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Laboratory and Clinical Characteristics of Patients Diagnosed With Hellp Syndrome Due To Microangiopathic Hemolytic Anemia and/or Thrombocytopenia

Mikroanjiyopatik Hemolitik Anemi ve/veya Trombositopeni Nedeniyle HELLP Sendromu Tanısı Alan Hastaların Laboratuvar ve Klinik Özellikleri

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ABSTRACT

Objective: We aimed to present the pregnant patients who were consulted with hematologists for microangiopathic hemolytic anemia and/or thrombocytopenia and were diagnosed HELLP syndrome.

Materials and Methods: A total of 32 patients, who were diagnosed with HELLP syndrome, were included in this study. Patients with other microangiopathic hemolytic anemia, including pre-eclampsia, eclampsia, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, disseminated intravascular coagulation etc. were excluded.

Results: The median age of all patients was 30.45 ± 16.22 (18-52) years. According to the Mississippi classification; 12 patients (37.5%) were in class 1 while 15 patients (46.9%) were in class 2, and there was acute renal failure in 4 patients (33.3%) in class 1 and 3 patients (20%) in class 2. There was no acute renal failure present in the class 3 including a total of 5 patients (15.6%). There was renal failure in 6 (42.9%) of 14 patients (43.7%) with HELLP syndrome, whose hemoglobin value was less than or equal to 8 gr/dl. In patients with HELLP syndrome, the renal failure risk of those whose hemoglobin value was less than or equal to 8 gr/dl was significantly higher than those whose hemoglobin value was greater than 8 gr/dl (OR: 12.75, p = 0.0285).

Conclusion: The mechanism of occurrence of HELLP syndrome is not clear and have many overlapping clinical aspects with the other thrombotic microangiopathic syndromes. Renal failure is a complication of HELLP syndrome. The most associated cases with renal failure are the presence of DIC and severe anemia in HELLP syndrome. The hemoglobin value of less than 8 gr/dl is a significant risk factor for renal failure in HELLP syndrome.

Key Words: Microangiopathic hemolytic anemia, thrombocytopenia, HELLP syndrome, renal failure

ÖZET

Amaç: Bu çalışmada mikroanjiyopatik hemolitik anemi ve/veya trombositopeni nedeniyle hematoloji bölümüne danışılan ve HELLP sendromu tanısı alan gebelerin verilerini sunmayı amaçladık.

Materyal ve Metod: Çalışmaya HELLP sendromu tanısı konan 32 dahil edildi. Pre-eklampsi, eklampsi, trombotik trombositopenik purpura, hemolitik üremik sendrom ve dissemine intravasküler koagülasyon gibi diğer mikroanjiyopatik hemolitik anemi tanılı hastalar çalışma dışı bırakıldı.

Bulgular: Hastaların ortanca yaşı 30.45±16.22 (dağılım 18-52) idi. Mississippi sınıflamasına göre hastaların 12 (37.5)'i sınıf 1 kategorisinde olup bunların 4 (%33.3)'ünde ve sınıf 2 kategorisindeki 15 (%46.9) hastanın 3 (%20)'ünde akut böbrek yetmezliği vardı. Sınıf 3 kategorisindeki 5 (%15.6) hastada ise böbrek yetmezliği saptanmadı. Hemoglobin değeri ≤ 8 gr/dl olan HELLP sendromlu 14 hastanın 6'sında (%42.9) böbrek yetmezliği vardı. HELLP sendromlu hastalarda, hemoglobin değeri ≤ 8 gr/dl olanların böbrek yetmezliği riski, hemoglobin değeri > 8 gr/dl olanlardan anlamlı derecede yüksek olduğu görüldü (OR: 12.75, p = 0.0285).

Sonuç: HELLP sendromunun meydana geliş mekanizması net değildir ve diğer trombotik mikroanjiyopatik sendromlar ile örtüşen birçok klinik yönü mevcuttur. Böbrek yetmezliği HELLP sendromunun bir komplikasyonudur. Bu çalışmada HELLP sendromunda böbrek yetmezliği ile en ilişkili durumun DIC varlığı ve aneminin derinliği olduğu bulunmuş ve hemoglobin değerinin ≤ 8 gr/dl olması böbrek yetmezliği için önemli bir risk faktörü olabileceği ortaya konulmuştur.

Anahtar Kelimeler: Mikroanjiyopatik hemolitik anemi, trombositopeni, HELLP sendromu, böbrek yetmezliği

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Introduction

The HELLP (H = Haemolysis, EL = Elevated Liver enzymes, LP = Low Platelets) syndrome is a serious complication in pregnancy and characterized by microangiopathic hemolytic anemia, elevated liver enzymes, and thrombocytopenia. HELLP syndrome is seen in 0.5 to 0.9% of all pregnancies and in 10–20% of cases with severe preeclampsia (1). HELLP syndrome could be present with non-specific symptoms that mimic viral infections such as nausea, vomiting, and fatigue. However, most common symptom is an abdominal pain and sign is tenderness on mid-epigastrium and right upper quadrants in HELPP syndrome (2,3). Furthermore, headache, ascites, and jaundice can be observed on disease course. Delaying on diagnosis of HELPP syndrome due to evaluating faint and non-specific symptoms and findings may results in disease progression and deaths (4). The pathogenesis of HELLP syndrome has not been precisely understood. While there have been arguments that HELLP syndrome is a form of severe pre-eclampsia. This argument is supported by the presence of hypertension and absence of proteinuria in pre-eclampsia in 15-20% of patients diagnosed with HELLP syndrome and proposed mechanism for this hypothesis is that abnormal placental development and placental dysfunction (5-7). HELLP syndrome to be an independent entity from pre-eclampsia. However, some authors suggest that HELLP syndrome is an independent entity from pre-eclampsia andthe abnormal activation of inflammation and coagulation system in the liver play a role in disease pathophysiology besides abnormal placental dysfunction (8-10). Serious maternal morbidities, such as disseminated intravascular coagulation (DIC), abruptio placentae, acute renal failure, pulmonary edema, subcapsular and intraparenchymal liver hematoma, and retinal detachment, can be observed at presentation or in the following period (11). The mainstay of treatment and the single most effective curative treatment is delivery when the condition of the mother is stable in HELLP syndrome (12). In this study, we reported that risk factors and relationship with the other clinical parameters for development of renal failure during HELPP syndrome.

Materilas and Methods

Patients: A total of 32 patients, who presented to medical faculty hospital from 2014 to 2018 and who were consulted with hematologists for hemolytic anemia and diagnosed with HELLP syndrome, were included in this study. Patients with other microangiopathic hemolytic anemia (MAHA), including pre-eclampsia, eclampsia, thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), disseminated intravascular coagulation (DIC) etc. were excluded.

The files of patients and the data in hospital system were recorded and analyzed retrospectively. Patients' demographic and clinical features including age, hemoglobin level, platelet count, serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (AST), lactat dehydrogenase (LDH), prothrombin time (PT), and proteinuria levels were analyzed retrospectively. The relationship between clinical and laboratory values was investigated according to the diagnosis of patients.

Diagnostic Criteria For HELLP Syndrome: We categorized patients according to The Mississippi-Triple Class Systema classification. In this classification, the disorder is classified based on the lowest platelet counts detected anytime during the disease course. Platelet counts is for the class 1 $\leq 50*10^6$ µl, for the class 2 $\leq 100*10^6$ µl and for the class 3 $\leq 150*10^6$ µl. In additon to platelet counts, classification system are associated with hemolysis (LDH $\geq$ 600 U/L) and mild – moderete liver injury (AST or ALT $\geq$ 70 U/L for the class 1 and 2, AST or ALT $\geq$ 40 U/L for the class 3). The class 3 in HELLP syndrome is considered as a clinical significant transition stage or a phase of the HELLP syndrome which has the ability of progression (13,14).

Ethics Consent: Ethics approval was obtained from the non-invasive clinical research ethics committee of the medical faculty (date/number: 31.01.2018/007). All aspects of the study, including periodical clinical and laboratorial checkups were performed according to the principles of the Declaration of Helsinki (64th, 2013).

Statistical Assessment: The Statistical Package for Social Sciences (SPSS) software (version 22.0) was used for the statistical evaluation of the research data**.** Quantitative measurements were described as mean, maximum, and minimum; categorical measurements were expressed as number and percentage. Independent samples T test and bivariate Pearson Correlation test were used in the investigation of the relationship among categorical measurements. The statistical

significance level was taken to be $p \leq 0.05$ for all tests.

Results

Patients´ Characteristics: Data from 183 patients diagnosed with MAHA were analyzed. Furthermore, HELLP syndrome was present in 32 patients (17.5%). The median age of patients with HELLP syndrome was 30.45±16.22 (age range 18-52) years. HELLP syndrome patients' characteristics including age, presence of anemia, and thrombocytopenia, eleveted liver function tests, prolongated PT test, proteinuria and acute renal failure are presented in Tables 1. In an assessment of patients with HELLP syndrome conducted according to the Mississippi classification; 12 patients (37.5%) were in class 1 while 15 patients (46.9%) were in class 2, and there was renal failure in 4 patients (33.3%) in class 1 and 3 patients (20%) in class 2. There was no renal failure present in class 3 including a total of 5 patients (15.6%) (Table 2). There was no significant relationship found between the Mississippi classification and renal failure. There was a prolongation in PT value in all patients with HELLP syndrome who developed renal failure. There was a statistically significant relationship between PT prolongation and renal failure (p = 0.007). There was renal failure in 6 (42.9%) patients with HELLP syndrome, whose hemoglobin value was less than or equal to 8 gr/dl. Furthermore, it was found to be statistically significant (p = 0.01). In patients with HELLP syndrome, the renal failure risk of those whose hemoglobin value was less than or equal to 8 gr/dl was significantly higher than those whose hemoglobin value was greater than 8gr/dl (OR: 12.75, p = 0.0285).

Correlation Analysis: Evaluating patients with the diagnosis of HELLP syndrome, there was a statistically significant negative correlation between creatinine values with hemoglobin levels (r = -0.204, p= 0.006) and platelet counts (r = -0.261, $p < 0.01$). In addition, there was a statistically significant positive correlation between creatinine elevation with ALT (r = 0.680, $p < 0.01$), AST (r = 0.580, $p < 0.01$) elevation, and amount of proteinuria (r = 0.152, p = 0.039).

Discussion

HELLP syndrome diagnosis can be established in during pregnancy as a result of detection of all findings of microangiopathic hemolytic anemia, liver enzyme elevation, and thrombocytopenia (11). Haemolysis, one of the major characteristics of the disorder, is due to a microangiopathic haemolytic anaemia. Red cell fragmentation caused by passage through damaged endothelium appears to represent the extent of small vessel involvement with endothelial dysfunction, intima damage and fibrin deposition (15). The other less common, but serious hematological conditions that may mimic HELLP syndrome, include haemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC). The other thrombotic microangiopathic syndromes (TMAs) may have similar clinical presentation as HELLP syndrome, however all TMAs must have a careful diagnostic evaluation due to required special therapies.

Hypertension (blood pressure ≥140 / 90 mmHg) and proteinuria are present in about 85% of patients with HELLP syndrome. Furthermore, one or both of these findings may not present in the some patients (11). There has been no consensus established on laboratory criteria in the diagnosis of HELLP syndrome. Mississippi classification is a common alternative that may be used to identify HELLP syndrome (16, 17). As stated above, there were microangiopathic hemolytic anemia, LDH, ALT, AST elevation, and thrombocytopenia in 32 patients included in this study. Those exhibiting these symptoms were considered to have HELLP syndrome.

Although results are generally good for all mothers with HELLP syndrome, there may be serious complications with some patients, such as disseminated intravascular coagulation (DIC) (21%), abruptio placentae (16%), acute renal failure (8%), pulmonary edema (6%), subcapsular liver hematoma (1%), and retinal detachment (1%) (10). Renal dysfunction does not take long in patients with HELLP syndrome, regardless of whether or not renal failure presents (18, 19). In this study, there was renal failure in 7 (21.8%) of 32 patients with HELLP syndrome, and this ratio was found to be greater than the ratios indicated in literature. There was a significant relationship among creatinine values with anemia, thrombocytopenia, proteinuria amount, and liver dysfunction. There was no relationship found between the Mississippi classification and renal failure in this study, in which HELLP syndrome was classified according to the Mississippi classification. Although there was a higher renal failure risk in class 1 when compared to class 2

Table 1. Clinical and laboratory findings of patients with HELLP syndrome

Characteristics	HELLP syndrome
Number of patients	32
Age, median (min-max)	29.25 (20-52)
Proteinuria, n (%)	15 (46.9%)
Anemia, n (%)	32 (100%)
Transaminase elevation, n (%)	32 (100%)
Thrombocytopenia, n (%)	32 (100%)
Prolonged prothrombin time, n (%)	9 (28.1%)
Acute renal failure, n (%)	7 (21.8%)

Table 2. Distribution of the patients with HELLP syndrome based on the Mississippi Classification System

Class	Total n (%)	Renal failure n (%)	Renal failure with Hb ≤ 8 g/dl n (%)
1	12 (37.5%)	4 (57.1%)	3 (50%)
2	15 (46.9%)	3 (42.9%)	1 (16.7%)
3	5 (15.6%)	0	2 (33.3%)
Total	32 (100%)	7 (100%)	6 (100%)

and class 3, and in class 2 compared to class 3; furthermore, it was not statistically significant.

Another point that should be considered in HELLP syndrome is the relationship between hemoglobin decrease and renal failure. In this study, in which those with hemoglobin value of 8 gr/dl or less and those with hemoglobin value of greater than 8 gr/dl were grouped separately, there was a serious increase in renal failure in the group with hemoglobin value of 8 gr/dl or less (OR: 12.75, p = 0.0285). There was a prolongation in PT value in all patients with HELLP syndrome and renal failure. There was a statistically significant relationship between PT prolongation and renal failure (p =0 .007). We propose that severe anemia and DIC presentation are significant risk factors for renal failure in HELLP syndrome. The physiopathological case causing this condition is probably vascular damage and ischemia presentation. These two cases emerge with DIC and anemia. Earlier prediction of renal failure risk, a significant complication in the course of HELLP syndrome, according to some other parameters, is perhaps the most important step that can be taken to prevent this complication.

In conclusion, the mechanism of occurrence of HELLP syndrome is not clear and have many overlapping clinical aspects with the other thrombotic microangiopathic syndromes. Renal failure is a complication of HELLP syndrome. The most associated cases with renal failure are the presence of DIC and severe anemia in HELLP syndrome. The hemoglobin value of less than 8gr/dl is a significant risk factor for renal failure in HELLP syndrome.

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References

1. Stone JH. HELLP syndrome: hemolysis, elevated liver enzymes, and low platelets. JAMA 1998; 280: 559.
2. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J Obstet Gynecol 1993; 169(4): 1000-1006.
3. Catanzarite VA, Steinberg SM, Mosley CA, Landers CF, Cousins LM, Schneider JM. Severe preeclampsia with fulminant and extreme elevation of aspartate aminotransferase and lactate dehydrogenase levels: high risk for maternal death. Am J Perinatol 1995; 12(5): 310-313.
4. Isler CM, Rinehart BK, Terrone DA, Martin RW, Magann EF, Martin JN Jr. Maternal mortality associated with HELLP (hemolysis, elevated liver

enzymes, and low platelets) syndrome. Am J Obstet Gynecol 1999; 181(4): 924-928.
5. Sibai BM, Taslimi MM, el-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. Am J Obstet Gynecol 1986; 155(3): 501-519.
6. Reubinoff BE, Schenker JG. HELLP syndrome--a syndrome of hemolysis, elevated liver enzymes and low platelet count--complicating preeclampsia-eclampsia. Int J Gynaecol Obstet 1991; 36(2): 95-102.
7. Sibai BM. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): much ado about nothing? Am J Obstet Gynecol 1990; 162: 311-316.
8. Abildgaard U, Heimdal K. Pathogenesis of the syndrome of hemolysis, elevated liver enzymes, and low platelet count (HELLP): a review. Eur J Obstet Gynecol Reprod Biol 2013; 166: 117-123.
9. Benedetto C, Marozio L, Tancredi A, Picardo E, Nardolillo P, Tavella AM, et al. Biochemistry of HELLP syndrome. Adv Clin Chem 2011; 53: 85-104.
10. Jebbink J, Wolters A, Fernando F, Afink G, van der Post J, Ris-Stalpers C. Molecular genetics of preeclampsia and HELLP syndrome - a review. Biochim Biophys Acta 2012; 1822(12): 1960-1969.
11. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. Obstet Gynecol 2004; 103: 981-991.
12. American College of Obstetricians and Gynecologists; Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122(5): 1122-1131.
13. Haram K, Svendsen E, Abildgaard U. The HELLP syndrome: clinical issues and management. A Review. BMC Pregnancy Childbirth 2009; 26: 9-8.
14. Martin JN Jr, Rose CH, Briery CM: Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child. Am J Obstet Gynecol 2006; 195: 914-934.
15. Baxter JK, Weinstein L: HELLP syndrome: the state of the art. Obstet Gynecol Surv 2004; 59: 838-845.
16. Martin JN Jr, Blake PG, Perry KG Jr, McCaul JF, Hess LW, Martin RW. The natural history of HELLP syndrome: patterns of disease progression and regression. Am J Obstet Gynecol 1991; 164(6): 1500-1509.
17. Martin JN Jr, Rinehart BK, May WL, Magann EF, Terrone DA, Blake PG. The spectrum of severe preeclampsia: comparative analysis by HELLP (hemolysis, elevated liver enzyme levels, and low platelet count) syndrome classification. Am J Obstet Gynecol 1999; 180(6): 1373-1384.
18. Jacquemyn Y, Jochems L, Duiker E, Bosmans JL, Van Hoof V, Van Campenhout C. Long-term renal function after HELLP syndrome. Gynecol Obstet Invest. 2004; 57(2): 117-120.
19. Drakeley AJ, Le Roux PA, Anthony J, Penny J. Acute renal failure complicating severe preeclampsia requiring admission to an obstetric intensive care unit. Am J Obstet Gynecol 2002; 186: 253-256.