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REVIEW

Contemporary Diagnostic Approach to HELLP Syndrome : a Clinical Review

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ABSTRACT

HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) is a clinical status which calls for an urgent therapy, mainly focused to a prompt parturition. The classical initial symptoms are epigastric or right upper quadrant pain, nausea and vomiting. The differential diagnostic problems of HELLP syndrome arise in relation to the mimicry symptomatic upper abdominal pain which can imitate : a) gastroenterologic diseases (e.g. cholelithiasis, appendicitis) ; b) liver diseases, such as viral hepatitis (elevated liver enzymes combined with hyperbilirubinemia) ; and c) thrombotic microangiopathies (due to thrombocytopenia in combination with haemolytic anaemia, neurological symptoms and renal failure). Regarding the common symptoms : thrombocytopenia, haemolysis, as well as signs of pre-eclampsia with or without renal failure the differentiation from various autoimmune diseases also can be difficult in special cases. Rare first manifestations and serious simultaneous diseases which can overlap the typical signs of HELLP syndrome show the full variety of HELLP syndrome. The delay of interdisciplinary approach in achieving a clear final diagnosis causes serious consequences, which could lead to deleterious effects on the mother and the fetus. Therefore, all pregnant women with upper abdominal pain, irrespective of symptoms of pre-eclampsia, should be considered to have HELLP syndrome. This requires an immediate laboratory evaluation and, in cases of doubt, an interdisciplinary consultation.

Key words : HELLP syndrome, diagnostic problems, liver function, microangiopathy

Since 1982, when Weinstein[1] described 29 pregnancies with pre-eclampsia-eclampsia, a new clinical entity has appeared, known by the name HELLP syndrome (haemolysis, elevated liver enzymes, low platelet). The diagnosis of HELLP syndrome is based on typical laboratory analysis. In large obstetrical centres this entity is found in one of each 150-200 deliveries.[2,3]

Hitherto no specific anamnestical risk profile has been established in HELLP syndrome. It is frequently diagnosed in primigravidas (52-81%), aged around 25 years.

Some researchers[4] place the commence of HELLP syndrome in the 34th gestational week, while the others state that it can be detected even prior to 24th gestational week.[5] Its diagnosis is established in 10-30% of the cases within the 72 hours after delivery, although it might develop during the first 6 postpartal day (postpartal HELLP syndrome).

The maternal mortality is around 3%, and the perinatal mortality ranges from 22.6-24.2%.[4, 6] The maternal complications can be found in 12.5-65% of the patients.[4,7]

The problems concerning this syndrome lie in its unpredictable course (progress, intermittent course, response to conservative therapy) ; while in cases with positive predictive parameters one can assess the course and prognosis of the malady.[8] On the other hand, clinical and laboratory parameters in HELLP syndrome can exert significant problems in differential diagnosis, such as link between epigastric pain and haematological, liver and kidney disorders, and, also, mimicry of other organ disorders. Reaching an adequate diagnosis in some cases requires an interdisciplinary approach.

In 5-20% of the patients there are either no clinical signs of pre-eclampsia, or they are very discrete, which might lead to improper laboratory interpretation in the incipient stage of the disease. Inadequate diagnosis and delayed treatment can bring the pregnant women or the fetus in a very dangerous state, through disseminated intravascular coagulation (DIC) or its consequences.[9] According to Siabai et al,[10] if the interval between establishing the diagnosis and delivery is 8 days (range 3-22 days) the incidence of DIC is 38%, and the perinatal mortality is 36.7%. The latent time prior is usually a consequence of improper diagnosis.

The timely and correct diagnosis with aggressive therapy decreases the rate of maternal complications and lethality, as well as perinatal mortality. With a contemporary approach, the maternal mortality is 0% and perinatal mortality around 5%.[11,12] The problems in HELLP syndrome differential diagnosis are based on the epigastric pain, haemolysis, liver and kidney disorders, and on obstructive microangiopathy

Table 1. General review of differential diagnosis for HELLP syndrome

1. Epigastric pain
   - Cholelithiasis
   - Hepatitis
   - Gastritis/Gastroduodenal ulcer
   - Hiatus hernia
   - Pancreatitis
   - Appendicitis
   - Pyelonephritis
2. Liver diseases
   - Acute viral hepatitis
   - Intrahepatic cholestasis in pregnancy
   - Acute fatty liver in pregnancy (extremely rare)
3. Thrombotic microangiopathy
   - haemolytic/uremic syndrome
   - thrombotic thrombocytopenic purpura
4. Autoimmune diseases
   - idiopathic (immunologic) thrombocytopenic purpura (ITP)
   - systemic lupus erythematosus (SLE)
   - antiphospholipid syndrome (APS)
   - Evans syndrome
5. Other early events

(Table 1).

1. Differential diagnosis of epigastric pain

The leading clinical symptom is the right upper quadrant pain, occurring in 80-90% of the patients. This requires search for anamnestic data on epigastric pain in all the patients with pre-eclampsia. This pain develops consequence of blood flow obstruction through the hepatic sinusoids, based on large hyaline deposits with periportal and focal parenchymatous necrosis. The histopathological findings are linked to the elevation of liver enzymes, found in HELLP syndrome. In some cases cellular necrosis and haemorrhage can be so extensive to cause liver infarction or subcapsular haematoma, even prior to classical clinical symptomatology, which necessarily calls for an ultrasonographic liver examination. Computerized tomography has no predictive value in these patients.[13]

It is believed that 15-20% of the patients with pre-eclampsia have no hypertension and that 5-10% present no proteinuria. Therefore, all the pregnant women with epigastric pain must be suspected for HELLP syndrome, regardless of hypertension or proteinuria.[14]

In cases of epigastric pain, the following diseases must be taken in consideration :[7,14]

- acute cholecystitis/cholelithiasis : typical anamnesis, upper abdominal ultrasonography, gamma-GT level (in cholestasis) ;
- acute pancreatitis : history of choleli thiasis/choledocholithiasis, amylase and lipase, hypocalcemia ;
- viral hepatitis : typical serological findings ;
- pyelonephritis ; fever, dysuria, lumbar pain, typical urine findings (bacteriuria, leucocyturia) ;
- acute appendicitis : in a cranially positioned appendix, the pain is localized in the upper right abdominal quadrant at the end of pregnancy, leucocytosis over 15,000/cu.mm., rectoaxillary temperature difference, pain in the Douglas's recess.

Generally speaking, the differential diagnosis between HELLP syndrome and diseases leading to upper abdominal pain can be reached through laboratory procedures. Nevertheless, some cases require interdisciplinary approach.

2. The differential diagnosis of liver disease

The main, target organ in HELLP syndrome is the liver. As a consequence to sinusoidal blood flow obstruction, the Glisson's capsule is distended (with epigastric pain), hepatocellular necrosis develops and transaminases are elevated. The basis for confluent haemorrhagic necrosis can be in a subcapsular haematoma (incidence 1.5-2%) which leads to liver rupture.[15] Doppler sonography confirmed that arterial vasoconstriction in HELLP syndrome is not so intense as in cases of pre-eclampsia without HELLP syndrome.[16] The cause of pathophysiological dominance of liver in HELLP syndrome still remain unresolved.

Furthermore, the differential diagnosis faces problems in other liver diseases followed by epigastric pain, high transaminase levels, hyperbilirubinemia, coagulation disorders and thrombocytopenia.

Acute viral hepatitis

The incidence of acute viral hepatitis in pregnancy is 0.04-1.5%.[14] The acute viral hepatitis is an aetiological factor for almost 40% of jaundice in pregnancy.[17] Based on clinical symptomatology, viral hepatitis with elevated transaminases might simulate incomplete HELLP syndrome. Therefore, in every patient with a high level of transaminases in pregnancy serological

evaluation must be carried out in order to exclude the possibility of viral hepatitis.

The remaining criteria for viral hepatitis are typical history, a very hight level of transaminases, a prompt elevation of bilirubin, and for HELLP syndrome thrombocytopenia, haemolysis and signs of pre-eclampsia (Table 2).

Intrahepatic cholestasis in pregnancy

Intrahepatic cholestasis occurs in 20% of the cases after viral hepatitis. The jaundice in pregnancy after viral hepatitis is twice as frequent compared to the general population of healthy pregnant women. The incidence of intrahepatic cholestasis is ranging between 1 : 500 and 1:10,000 of pregnant women.[17] In 64% of the cases the disease is diagnosed in the third trimester. The differentiation of intrahepatic cholestasis in pregnancy from HELLP syndrome is not difficult. The leading symptom of cholestasis - itching, besides jaundice, enables establishing the correct diagnosis. The laboratory differentiation is obvious, based on thrombocytopenia, haemolysis and proteinuria (Table 2). In cholestasis, the blood level of gamma-GT is slightly elevated, alkaline phosphatase is increased 2-3 times, and the bile acids (mainly cholic and chenodeoxycholic) are almost 10-100 times over normal values.[18] While 47-62% patients with HELLP syndrome present an elevation in indirect bilirubin, the pregnant women with intrahepatic cholestasis have direct bilirubin elevation as an obligatory finding.[11]

Acute idiopathic fatty liver in pregnancy

The acute idiopathic fatty liver in pregnancy is a very rare, but life-threatening disease. The incidence is 1 : 13,000 pregnancies, and it commences most frequently, similar to HELLP syndrome, in the third trimester. The first findings are neurological : lethargy and depression, followed by nausea. vomiting and epigastric pain occur in 60% of the patients with HELLP syndrome, and in almost all patients with acute idiopathic fatty liver in pregnancy. In 30-60% of the patients there are signs of pre-eclampsia.[7] According to Minami et al[19] there is a common morphological correlation between HELLP syndrome and acute idiopathic fatty liver in pregnancy - a microvesicular accumulation of fat

Table 2. Comparative analysis of HELLP syndrome differential diagnostic entities

Parameter	Acute viral hepatitis	Intrahepatic cholestasis in pregnancy	TTP	ITP	HUS	APS	SLE
Haemolysis	-	-	+++	-	+++	+	+(+)
Liver enzymes	+++	+	(+)	-	(+)	-	-
Thrombocytopenia	-	Alkaline phosphatase ↑↑	+++	+++ Antibodies !	+++	+++	+(+)
Hypertension	-	-	-	-	Secondary	Secondary	Secondary
Proteinuria	-	-	+	-	++	Secondary	++
Inflammatory signs	++	-	-	-	+	-	+++
Renal involvement	-	-	+	-	+++	Possible	+++
Central symptoms	-	-	+++	-	Secondary	-	+
Jaundice	+++	++	++	-	++	-	-
Other criteria	Bilirubin ↑	Bilirubin ↑		I & II trimester	Postpartal	APA*	ANA*

* APA : Antiphospholipid antibodies

* ANA : Antinuclear antibodies

particles in hepatocytes. Conversely, Usta et al[20] underline the clear morphological difference between the two entities mentioned, and suggest liver biopsy for establishing the correct diagnosis. In 10 out of 14 patients with presumed acute fatty liver in pregnancy, liver biopsies were carried out, with no complications (bleeding). On the other hand, Wilkinson[21] states that there is a high risk of bleeding after liver biopsy. Therefore, the diagnosis of very rare acute fatty liver in pregnancy is confirmed in patients with jaundice, fever, elevated white blood cell count (20,000-30,000/cu.mm.) and with hypoglycemia which is a consequence of progradient hepatic insufficiency (Table 2). Furthermore, it comprises a marked coagulation disorder (protracted PTT/PT), followed by consecutive bleeding from the gastrointestinal tract, kidneys and the central nervous system.[22]

3. Differential diagnosis of thrombotic microangiopathy

The pathophysiological mechanism in HELLP syndrome is obstructive thrombotic microangiopathy. The target organ in haemolytic-uremic syndrome is the kidney, in thrombotic thrombocytopenic purpura it is the central nervous system, and in HELLP syndrome the liver. The morphological connection between these topographically difference and serious disorders are hyaline blood clots in arterioles and capillaries with subsequent organ necrosis and haemorrhage, although the lesion of endothelium is caused by different aetiological agents.[6,7,23] The clots develop through a biochemical cascade, caused by decreased prostacyclin synthesis in damaged epithelium, stimulation of arachidonic acid exchange and lipid peroxide appearance, as well as by metabolic disorders of von Willebrand factors.[24] The thrombotic thrombocytopenic purpura and the haemolytic-uremic syndrome might mimic HELLP syndrome or pre-eclampsia, because of haemolytic anaemia, thrombocytopenia and different degree of renal function failure.[25]

Thrombotic thrombocytopenic purpura (TTP)

The classic symptoms of thrombotic thrombocytopenic purpura are : 1. severe form of Coombs-negative microangiopathic-haemolytic anaemia, 2. thrombocytopenia, 3. fever (in around 60% of the patients), 4. neurologic symptoms (convulsions and hemiparesis), and 5. renal function disorder. These five symptoms (pentalogy) are found in 40% of the patients, while the triad : anaemia, thrombocytopenia and neurologic disorders, exists in 75% of the patients[22,26] (Table 2).

The pathophysiology of thrombotic thrombocytopenic purpura (Moschkowitz syndrome) remains yet unknown. It is presumed that in predisposed patients some noxiousness act upon the endothelial cells. Microangiopathy develops on the basis of adhesion, i.e. the aggregation of platelets.[27]

The incidence of the TTP development in pregnancy is as high as 40%, and the common opinion is that the pregnancy itself presents as a predisposing factor in the development of this pathological state.[22] Contrary to the HELLP syndrome, which is much more frequent in the third trimester, Weiner[28] states that the TTP symptoms commence in the second trimester (in 60% of the patients in 24th gestational week). TTP presents with fever, haemolysis, thrombocytopenia, jaundice, and dominant neurological symptoms, and HELLP syndrome has a normal level of von Willebrand factor multimers in peripheral blood.[25,26,29]

Conversely to idiopathic thrombocytopenic purpura (ITP) with transplacental IgG antiplatelet

antibodies transfer and neonatal thrombocytopenia, TTP has neither anaemia nor neonatal thrombocytopenia.

The mortality in a nontreated TTP is around 80%. The success rate by plasmapheresis is 80-90%.[25,30] The administration of concentrated platelets is contraindicated.[26]

Haemolytic-uremic syndrome

The classic haemolytic-uremic syndrome (HUS) develops in a few days, or up to 10 weeks after the termination of a normal pregnancy.[31] As HELLP syndrome is diagnosed postpartally in 30% of the cases, the differential diagnosis can often be difficult.[5] Atypical presentation of a haemolytic-uremic syndrome (Gasser's syndrome) comprises microangiopathic-haemolytic anaemia, thrombocytopenia and acute renal failure, though fever and neurological symptoms are not rare.[27] In 80% of the patients a prepartal diagnosis of pre-eclampsia was established. These authors find the haemolytic-uremic disorder to be a typically secondary disturbance, developed after severe hypertension, systematic diseases (SLE and scleroderma), as well as after administration of different drugs (i.e. oral contraceptives). HUS can develop after placental lysis, after caesarean section and after pre-eclampsia.[32] It must be stressed that HUS and TTP are different outcomes of a same pathophysiological process. The main feature in HUS is kidney lesion, while TTP has dominant neurological symptoms. Chronic renal failure can be found in 15-20% of the patients. The laboratory findings include an elevation of LDH level, while the liver enzymes are within normal range.[14] In HUS it is possible to decrease maternal mortality to 10-30% by plasmapheresis[22] (Table 2).

4. Differential diagnosis of autoimmune diseases

The differential diagnosis between HELLP syndrome and different autoimmune diseases is based primarily on thrombocytopenia, haemolysis and symptoms of pre-eclampsia with or without renal function disorders.

Idiopathic (immune) thrombocytopenic purpura

Idiopathic (immune) thrombocytopenic purpura (ITP) is the most common cause of thrombocytopenia in the first and second trimester of pregnancy (3-4% of pregnant women). It is marked by isolated thrombocytopenia based on antiplatelet IgG antibodies.[22] Fetuses are mainly targeted in the acute form, while chronic form (Werlhof disease) more affects pregnant women. This thrombocytopenia can be differed from the HELLP syndrome on the basis of megakaryocytopoiesis and the presence of antiplatelet antibodies in pregnant woman's peripheral blood (in 90% of the cases). ITP presents with petechial haemorrhage on lower extremities, chest, occipitum and mucosa, symptoms which, generally speaking, are not found in patients with HELLP syndrome.

According to the literature data, 15-65% of neonates have thrombocytopenia (antiplatelet IgG antibodies pass the placental barrier).[33] However, the neonates of pregnant women suffering from HELLP syndrome have thrombocytopenia in 25-47% of the cases,[34] though there is no reliable correlation with haematological disorders in mothers. An isolated thrombocytopenia in pregnancy without known cause supports the diagnosis of ITP.

From the pathophysiological point of view,

the so-called pseudo-ITP, or pregnancy-induced ITP in otherwise healthy pregnants presents as an unclear entity. According to the opinion or numerous authors, the risk for severe neonatal thrombocytopenia in these pregnants is insignificant, and the elective caesarean section is n recommended.[22]

The diagnosis of ITP is established by exclusion of other entities.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is also of great importance in differential diagnosis, considering the fact that 50% of the pregnants suffering from SLE also have a renal function disorder. The proteinuria is often the leading symptom. In pregnants with SLE pre-eclampsia can be the only specific complication, with an incidence of 2.8-25%.[34,35] Lupus nephropathy predisposes the development of pre-eclampsia.[36,37] The diagnosis of SLE is established through symptoms cited in Table 3. At least 4 criteria must be fulfilled for establishing the diagnosis of SLE.

The differential diagnosis mainly deals with lupus-nephropathy (with an incidence of 60-70%), proteinuria (in 75% of the cases), haematuria and pyuria (in 40% of the patients), as well as signs of nephrotic syndrome and renal failure. In these pregnants, a Coombs-positive haemolytic anaemia and thrombocytopenia (< 100,000/cu.mm.) can be found in 14-26%. Leucocytopenia and lymphocytopenia can be found in 80-90% of the cases, with associated fever, nausea and vomiting.[38] Contrary to HELLP syndrome, in SLE there is no transaminase elevation.

The diagnosis of SLE can be established by a typical history and by the presence of antinuclear antibodies in almost 98% of the patients.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is known upon its venous-arterial thrombosis, autoimmune thrombocytopenia and increased incidence of pregnancy losses. This syndrome comprises development of antiphospholipid antibodies. The non-specific symptoms are Coombs-positive

Table 3. Diagnosis of SLE

A. Presence of antinuclear antibodies
B. Criteria of American College of Rheumatology
1. Butterfly erythema
2. Discoid lupus erythematosus
3. Photosensibility
4. Oral mucosa ulcers
5. Non-deforming polyarthritis
6. Pericarditis, pleuritis
7. Renal function disorder (proteinuria over 5g/dl or cylindruria)
8. Neurologic disorders
9. Haematological disturbances (-cytopenias)
10. Antinuclear antibodies

haemolytic anaemia (as in SLE), livedo reticularis, and associated cardiovascular disorders. Pre-eclampsia develops in almost a half of patients with APS. The secondary APS can arise in other autoimmune diseases, such as SLE. In 15-20% of pregnants with SLE an APS also exists, commonly associated with thrombocytopenia and pre-eclampsia development.[39] The primary APS is defined as a state without other immune disorders. A reliable differentiation of APS from HELLP syndrome is possible through identifying antiphospholipid antibodies, but only a small number of laboratories can perform this kind of analysis. Hitherto there are assays for three species of antiphospholipid antibodies : BF-STS, Lupus antibodies and IgG anticardiolipin antibodies.[40] In APS there is no transaminase elevation as in HELLP syndrome.

Evans syndrome

Evans syndrome includes autoimmune haemolytic anaemia, combined with immunologic thrombocytopenia. Therefore, in Evans syndrome, the anaemia is Coombs positive, and in HELLP syndrome it is Coombs negative.

Table 4. Rare early events and associated diseases in HELLP syndrome

- Hypoglycemia with coma
- Cortical blindness
- Retinal ablation caused by bleeding
- Insipid diabetes
- Pleural effusion/Ascites
- Gastritis
- Cerebral symptoms
- Diabetes mellitus (Type I)
- Hyponatremia
- Uncontrollable nasal bleeding
- Acute pericarditis
- Pyelonephritis
- HIV-associated thrombocytopenia
- Carotid artery stenosis

5. Other early events

The early events and the associate disorders which arise in HELLP syndrome are presented in Table 4 and are indeed complex.

In order to evaluate the broad spectrum of HELLP syndrome differential diagnosis, an interdisciplinary approach is inevitable.[41-44] Generally speaking, searching for a final diagnosis without interdisciplinary approach often leads to serious, deleterious effects on the mother and her fetus. All pregnant women, which present with upper abdominal pain, should be suspected for HELLP syndrome, irrespectively of pre-eclampsia symptoms, and immediate laboratory evaluation has to be carried out.

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