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REVISION ARTICLE

Updateon HELLP síndrome

Actualización sobre el síndrome de HELLP

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ABSTRACT

Introduction: HELLP syndrome is a rare hypertensive disorder of pregnancy with severe maternal-fetal complications.
Objective: to describe the clinical manifestations, pathophysiological mechanism, possible complications and treatment of HELLP syndrome.
Methods: A search for information was carried out in the period March-June 2022 in the databases PubMed/MedLine, SciELO and Scopus, as well as in the ClinicalKeys services and the Google Scholar search engine. Original articles and systematic reviews written in the last 5 years, in Spanish or English, were selected.
Development: HELLP syndrome is characterized by hemolysis, elevated liver enzymes and thrombocytopenia. The main clinical manifestations are epigastric pain, abdominal pain located in the right upper quadrant, nausea and vomiting. Among the main complications are severe postpartum hemorrhage, which requires transfusion of blood products, coagulopathy, hemorrhage and disseminated intravascular coagulation.
Conclusions: immunological mechanisms secondary to inflammatory responses triggered by hypoxia/ischemia processes are involved in the genesis of this disease. This entity can be confused with others such as preeclampsia because it presents common symptoms. Laboratory tests confirming the presence of all or part of its components are required for definitive diagnosis. There is currently no specific treatment for HELLP syndrome, hence termination of pregnancy is considered as a solution, which requires stability of the patient's bioparameters.

Keywords:HELLP Syndrome; Pre- Eclampsia; Hemolysis; Thrombocytopenia.

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RESUMEN

Introducción: el síndrome de HELLP es un trastorno hipertensivo del embarazo poco común, con severas complicaciones materno-fetales.
Objetivo:describir las manifestaciones clínicas, mecanismo fisiopatológico, posibles complicaciones y tratamiento del síndrome de HELLP.
Método: se realizó una búsqueda de información en el periodo marzo-junio de 2022 en las bases de dato PubMed/MedLine, SciELO y Scopus, así como en los servicios ClinicalKeys y el buscador Google Académico. Se seleccionaron los artículos originales y revisiones sistemáticas redactados en los últimos cinco años, en idioma español o inglés.
Desarrollo: el síndrome de HELLP se caracteriza por hemólisis, elevación de enzimas hepáticas y trombocitopenia. Las manifestaciones clínicas principales son dolor epigástrico, dolor abdominal localizado en cuadrante superior derecho, náuseas y vómitos. Ente las principales complicaciones se encuentran la hemorragia postparto severa, la cual requiere transfusión de hemoderivados, coagulopatía, hemorragia y coagulación intravascular diseminada.
Conclusiones: en la génesis de esta enfermedad se encuentran implicados mecanismos inmunológicos secundarios a respuestas inflamatorias desencadenadas por procesos de hipoxia/isquemia. Esta entidad puede confundirse con otras como la preeclampsia al presentar síntomas comunes. Para el diagnóstico definitivo se requieren pruebas de laboratorio que confirmen la presencia de todos sus componentes o parte de ellos. No existe un tratamiento específico en la actualidad para el síndrome de HELLP, de ahí que se considere como solución la interrupción del embarazo, para lo cual se necesita estabilidad de los bioparámetros de la paciente.

Palabras clave:Síndrome HELLP; eclampsia; preeclampsia; hemolisis; trombocitopenia.

INTRODUCTION

HELLP syndrome is characterized by hemolysis, elevated liver enzymes and thrombocytopenia. It is considered as one of the possible multisystemic complications of pregnancy, it may present with preeclamsia-eclampsia, however, hypertensive disease and proteinuria is not always present (15-20 % of cases).[1,2]

Although it has been a known complication for many years, it was not until 1982 that the term HELLP was coined, which comes from its acronym in English, H: haemolyisis, EL: elevated liver enzymes and LP: low platelets, which were proposed by Weinstein, following a study conducted with 29 pregnant patients.[2,3]

It exhibits high maternal morbidity and mortality, affecting approximately 0,1 to 0,9% of pregnant women, mainly between 27 to 37 weeks of pregnancy; between 10 and 20% manifest with preeclamsia.[4]

According to the Ministry of Public Health, in Ecuador it is estimated that HELLP occurs in 3 out of every thousand pregnancies, causing a maternal mortality of 1 to 2% and fetal mortality of 10 to 35%, recurring in the next pregnancies in 27%.[5] After the pregnant woman suffers HELLP, the newborn may also be affected; this is due to the fact that there is a delay in both diagnosis and medical treatment.[3]

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In view of the above and the need for updated information, the present research was developed with the aim of describing the clinical manifestations, pathophysiological mechanism, possible complications and treatment of HELLP syndrome.

METHODS

A search for information was carried out in the period March-June 2022 in the databases PubMed/MedLine, SciELO and Scopus, as well as in the ClinicalKeys services and the Google Scholar search engine.

Advanced search strategies were used to retrieve the information by structuring search formulas using the terms "HELLP", "eclampsia", "preeclampsia", "hemolysis" and "thrombocytopenia", as well as their English translations. Boolean operators were used to combine the terms, creating search formulas according to the syntax requested by each database.

From the resulting documents, we selected those written in the last 5 years, in Spanish or English, that provided updated information on HELLP syndrome. In addition, in order to achieve a review based on the best possible evidence, only those studies of the original research or systematic review type were selected.

RESULTS

During the search and review of this disease, it could be seen that in Latin America research efforts on HELLP syndrome have increased. However, in Ecuador data are scarce and limitations in research processes are evident. For this reason, there is an interest in acquiring basic knowledge that can be exposed to the medical and scientific community, to guide in the early recognition of this syndrome.

Physiopathology

It has been postulated that microvascular endothelial activation and cellular injury leads to thrombocytopenia, hemolysis and hepatic dysfunction; however, the exact pathophysiology of this condition is still not well defined. Several theories mention that HELLP is a variation of preeclampsia so the pathophysiology comes from a similar origin.[6]

Essentially what happens in the pathophysiology is that in weeks 16 to 22 of embryonic development there is a lack in the second wave of trophoblastic invasion, being insufficient vascular remodeling when it reaches the junction zone of the pregnant endometrium, preserving arteries of high resistance and low distensibility, resulting in an inadequate blood supply to the placenta, so it develops an ischemic environment and suffers oxidative stress.[6,7]

Subsequently, the hypoxic placenta releases different placental factors such as soluble vascular endothelial growth factor receptor 1 (sVEGFR-1), which will bind to vascular endothelial growth factor (VEGF) and placental growth factor (PGF), which will cause the alteration of the endothelial cells and the placenta, resulting in hypertension, proteinuria and elevated platelet activation and aggregation.[6,7]

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Platelet consumption also occurs due to the activation of the coagulation cascade caused by adhesion on a damaged and activated endothelium, in addition to microangiopathic hemolysis caused by the fractionation of erythrocytes when crossing capillaries filled with fibrin and platelets. Therefore, the contributors to the development of HELLP will be multiorgan microvascular injury and hepatic necrosis that cause hepatic dysfunction.[6,7]

As far as histopathological findings are concerned, there is similarity between preeclampsia and HELLP syndrome, however, the latter is associated with higher rates of maternal placental vascular supply and small for gestational age lesions.[6]

For didactic purposes the immune pathophysiology hypothesis can be classified into 4 stages:
- Stage 0: this will be preconceptional, it starts with maternal exposure to semen which contains paternal antigens, i.e. by presentation to the major histocompatibility complex (MHC). It will stimulate the accumulation of regulatory T cells, which cause the mother to be tolerant to feto-paternal alloantigens, thus increasing the risk of developing preeclampsia.
- Stage 1: immune dysregulation occurs due to a partial failure of the mechanism described in stage 0, which causes Natural Killer cells and macrophages to act.
- Stage 2: occurs when the maternal immune system distinguishes the extravillous trophoblast through the interrelation of its receptors and surface molecules respectively, causing a deficient trophoblast invasion.
- Stage 3: in this stage clinical manifestations will be observed due to the exalted systemic inflammatory reaction, endothelial dysfunction, platelet activation and aggregation, and arterial hypertension.[7]

We can summarize that hemolysis is the cause of the rapid decrease in the number of erythrocytes, by cell loss due to fibrin deposition, generated by endothelial damage followed by a rupture of red blood cells by contact with the damaged area, consistent with microangiopathic hemolytic anemia.[2]

Necrosis of the periportal parenchyma is found with fibrin deposits in the sinusoidal space, which could be the promoters of liver enzyme elevation, since these deposits impede hepatic blood flow causing liver distension. Consequently, there is tension in the Glisson capsule, which originates pain in the epigastrium and right hypochondrium, so the elevation of hepatic enzymes is a mirror of the hemolytic process and hepatic distension.[2]

The low platelet count is due to the fact that platelets are activated and adhere to damaged vascular endothelial cells, increasing their turnover and decreasing their lifespan. Thus, thrombocytopenia is the early and main cause of coagulation alteration in this syndrome.[2]

Clinical manifestations

At the onset of this syndrome, patients may present signs and symptoms similar to those of preeclampsia, so they are commonly unnoticed, leading to a poor differential diagnosis and therefore to an inadequate preliminary treatment.[2,6]

Several authors agree that the symptoms may be nonspecific, but it could be said that the main clinical manifestations are epigastric pain, abdominal pain located in the right upper quadrant, nausea and vomiting. In some cases headache and visual changes have been described, 85 % of the cases present proteinuria and hypertension, edema and weight gain are also frequent in the first days.[2,8] Usually the symptoms evolve rapidly, presenting unforeseen aggravations; spontaneous regression of the symptoms occurs in an unusual way.[8]

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Diagnosis

HELLP syndrome is often confused with pregnancy-specific hypertensive disease because the symptoms are usually similar. For this reason, specific laboratory tests are required, consisting of the triad that makes up the acronym that forms its name as described above.[9,10]

To define HELLP syndrome as complete or true, the Tenesseesystem,[8,11] states that the following criteria must be met:
1. platelet count less than 100 000/µL.
2. liver abnormality evidenced by an AST value ≥70 IU/L, serum DHL value ≥ 600 IU/L or indirect bilirubin of 1,2 mg/dL or greater.
3. presence of a peripheral blood smear evidencing hemolysis.

Meanwhile, the Mississippi system[8,11] classifies patients into 3 groups, establishing especially in their platelet count without taking into account the quantification of bilirubin or the findings in the peripheral blood smear, being these:
- Class 1: LDH: > 600 IU/L; AST: ≥ 70 IU/L; platelets: ≤ 50x109/L.
- Class 2: LDH: > 600 IU/L; AST: ≥ 70 IU/L; platelets: > 50x109/L and ≤ 100x109/L.
- Class 3: LDH: > 600 IU/L; AST: ≥ 40 IU/L; platelets: > 100x109/L and ≤ 150x 109/L.

It is commonly classified as complete HELLP when all the parameters of the basic triad are present and incomplete when only one or two elements are present, these being:[2,8]
- ELLP when there is no hemolysis,
- EL when there is only an increase in liver enzymes,
- HELL when there is hemolysis associated with increased liver enzymes,
- LP representing the low platelet count,

It should be noted that the prognosis worsens when they progress to a complete variant.[2,8]

In addition to being confused with pregnancy-specific hypertensive disease, HELLP can also be confused with acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, systemic lupus, and antiphospholipid syndrome. In addition, it can be differentiated with certain infectious processes of the liver and biliary tract such as hepatitis and cholangitis. Consequently, a careful diagnostic evaluation should be made to avoid clinical errors that may worsen the maternal and perinatal prognosis.[2]

Complications

Several complications that the mother presents when suffering from this syndrome have been described. Among the main ones are severe postpartum hemorrhage, which requires transfusion of blood products, coagulopathy, hemorrhage and disseminated intravascular coagulation. These occur in 15 to 38% of pregnant women who suffer from this syndrome, and for this reason patients will require urgent termination of pregnancy and multidisciplinary care.

There is a 40% incidence of intracerebral hemorrhage, being this the most common cause of death, in addition to acute respiratory distress syndrome which affects less than 1% with a prepartum mortality of 23% and postpartum mortality of 50%.[12]

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Other complications are acute renal failure, ascites, hepatic rupture; the latter has a mortality for both mother and child of up to 80 %.[13,14]Subcapsular hepatic hematoma is another complication that will affect mothers with HELLP in 0,9 to 1,6 % and its management is usually surgical.[12,15]

Chronic hypertension, acute myocardial infarction and cerebrovascular accidents are closely related to HELLP syndrome since they are considered to have long-term cardiovascular repercussions.[12]

Among the fetal complications, placental insufficiency produces premature detachment of the placenta, causing prematurity in the newborn; these are usually born between 33 and 34 weeks. Other fetal complications include cerebral hemorrhage, respiratory distress, bronchopulmonary dysplasia, perinatal asphyxia, hypoglycemia, thrombocytopenia, hyperbilirubinemia, and necrotizing enterocolitis.[12,13]

Prevention and treatment options

Given the relationship of HELLP syndrome, preeclamsia and eclampsia, early blood pressure monitoring is imperative to rule out chronic hypertension, as well as after 20 weeks, possible gestational hypertension and preeclamsia. Although the definitive treatment is termination of pregnancy, prior stabilization of the patient is necessary, in which case magnesium sulfate has shown efficacy in the treatment and prevention of eclampsia.[11]

Other drugs such as low-dose aspirin and calcium have shown efficacy when used late in the first trimester as prophylactic measures in women with risk factors.

Early and immediate recognition of the diagnosis is critical for treatment. Although delivery is the only definitive therapy, multidisciplinary management is needed, since gestation cannot be terminated if the maternal condition is not stable. Considering that this syndrome is a variant of severe preeclampsia,[6,12] management consists of controlling maternal and fetal status by monitoring blood pressure, maternal heart rate and oxygen saturation.

The patient should be fasted until stabilization or termination of pregnancy, and minimal diuresis (0.5 ml/kg/h) should be ensured. General obstetric examination is required, which includes uterine/umbilical/fetal doppler, fetal growth estimation and RCTG; a coagulation and biochemical study will be performed, including hepatic and renal profile.[12]

Antihypertensive drugs such as hydralazine are used for immediate blood pressure control, and drugs such as nifedipine and labetalol are used to stabilize blood pressure in the short and long term.[2,6,12] The use of intrapartum magnesium sulfate as prophylaxis and in case of suspected eclampsia is indicated, specifically in HELLP.[6,12]

The neonate, due to its risk of prematurity, should receive corticosteroid therapy such as betamethasone or dexamethasone at high doses, for pulmonary maturation. The use of corticosteroids in the mother will help us to increase or stabilize platelets.[2,12]

When the platelet count is less than 40000 IU/L in the case of cesarean section, or 20000 IU/L in the case of vaginal delivery, platelet transfusion should be performed prior to delivery.[12]

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Pregnancy should be terminated when patients have a gestational age greater than 34 weeks or less than 24 weeks, as soon as possible after the diagnosis of this syndrome has been confirmed. Waiting longer may result in more severe maternal-fetal complications; termination at less than 24 weeks is in the maternal interest only, as there is no evidence that termination at this week is helpful for perinatal outcome.(6)

Herbal medicine plays a fundamental role in our society, as there is a widespread belief that they are "natural and safe remedies". A recent survey in the USA showed that up to 30% of pregnant women reported having consumed herbal products during pregnancy; the risk of underlying hepatotoxicity could mask the liver damage produced in preeclampsia and vice versa.(14)

It is important for health professionals to be aware of the signs, symptoms and complications of HELLP in order to provide appropriate management, thus helping to reduce mortality rates.(15)

CONCLUSIONS

Immunological mechanisms secondary to inflammatory responses triggered by hypoxia/ischemia processes are involved in the genesis of this disease. This entity can be confused with others such as preeclampsia because it presents common symptoms. Laboratory tests confirming the presence of all or part of its components are required for definitive diagnosis. There is currently no specific treatment for HELLP syndrome, hence termination of pregnancy is considered as a solution, for which stability of the patient's bioparameters is required.

Conflict of Interest
The authors declare that there is no conflict of interest.

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Authorship Contribution
All authors participated in conceptualization, research, writing - initial draft, writing - revision and editing.

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