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Perspective

Clinical diagnosis and treatment of "atypical" HELLP syndrome

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ABSTRACT

HELLP syndrome is regarded as one of the most serious manifestations of preeclampsia, but approximately 15% of patients with HELLP syndrome have no clinical manifestations of preeclampsia; furthermore, although most cases of HELLP syndrome occur after 34 weeks, some cases occur at a much earlier gestational stage, even before 20 weeks of gestation, the underlying pathogenesis of "atypical" HELLP syndrome with very early onset or the basis of non-preeclampsia manifestations should be more actively explored. Obstetricians should carefully identify the potential etiology of "atypical" HELLP syndrome in order to provide a reasonable treatment and improve maternal and fetal prognosis.

In 1954, Pritchard JA[1] first described three patients with intravascular hemolysis, thrombocytopenia and hematologic abnormalities on the basis of severe preeclampsia, in 1982, Weinstein[2] put together the data for 29 patients with similar clinical features that result in the famous article "Syndrome of hemolysis , elevated liver enzymes , and low platelet count: A severe consequence of hypertension in pregnancy", due to the potential fatality of the disease, he developed a name for the disease with "warning" significance: hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.[3] Today, obstetricians have a better understanding of HELLP syndrome, and most cases of HELLP syndrome that are based on preeclampsia are easy to address, but the diagnosis of HELLP syndrome without preeclampsia manifestations is still difficult. For HELLP syndrome that occurs in the earlier stages of pregnancy, the differential diagnosis of this "atypical" syndrome is still difficult. How to deal with cases of "atypical" HELLP syndrome is a challenge for obstetricians. In this paper, we analyze the current diagnostic criteria of HELLP syndrome. The existing clinical treatment strategies for HELLP syndrome are explored in combination with the pathogenesis, and the differential diagnosis of atypical HELLP syndrome is introduced to provide a reference for obstetric clinical practice.

1. Diagnostic criteria for HELLP syndrome

Although Weinstein proposed the nomenclature of HELLP syndrome, the diagnostic criteria for HELLP syndrome that are used for clinical diagnosis and research are not actually uniform. Both the relatively strict Tennessee criteria[4] and Mississippi grades[5] that define disease severity situation exist. In 2004, Sibai[6] proposed controversial problems in the diagnostic criteria for HELLP syndrome. The differences in these diagnostic criteria arise from the large range of variations in the experimental diagnostic criteria themselves on the one hand and from the knowledge of physicians or researchers about the development process of HELLP syndrome on the other hand. Based on the guidelines for the diagnosis and treatment of hypertensive disorders of pregnancy in China,[7] the diagnostic criteria for HELLP syndrome used include the following: microvascular hemolysis (H), including elevated lactate dehydrogenase (LDH) levels, fragmented red blood cells and spherocytes in peripheral blood smears, bilirubin levels $\geq$20.5 μmol/L, and mildly decreased hemoglobin levels; elevated transaminase levels (EL), including alanine aminotransferase (ALT) levels $\geq$40 U/L or aspartate aminotransferase (AST) levels $\geq$70 U/L; and decreased platelet counts (LP), including platelet counts $<100 \times 10^9$/L.

As shown through the above diagnostic criteria, preeclampsia-related clinical manifestations are not necessary for the diagnosis of HELLP syndrome; moreover, the diagnostic criteria of partial HELLP syndrome actually overlap with those of severe preeclampsia (SPE). Over the years, it has been traditionally believed that HELLP syndrome is closely associated with SPE, and approximately 2%~12%[8] of patients with preeclampsia develop HELLP syndrome; however, HELLP syndrome has special characteristics independent of preeclampsia: its diagnostic criteria include neither the time limit of 20 weeks of gestation that is required for the diagnosis of preeclampsia nor the inclusion of the symptomatology-related manifestations of preeclampsia. In clinical work, approximately 15% of patients with HELLP syndrome have no clinical manifestations of preeclampsia, such as hypertension or proteinuria, which requires us to break the concept that there is an inevitable association between preeclampsia and HELLP syndrome, and on the basis of recognizing that HELLP syndrome is a serious clinical manifestation of hypertensive disorders of pregnancy, some cases of HELLP syndrome with "atypical" clinical manifestations should also be fully recognized and considered.[9,10]

2. Debate on the current diagnosis and management of HELLP syndrome

As mentioned above, in the current clinical work, HELLP syndrome is

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regarded as one of the most serious manifestations of hypertensive disorders of pregnancy in most cases, so the treatment of such patients is similar to that of patients with SPE and involves maternal supportive treatment, fetal monitoring, antenatal corticosteroid therapy for fetal lung maturation, magnesium sulfate therapy to prevent convulsions and the timely delivery of pregnancy. Through the above introduction of the diagnostic criteria for HELLP syndrome, we also recognized that the current diagnostic and classification criteria for HELLP syndrome do not actually reflect the underlying pathogenesis of patients and the severity of the disease well, so the precise treatment of such patients cannot be conducted.

In clinical work, when hypertension, microangiopathic hemolytic anemia (MAHA), thrombocytopenia and other manifestations occur in the third trimester of pregnancy, most obstetricians will directly diagnose HELLP syndrome, and the underlying pathogenesis of HELLP syndrome is not understood deeply enough, its treatment is very singular. It is true that early delivery can ensure maternal safety, but for patients with HELLP syndrome that occurs at less than 24–26 weeks of gestation, fetal loss occurs as a result of the termination of pregnancy to ensure maternal safety. It is worth exploring that after the termination of pregnancy, if a patient's condition is not alleviated as predicted and other clinical manifestations such as renal failure occur, the diagnosis of HELLP syndrome should be evaluated and the occurrence of pregnancy-associated thrombotic microangiopathy (TMA), such as postpartum hemolytic-uremic syndrome (PHUS), should be differentiated. In 2016, Tsai HM[11] provided a thought-provoking case report of a patient who was diagnosed with SPE during the first pregnancy, HELLP syndrome during the second pregnancy, and PHUS during the third pregnancy due to postpartum renal failure, which was diagnosed by complement testing; this patient achieved good efficacy with anti-complement therapy. This forced us to examine the current overall treatment strategy for HELLP syndrome and initiate a re-exploration of its potential pathogenesis: is active prenatal termination of pregnancy the only treatment option for patients with HELLP syndrome? Should the underlying pathogenesis of "atypical" HELLP syndrome with very early onset or the basis of non-preeclampsia manifestations be more actively explored? Should the existing diagnostic criteria based on clinical manifestations be broken to break the constraints of the treatment principles, and should the disease be reclassified according to its pathogenesis to guide clinical treatment?

3. Exploring new options for the treatment of atypical HELLP syndrome based on the pathogenesis

Since there is an overlap between the current diagnostic criteria for partial HELLP syndrome and SPE, and clinical manifestations such as MAHA and thrombocytopenia are highly similar to PHUS, in recent years, it has been proposed that HELLP syndrome and PHUS as well as SPE are all included in pregnancy-related TMAs.[12]

At present, many studies have confirmed that 50% of patients with PHUS have gene mutations of complement Factor H (CFH), the alternative pathway inhibitor of the complement system, which in turn leads to the inactivation of CFH function, as well as an abnormal activation of the complement system through the alternative pathway, resulting in hypertension, thrombocytopenia, MAHA and acute kidney injury (AKI).[13,14] An increasing number of studies have suggested that HELLP syndrome, which is rare in clinical practice (incidence of approximately 0.2%), may have a pathogenesis that is more consistent with that of PHUS than that of SPE: aberrant activation of the complement system plays a more important role in HELLP syndrome and PHUS. Through gene sequencing of patients who were clinically diagnosed with HELLP syndrome, it was found that approximately 30–40% of the patients had mutations in rare complement system-related genes, similar to those in PHUS patients, and these mutations occur at a very low rate (<10%) in patients with SPE.[15–18] The use of the complement system activation product C5a antagonist eculizumab can significantly improve the prognosis of patients with PHUS. Given the similarity in pathogenesis between HELLP syndrome and PHUS, is this treatment for PHUS also suitable for HELLP syndrome? In 2013, Burwick RM[19] first reported a successful case of HELLP syndrome treated with eculizumab, which prolonged the pregnancy of a patient with HELLP syndrome diagnosed at 26 weeks by 16 days, thus greatly improving the neonatal prognosis and leading to the relevant clinical exploration of eculizumab in the treatment of HELLP syndrome. These successful cases suggest that for HELLP syndrome with a clinical onset earlier than 30 weeks, in addition to actively delivery according to the diagnosis and treatment norms of SPE, the potential causes of such HELLP syndrome cases should be analyzed from the perspective of pathogenesis, and various treatment options should be explored to improve the overall prognosis of the mother and child.

4. Clinical differential diagnosis of "atypical" HELLP syndrome

When pregnant women develop MAHA and thrombocytopenia, obstetricians will first consider SPE or HELLP syndrome, which are more common in clinical practice, and then consider other rare pregnancy-related TMAs, such as PHUS (incidence of approximately 1/25,000[12]). This is also in line with normal diagnostic ideas, but attention should be given to the differential diagnosis of other diseases when patients present with HELLP syndrome and have atypical clinical manifestations. Among the many non-pregnancy-induced idiopathic diseases that can lead to severe thrombocytopenia as well as MAHA, some first occur during pregnancy, and some have similar clinical manifestations to HELLP syndrome. These diseases mainly include systemic lupus erythematosus, thrombotic thrombocytopenic purpura (TTP), PHUS and antiphospholipid syndrome (APS). When the diagnosis of HELLP syndrome is questionable, the following clinical parameters can contribute to differential diagnosis: the degree of thrombocytopenia, the severity of neurological symptoms, the severity of AKI, the rate of postpartum recovery, the degree of abnormal liver function, whether the disease occurs before 30 weeks of gestation and whether it is relieved spontaneously after delivery.

4.1. HELLP syndrome

Most cases of HELLP syndrome occur after 34 weeks. In the cohort reported by the University of Oklahoma Medical Center,[20] 838 patients were diagnosed with preeclampsia, HELLP syndrome, or eclampsia, with 1 (0.1%) diagnosed at 10–19 weeks, 9 (1.1%) diagnosed before 25 weeks, and 46 (5.6%) diagnosed before 30 weeks, suggesting that the incidence of HELLP syndrome is very low before 30 weeks of gestation. Attention should be given to identify other possible diagnoses in addition to HELLP syndrome when symptoms occur before 30 weeks of pregnancy. In some cases, which are mostly reported in the form of case reports, HELLP syndrome may occur before 20 weeks of gestation due to fetal factors, often suggesting chromosomal abnormalities of the fetus, such as trisomy 13 and trisomy 18.[21–23] Unlike PHUS, although HELLP syndrome can lead to AKI, injuries usually result from pronephric factors and usually does not lead to severe AKI.[24] Therefore, severe AKI usually suggests that other etiologies should be investigated.

4.2. TTP

The pathogenesis of TTP is a decrease in ADAMTS 13 activity (<10%) due to genetic or acquired (the presence of functional inhibitory antibodies to ADAMTS 13) factors, so laboratory testing for ADAMTS 13 activity is required to confirm its diagnosis.[25,26] The clinical manifestations of both hereditary and acquired TTP are highly similar to those of HELLP syndrome. Although the incidence of TTP during pregnancy is very low, obstetricians should pay attention to the differential diagnosis of TTP because it may lead to maternal death if left untreated.

Patients with hereditary TTP often have severe adverse pregnancy outcomes. Of the 61 pregnancies in 35 patients with hereditary TTP

Table 1
Comparison of typical clinical features and specific management of disorders with microangiopathic hemolytic anemia and thrombocytopenia during pregnancy.

Clinical feature	Preeclampsia/HELLP	TTP	PHUS	CAPS
Incidence	100 in 10,000 pregnancies	1 in 10,000 pregnancies	Unknown. May be similar to TTP.	Unknown.
Time of occurrence	By definition, occurs after 20 weeks of gestation; more common near term and within three days postpartum	May occur throughout pregnancy, but most common near term and several weeks postpartum	May occur throughout pregnancy, but most common postpartum	May occur throughout pregnancy, but most common near term and several days postpartum
Vital signs	Hypertension, by definition, BP ≥ 160/110mmHg	Normal BP, fever may be present but is rare	Hypertension due to AKI	Multi-organ thrombosis
Neurologic abnormalities	Headache, vision changes. Less commonly eclamptic seizures, stroke.	Severe in 41% (transient focal defects, seizure, stroke); minor in 30%	None	Headache, vision changes, transient focal defects, seizure or stroke
Microangiopathic hemolysis/ schistocytes	Moderate	Severe	Moderate	Severe
Kidney injury	Usually mild, but severe AKI is possible. Dialysis is rarely required.	Usually mild or absent; severe AKI requiring dialysis in <5%	Severe, typically dialysis is required	Usually mild, but severe AKI is possible. Dialysis is rarely required.
Liver function tests: ALT, AST	From normal to markedly increased	Normal or slightly increased	Normal	From normal to markedly increased
Typical course following delivery	Stabilization or improvement within 48 hours	No stabilization or improvement within 48 hours	Increasing serum creatinine	Most unchanged, but may improve after delivery
Specific management	Delivery of infant is curative	Plasma exchange, immunosuppression if acquired autoimmune TTP suspected. If hereditary TTP is strongly suspected, plasma infusion is sufficient	Anti-complement agent	Plasma exchange, glucocorticoids, IVIG, anticoagulant

PE/HELLP: preeclampsia/hemolysis, elevated liver enzymes, low platelets; TTP: thrombotic thrombocytopenic purpura; PHUS: postpartum hemolytic-uremic syndrome; CAPS: catastrophic antiphospholipid syndrome; AKI: acute kidney injury; IVIG: intravenous immune globulin; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

reported by Kasht R et al.,[27] 34 (97%) had severe pregnancy complications, and two died during pregnancy. In view of this, if a woman has experienced a successful pregnancy and childbirth, the possibility of genetic TTP is ultimately not considered. Acute exacerbations of hereditary TTP often occur relatively early in pregnancy, with most occurring earlier than 30 weeks of gestation. In populations, the incidence of acquired autoimmune TTP is approximately 2–3 per million population/year, while the occurrence of hereditary TTP is even lower.[28] However, since many patients with hereditary TTP have their initial TTP symptoms during their first pregnancy, the relative frequency of hereditary TTP compared to acquired TTP increases remarkably during pregnancy. At the French Thrombotic Microangiopathy Research Center, there were 32 women diagnosed with TTP during pregnancy, and 10 (31%) had hereditary TTP.[29] Therefore, when TTP is diagnosed during pregnancy, both hereditary and acquired TTP should be considered.

The most important laboratory value for distinguishing PE/HELLP from TTP is the platelet count. Approximately 5% of patients with HELLP syndrome have platelets $<60 \times 10^9$/L and 1% have platelets $<30 \times 10^9$/L, while patients with acquired TTP have lower platelet counts, and approximately 2% of patients with acquired TTP have platelet counts $>30 \times 10^9$/L.[20] Although patients with hereditary TTP usually have worse clinical outcomes, their platelet levels are generally higher than those of patients with acquired TTP. The treatment of TTP is mainly to assume an acquired etiology and start plasma exchange or corticosteroid therapy. It should be pointed out that TTP and HELLP syndrome sometimes cannot be distinguished in time in clinical work, and plasma exchange therapy should also be initiated as early as possible to ensure maternal safety.

4.3. PHUS

As mentioned above, PHUS is associated with gene mutations that cause increased complement activation by the alternative pathway. PUHS is usually induced by pregnancy and occurs mostly in the postpartum period. Compared with patients with TTP, patients with PHUS usually have relatively mild thrombocytopenia and MAHA but develop severe AKI, which is the most important clinical manifestation that can distinguish PHUS from TTP and HELLP syndrome. Physicians should consider PHUS in women who deliver because of presumed PE/HELLP syndrome with renal injury that does not resolve in the first 48–72h postpartum, and plasma exchange or eculizumab should be initiated as early as possible.[13,14]

4.4. APS

The diagnosis of APS relies on persistent high titers of antiphospholipid antibodies (aPLs), mainly including lupus anticoagulants, anticardiolipin IgG/IgM antibodies, and anti-β2 glycoprotein I IgG/IgM antibodies, and obstetric antiphospholipid syndrome (OAPS) is characterized by adverse pregnancy outcomes. Previous studies have shown that patients with APS are at high risk of developing HELLP syndrome during pregnancy, which usually occurs before 30 weeks of gestation. An earlier study by Le TTD et al.[30] found that 44% of APS patients developed HELLP syndrome before 28 gestational weeks. A recent multicenter case–control study[31] showed that positive aPLs are an important indicator of poor pregnancy prognosis in patients with HELLP syndrome, thus suggesting that patients with HELLP syndrome occurring before 30 weeks of gestation should have an aPL examination to exclude the possibility of APS and avoid delaying the initiation of anticoagulant therapy.

In addition to the diseases listed above, acute fatty liver of pregnancy (AFLP) is also a possible potential disease leading to MAHA and thrombocytopenia. Physicians should pay attention to making a differential diagnosis. Comparison of typical clinical features and specific management of disorders with MAHA and thrombocytopenia during pregnancy are shown in Table 1.

In summary, it is not difficult to make a diagnosis of HELLP syndrome in clinical work; however, when HELLP syndrome occurs without preeclampsia manifestations or in early stage of gestation, physicians should pay attention to the differential diagnosis of a variety of diseases that can lead to thrombocytopenia and MAHA. A multidisciplinary team including maternal-fetal medicine specialists, nephrologists, hematologists, and immunologists should be established, and appropriate treatment should be provided according to the underlying pathogenesis of atypical HELLP syndrome to improve maternal and fetal outcomes.

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Conflict of interest

All authors declare that there is no conflict of interest.

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