 mg intravenous dexamethasone every 6 hours for 2 additional doses. For selected patients at highest risk, including those with profound thrombocytopenia (<20.000/mm3) or with central nervous system dysfunction (ie, blindness, paralysis) is as follows: 20 mg intravenous dexamethasone every 6 hours for up to 4 doses [8]. We believe that glucocorticoids may be used for maternal benefit even if the patient has previously received this medication for fetal lung maturity in the current pregnancy. We therefore attempt to delineate maternal versus fetal indications for the use of glucocorticoids in patients with HELLP syndrome.

Transfusions

Platelet transfusions are indicated either before or after delivery in all patients with HELLP syndrome in the presence of significant bleeding from puncture sites, wound, intraperitoneal, and extensive echymosis. Transfusion is indicated in all antepartum patients whose platelet count is less than 20.000/mm3. Platelets, red cells and fresh-frozen plasma may also be needed in patients with more severe coagulopathies.

Prognosis

The majority of these patients demonstrate progressive deterioration in either maternal or fetal condition. The potential risks associated with conservative management of HELLP syndrome include abruptio placenta, pulmonary edema, acute renal failure, eclampsia, perinatal death, and maternal death.

In a study by Osmanagaoglu et al., [30] in 11 maternal deaths, four patients died because of cerebral hemorrhage, three patients died because of anoxic encephalopathy and brain death associated with severe cerebral edema, two patients died because of disseminated intravascular coagulation (DIC), and two patients died because of ARDS. As a result, the most common primary cause of maternal death for this patient population was intracranial hemorrhage (36% of cases). The remaining maternal deaths were due to hypoxic ischemic encephalopathy (27%), DIC (18%) and ARDS (18%).

Conclusion

The greatest challenges in the management of women with HELLP syndrome are appreciating the diagnosis, instituting timely interventions, and avoiding associated complications. The addition of high-dose glucocorticoids to the therapy for HELLP syndrome may improve outcomes for both the mother and fetus. Delivery is the ultimate cure and optimizing the status of a seriously ill patient before delivery improves outcome.

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