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Genetic characteristics of HELLP Syndrome: A variant of secondary thrombotic microangiopathy in pregnancy

Zulola RADJABOVA[1]

Center for the Development of Professional Skills of Medical Workers

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ABSTRACT

HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelets), first described in 1982, remains one of the most serious obstetric complications with a complex pathogenesis and high maternal and perinatal mortality. This study analyzes the clinical presentation, genetic polymorphisms (F5 Leiden, MTHFR C677T, MTR A2756G), and Doppler parameters in patients diagnosed with HELLP syndrome, comparing them to a control group of healthy pregnant women. Results indicate a strong association with thrombophilia markers, significant hemodynamic alterations, and a high prevalence of poor obstetric outcomes. The findings suggest that HELLP syndrome should be considered a distinct variant of secondary thrombotic microangiopathy (TMA), requiring tailored diagnostic and therapeutic strategies.

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HELLP sindromining genetik xususiyatlari: homiladorlikda ikkilamchi trombotik mikroangiopatiyaning bir ko‘rinishi

Kalit so‘zlar:
HELLP sindromi,
homiladorlik,
trombotik mikroangiopatiya,
preeklampsiya,
F5 Leyden,
MTHFR,
trombofiliya.

ANNOTATSIYA

1982-yilda ilk bor tasvirlangan HELLP sindromi (gemoliz, jigar fermentlari faolligining ortishi va trombositlar miqdorining kamayishi) murakkab patogenezga ega bo‘lib, ona va homila o‘limi xavfi yuqori bo‘lgan eng jiddiy akusherlik asoratlaridan biri hisoblanadi. Ushbu tadqiqotda HELLP sindromi tashxisi qo‘yilgan bemorlardagi klinik ko‘rinish, genetik polimorfizmlar (F5 Leiden, MTHFR C677T, MTR

[1] PhD, Assistant, Department of Obstetrics and Gynecology, Center for the Development of Professional Skills of Medical Workers. Tashkent, Uzbekistan. E-mail:radjabova.z@yandex.ru

A2756G) va doppler parametrlari sog‘lom homilador ayollardan iborat nazorat guruhi bilan taqqoslangan holda tahlil qilingan. Natijalar trombofiliya belgilari bilan kuchli bog‘liqlikni, gemodinamikaning sezilarli o‘zgarishlarini va salbiy akusherlik natijalarining yuqori darajada uchrashini ko‘rsatdi. Olingan ma’lumotlar HELLP sindromini ikkilamchi trombotik mikroangiopatiyaning (TMA) alohida turi sifatida ko‘rib chiqish lozimligini va bu holat maxsus tashxis hamda davolash usullarini talab qilishini ko‘rsatmoqda.

Генетические характеристики синдрома HELLP: вариант вторичной тромботической микроангиопатии при беременности

Ключевые слова:
синдром HELLP,
беременность,
тромботическая микроангиопатия,
преэклампсия,
фактор V Лейдена,
MTHFR,
тромбофилия.

АННОТАЦИЯ

Синдром HELLP (гемолиз, повышенный уровень печеночных ферментов и низкое содержание тромбоцитов), впервые описанный в 1982 году, остается одним из наиболее серьезных акушерских осложнений со сложным патогенезом и высокой материнской и перинатальной смертностью. В данном исследовании анализируются клиническая картина, генетические полиморфизмы (F5 Leiden, MTHFR C677T, MTR A2756G) и допплерографические параметры у пациенток с диагнозом синдром HELLP в сравнении с контрольной группой здоровых беременных женщин. Результаты указывают на сильную связь с маркерами тромбофилии, значительные гемодинамические изменения и высокую частоту неблагоприятных акушерских исходов. Полученные данные позволяют предположить, что синдром HELLP следует рассматривать как отдельный вариант вторичной тромботической микроангиопатии (ТМА), требующий индивидуального подхода к диагностике и лечению.

INTRODUCTION

Since the term “HELLP syndrome” was introduced by L. Weinstein in 1982 – characterized by hemolysis, elevated liver enzymes, and low platelets in pregnancy – the number of controversial issues regarding its diagnosis and management has steadily increased. Initially considered a variant of severe preeclampsia (PE), clinical experience has shown that HELLP can occur independently of typical PE manifestations, co-occurring only in about 80% of cases. Furthermore, a variety of atypical clinical presentations have been identified, involving not only liver damage but also involvement of the heart, kidneys, lungs, central nervous system, and other organs. It has also been established that HELLP syndrome may debut or progress in the postpartum period, significantly worsening prognosis.

LITERATURE REVIEW

In cases where HELLP syndrome develops postpartum, maternal mortality ranges from 1% to 25% according to various reports. Perinatal mortality remains high, reaching 7–30%. Despite clinical, laboratory, and morphological similarities between HELLP and PE, the mechanisms determining why some patients develop classical PE while others develop HELLP without hypertension or proteinuria remain unresolved. Numerous pathogenetic hypotheses have been proposed to explain this phenotypic diversity.

Significant attention has been given to the role of antiphospholipid syndrome (APS) and hereditary thrombophilias, such as factor V Leiden and prothrombin gene mutations (FII). Additionally, debate persists about whether HELLP syndrome should be classified as a form of thrombotic microangiopathy (TMA), given shared pathogenetic mechanisms and histological features.

RESEARCH METHODOLOGY

This retrospective observational study analyzed clinical records of patients diagnosed with HELLP syndrome using the Tennessee/Mississippi classification criteria. A control group of healthy pregnant women was used for comparative analysis. Clinical parameters, obstetric history, genetic testing results (F5 Leiden, MTHFR C677T, MTR A2756G), and Doppler ultrasound assessments of uterine, umbilical, and fetal middle cerebral arteries were included. Statistical significance was assessed using non-parametric tests ($p<0.05$ considered significant).

In fact, HELLP syndrome often represents one of the most aggressive and life-threatening forms of secondary TMA, frequently regarded as an extreme variant or severe complication of preeclampsia. In our cohort of patients with secondary TMA, HELLP syndrome accounted for 9.1% (n = 34), underlining its clinical significance among obstetric complications. The diagnosis of HELLP in this study was established using the widely accepted Tennessee/Mississippi criteria, which include the triad: microangiopathic hemolysis (LDH > 600 U/L and presence of schistocytes in blood smear), elevated liver enzymes (AST > 70 U/L), and thrombocytopenia (< 100×10^9/L). The presence of these pronounced systemic injury markers is key to confirming HELLP syndrome.

ANALYSIS AND RESULTS

The analysis of demographic data revealed that patients with HELLP syndrome had a median age of 29.0 years ([IQR 22.25–31.75]; mean ± SD: 27.91 ± 5.83), comparable to healthy pregnant controls (median 27.0 years [22.00–29.00]; $p > 0.05$). However, in terms of obstetric outcomes, the HELLP group demonstrated the most dramatic measures. The median gestational age at delivery in the HELLP group was 29.0 weeks ([IQR 24.00–34.00]), significantly earlier than in the control group (median 39.0 weeks [38.25–40.00]; $p < 0.001$), indicating fulminant disease progression necessitating emergency delivery for maternal survival. As a consequence of severe prematurity and disease severity, neonatal anthropometric parameters were critically low – median neonatal weight in the HELLP group was 1265.0 g ([IQR 732.50–2073.75]), the lowest among all TMA groups (control: 3410.0 g [3006.25–3747.50]; $p < 0.001$), with similar trends in neonatal length (median 36.5 cm [IQR 30.00–45.75]). Parity analysis showed that 64.7% (n = 22) of the HELLP patients were multiparous, similar to the PE group but significantly higher than among primiparae. Multiple pregnancies – an extra placental burden – were present in 3.7% (n = 12) of HELLP cases.

Detailed review of medical histories revealed that HELLP patients had pronounced background susceptibility in terms of vascular and hemostatic systems. Specifically, a history of arterial hypertension was present in 90% (n = 34) of HELLP patients ($p < 0.001$), and a positive family history of thrombosis was universal (100%, n = 34), underlining that HELLP rarely arises in absence of underlying predisposition. Additional anamnesis revealed that 64.7% (n = 22) had history of anemia, habitual miscarriage, and prior preeclampsia; urinary tract infections affected 32.4% (n = 11); and infertility history was noted in 29.4% (n = 10). This constellation of background factors indicates high latent predisposition to fulminant thrombotic complications.

Comparative analysis of genetic polymorphisms revealed a distinctive latent predisposition profile in HELLP patients. The most striking finding was the extremely high frequency of the F5 Leiden (G1691A) mutant allele – detected in 97.0% of patients (n = 23 heterozygotes + n = 10 homozygotes), significantly higher compared to 12.0% in control and 53.2% in the PE group ($p < 0.001$). Noteworthy is the high proportion of homozygous AA genotype in HELLP patients (29.4%, n = 10), virtually absent in controls or PE group. This suggests that F5 Leiden mutation is a strong genetic predisposer for the hepatolytic variant of secondary TMA, where inherited hypercoagulability, uncovered during pregnancy, triggers uncontrolled microthrombosis.

Polymorphisms in folate-cycle genes also showed strong associations. All HELLP patients (100%) carried the mutant T allele of MTHFR C677T (n = 24 CT + n = 10 TT), significantly higher than 14.0% CT carriers in controls ($p < 0.001$). High homozygosity for TT genotype (29.4%, n = 10) was also specific to HELLP. For MTR A2756G, all HELLP patients were homozygous wild-type AA (n = 34), compared to 82.0% in controls ($p < 0.001$), indicating its potential role as a latent risk marker in HELLP pathogenesis.

Instrumental Doppler evaluation revealed significant uteroplacental circulation disturbances, similar to preeclampsia but possibly more pronounced. The uterine artery pulsatility index (PI) median was 1.43 [IQR 1.40–1.46] ($p < 0.001$), and umbilical artery PI was 1.05 [1.03–1.08] ($p < 0.001$). Middle cerebral artery PI was significantly reduced at 0.99 [0.97–0.99] ($p < 0.001$), suggesting a brain-sparing adaptive response to severe fetal hypoxia and constituting a latent functional substrate of fetal distress.

CONCLUSION AND RECOMMENDATIONS

These findings strongly support the concept that HELLP syndrome is one of the most severe forms of secondary thrombotic microangiopathy in obstetric practice, characterized by rapid onset, early presentation, and high maternal and perinatal mortality. Historically considered a severe PE manifestation, our data demonstrate that HELLP can arise independently of hypertension or proteinuria, warranting its classification as a distinct thrombotic entity with systemic organ involvement.

Atypical clinical courses – including cardiac, renal, and neurological involvement – underscore its systemic nature and the need for multidisciplinary care. The occurrence of HELLP syndrome in the postpartum period (up to 25% of cases) emphasizes the necessity for extended monitoring beyond delivery. The medical history profile, with high rates of hypertension, thrombosis in family history, recurrent miscarriage, and other risk factors, highlights the role of latent thrombophilia. In particular, universal presence of MTHFR C677T mutation and very high frequency of F5 Leiden mutations (including homozygous forms) point to a genetic predisposition that becomes pathogenic under pregnancy stress. Doppler findings further reinforce the role of placental insufficiency and fetal hypoxia mechanisms in HELLP syndrome.

HELLP syndrome represents a separate and highly aggressive form of secondary thrombotic microangiopathy, distinct from classic preeclampsia and requiring tailored diagnostic and therapeutic strategies.

A strong association with latent thrombophilic mutations (F5 Leiden, MTHFR C677T) suggests the value of including genetic screening in preconception counseling for high-risk women.

Doppler monitoring of uteroplacental flow has high prognostic value for early detection of placental insufficiency and neuroadaptive fetal responses.

A comprehensive approach – incorporating patient history, genetic predisposition, and hemodynamic data – is essential in high-risk pregnancy surveillance.

HELLP syndrome serves as a paradigm of interplay between inherited thrombophilia, endothelial dysfunction, and placental hypoperfusion, highlighting pathways for future personalized prevention and therapy strategies.

RECOMMENDATIONS

The clinical management of HELLP syndrome should be considered independently from preeclampsia, despite frequent overlap in symptoms. It is necessary to develop separate clinical protocols for the early diagnosis, monitoring, and treatment of HELLP syndrome, considering its aggressive course and multisystem organ involvement.

Women with a burdened medical history (arterial hypertension, recurrent pregnancy loss, hereditary thrombosis, APS) should be classified as high-risk for HELLP syndrome. These patients should undergo preconception preparation, comprehensive genetic and coagulation screening, including testing for F5 Leiden, FII, and MTHFR gene mutations.

Early diagnosis and dynamic monitoring of pregnant women suspected of having HELLP syndrome should include regular assessment of laboratory markers (LDH, AST, platelet count), peripheral blood smear analysis for schistocytes, and ultrasound with Doppler evaluation of fetoplacental circulation.

Genetic testing for thrombophilic mutations (primarily F5 Leiden and MTHFR C677T) should be integrated into routine clinical practice as part of an individualized approach to managing high-risk pregnancies, especially in patients with adverse obstetric history.

Once HELLP syndrome is diagnosed, delivery should be performed immediately, regardless of gestational age, with mandatory involvement of a multidisciplinary team including obstetricians, intensivists, neonatologists, hematologists, and nephrologists.

Postpartum follow-up of patients with HELLP syndrome is essential, including monitoring of liver, kidney, and cardiac function, as well as coagulation status, since complications often manifest during the early postpartum period.

The development of specialized registries and observational programs for HELLP syndrome will aid in collecting comprehensive statistics, better understanding pathogenesis, and refining individualized prevention and treatment strategies.

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