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RESEARCH ARTICLE

Relationship between Lactate Dehydrogenase and Schistocytes in Patients with HELLP Syndrome

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Abstract

Introduction: Hypertensive disorders of pregnancy constitute a high incidence pathology and a significant cause of maternal and fetal morbidity and mortality. Therefore, HELLP syndrome is one of the most feared complications. Objective: Establish the relationship between plasma LDH levels and the presence of schistocytes in peripheral blood smears, as well as clinical symptoms and lab results present in this syndrome.

Materials and methods: Descriptive observational study of cut longitudinal, with the clinical records of hospitalized patients with HELLP syndrome in the University Hospital of Los Andes (IAHULA) Merida-Venezuela, period 2011-2021, in a sample of 148 patients with the inclusion criteria.

Results: Average age of 27 years, the majority between 26 and 35 (40%). 56.8% presented epigastric pain, 63.5% exalted tendon reflexes, 75% headache, phosphenes in 45.9%, and tinnitus in 39.2%. The mean of LDH was 768.1 I/U and schistocytes were found in all these patients, systolic blood pressure of 141-160 mm/Hg (40.5%), and 56.1% diastolic pressure between 91 and 110 mm/Hg. In 63.5% platelets levels were below 100,000 mm3. It was found that Lactate Dehydrogenase equal to or above 600 IU/l is a risk factor for patients developing HELLP syndrome, who had 6.9 times more likelihood of peripheral blood smear with schistocytes.

Conclusion: LDH is important in the follow-up of patients with hypertensive disorders of pregnancy, and its elevation above 600 IU/l, associated with symptoms such as epigastralgia, headache, tinnitus, and phosphenes, is an indicator that a HELLP syndrome has been established.

Keywords

HELLP syndrome, LDH Lactate Dehydrogenase, Hypertensive disorders

Introduction

HELLP (Hemolysis, Elevated Liver enzyme levels, Low Platelet count) represents a syndrome associated with hypertensive disorders of pregnancy. However, it could be found in a small percentage in non- hypertensive obstetric patients [1]. It has been determined that the pathological substrate of this entity is a generalized microangiopathy, which leads to hemolytic anemia, activation and platelet consumption, and fibrin deposits in the hepatic sinusoids [2]. It is currently accepted that severe preeclampsia and eclampsia are related to HELLP syndrome and that their forms of presentation overlap. The identification of this syndrome is expressed by the relevance given to laboratory findings as a necessary condition for diagnosis.

It occurs in less than 1% of all pregnancies, but it is found in 20% of pregnancies complicated by hypertensive disorders with severe features. May occur with pregnancies at term (18%), premature (53%, including 11% before 27 weeks), or postpartum (30%). Risk factors include a family history of HELLP and preeclampsia in previous pregnancies, occurring in 10-20% of patients [3]. The medical literature indicates that 70% develop before delivery, between weeks 27 and 37 of gestation, 10% occur at weeks 27, and 20% go beyond week 37 [4].

According to the data published, hypertensive disorders in pregnancy and their complications constitute the leading causes of maternal morbidity and mortality,

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together with hemorrhages and infections [5]. Regarding the paraclinical alterations of this syndrome, there is the presence of microangiopathic hemolytic anemia, which is defined by LDH (Lactate Dehydrogenase Enzyme) of 600 IU/L or more, the elevation of indirect bilirubin above 1.2 mg/dl, decreased levels of haptoglobin or identification in peripheral blood smear of schistocytes, all as indicators that the patient is presenting with a hemolytic condition of non-autoimmune origin as a consequence of the primary hypertensive pathology; on the other hand, we find a decrease in platelets and the alteration of liver enzymes [6].

The clinical picture of this syndrome is characterized by epigastralgia, phosphenes, tinnitus, headache, exalted osteotendinous reflexes, among others, which are similar to those observed in severe preeclampsia [7].

The criteria proposed for diagnosing HELLP Syndrome are strongly related among themselves, thus determining the diagnostic triad that defines this pathology. There are two classification systems for HELLP syndrome. One of them was developed in The University of Mississippi Jackson by Martin, et al. [8]. This system proposes the platelet level as the most easily measurable index of disease severity. It considers the levels of these cells to define three classes of HELLP syndrome. In each of these, there must be evidence of microangiopathic hemolytic anemia and liver enzyme disturbances.

The system is as follows:

- CLASS I: platelet count of 50,000/mm^3 or less.
- CLASS II: platelet count between 50,000 - 100,000/mm^3
- CLASS III: platelet count between 100,000 - 150,000/mm^3 [8].

The second of the HELLP syndrome classification systems was proposed by Sibai, et al. [9]. This system is known as the Tennessee classification. It determines the expression of the syndrome as complete or partial; for this reason, we speak of complete HELLP syndrome when LDH is 600 IU/l or higher, platelet count less than 100,000/mm^3, and ALT of 70 UI / l or more. And it complements that there is partial or incomplete HELLP syndrome when the patients present one or two alterations in LDH, platelets, or ALT in laboratory findings.

Lactate Dehydrogenase, also called “Lactic Acid Dehydrogenase” (LDH), is an enzyme found in practically all tissues of the human body playing an essential role in cellular respiration. Although LDH is abundant in tissue cells, levels in the blood are generally low. However, when tissues are damaged due to injury or disease, they release more LDH into the bloodstream. There are certain conditions that usually cause this increase in the amount of LDH in the bloodstream, such as liver disease, heart attacks, anemia, muscle trauma, bone fractures, cancer, meningitis, encephalitis, or HIV [2].

Therefore, to achieve the diagnosis of HELLP syndrome, the symptoms and signs must be considered [1,10]. Once the diagnosis is suspected, laboratory tests should be requested to help confirm the suspicion and assess the severity of any target organ involvement [11].

For this reason, this work aims to establish the association of these parameters, specifically Lactate Dehydrogenase, as indicated Hemolysis, to analyze this elevation with the presence of fragmented blood formed elements (erythrocytes) that receive the name of schistocytes, being these the confirmatory pattern of the damage that is occurring at the level of the microvasculature, compare the effectiveness and reliability of LDH in early identification and timely treatment of this pathology and to be able to act immediately minimizing the risks that may have a severe impact on patients with HELLP Syndrome [4].

The study’s general objective is to analyze the relationship between Lactate Dehydrogenase (LDH) levels and the presence of schistocytes in peripheral blood smears in patients with HELLP syndrome treated at the Autonomous Institute Hospital Universitario de Los Andes (IAHULA) during the period 2011-2021.

The specific objectives are: 1. Determine the sociodemographic characteristics of this group of patients with HELL Syndrome. 2. Determine LDH levels in patients with HELLP syndrome, attended at IAHULA. 3. Determine the presence of schistocytes in peripheral blood smear in HELLP syndrome patients. 4. Establish the relationship between LDH levels and the presence of Schistocytes in peripheral blood smear in patients with HELLP syndrome. 5. Establish the relationship of the presence of schistocytes with other hemolysis parameters such as indirect bilirubin and hemoglobin in patients with HELLP syndrome, seen at IAHULA. 6. Associate the presence of symptoms and LDH levels in patients with HELLP syndrome, seen at IAHULA.

Material and Methods

A descriptive, cross-sectional, observational study was conducted to determine the relationship between LDH levels, and the presence of schistocytes in peripheral blood smears in patients with HELLP syndrome diagnosed in the obstetric emergency of the Autonomous Institute Los Andes University Hospital (IAHULA) in the period 2011-2021. The medical records of patients diagnosed with HELLP syndrome who had peripheral blood smears with schistocytes were reviewed in that period.

Sample

Patients with HELLP Syndrome cared at IAHULA, in the period 2011-2021 who gathered the following criteria.

Inclusion criteria: Obstetric patients diagnosed with HELLP syndrome at IAHULA with paraclinical and clinical alterations as high blood pressure or neurological symptoms, assessed by the hematology service of the IAHULA, who performed peripheral blood smears during the hospital stay.

Exclusion criteria: Patients with pre-existing chronic liver disease, thrombocytopenic purpura, uremic-hemolytic syndrome, or any other pregnancy-induced liver disease, including intrahepatic cholestasis and acute yellow atrophy in pregnancy.

Variables system

Main variables: LDH levels in obstetric patients with HELLP syndrome. Presence or absence of schistocytes in peripheral blood smear.

Paraclinical variables: Indirect bilirubin levels, hemoglobin, TGP, and platelets in patients with HELLP Syndrome.

Clinical variables: Presence of epigastralgia, exalted tendon reflexes, headache, phosphenes, tinnitus.

Demographic variables: Age, marital status, origin, educational level.

Statistical analysis

The data obtained were analyzed using the statistical program SPSS version 19.0 for Windows. The qualitative variables were expressed in frequency, ratio, and proportion; quantitative variables were analyzed by applying the measures of central tendency (mean, median, and mode) and the measurements of dispersion (range, variance, and standard deviation); it was necessary to do bivariate analyzes for the qualitative variables using Chi-square with a $P < 0.05$ for significance. The results obtained were presented in tables and graphs [6].

Results

Two hundred records of hospitalized patients with HELLP Syndrome in the Unit of Obstetrics and Gynecology of the Autonomous Institute Hospital Universitario de Los Andes (IAHULA) were reviewed during 2011-2021.

Sociodemographic characteristics of the patients

Starting from the descriptive analysis, the demographic data are presented in Table 1. The average age of the patients with HELLP Syndrome was 27 years, with 40% between 26 and 35 years of age, 34% were

Table 1: Distribution of the Sociodemographic data of patients treated at the Obstetrics and Gynecology Unit of the IAHULA during 2011-2021.

Variables	Categories	Frequency	Percentage
Age (years old)	Under 15	11	7.4
	From 16 to 25	50	33.8
	From 26 to 35	59	39.9
	Older than 36	28	18.9
Educational level of the Patients	Incomplete Primary High school	9	6.1
	Medium-Technician TSU	49	33.1
	University	22	14.9
		8	5.4
		33	22.3
		27	18.2
Place of Origin or Sanitary District	Mucuchíes Libertador Lagunillas Tovar	12	8.11
	El Vigía Another State	64	43.24
		11	7.43
		5	3.38
		23	15.54
		33	22.30
Civil Status of Patients	Single Married/United	59	39.9
	Divorcee	77	52.0
		12	8.1
Sector	Urban Rural	98	66.2
		50	33.8

Source: Collection instrument based on the clinical records with HELLP Syndrome from IAHULA, period 2011-2021; own calculations.

among the patients between 16 and 25 years of age. Nevertheless, 19% were found to be older than 36 years and 7% younger than 15. Most of the patients, 33.1%, had complete primary school, followed by technician 22.3%, university 18.2%, high school 14.9%, incomplete only 6.1% and intermediate technical 5.4%. 43.24% of the patients came from the Liberator municipal, which covers the town of Mérida and Campo Elías, 22.3% from other states such as Zulia (Santa Bárbara del Zulia, Caja Seca), Barinas, San Cristóbal, 15.54% from El Vigía, 8.11% from Mucuchíes; 7.43% from Lagunillas and to a lesser extent from the Mocotíes area (Tovar, Santa Cruz and Pueblos del Sur) with 3.38%. It was observed that 52% of the patients were married, 39.9% single and 8.1% divorced. 66.2% were from the urban area and 33.8% from the rural area.

Clinical and paraclinical characteristics of patients with HELLP syndrome

Most of the patients with HELLP syndrome (56.8%) presented epigastralgia. In 63.5%, the tendon reflexes were exalted, headache was observed in 75% of cases, phosphenes in 45.9%, and finally, the presence of tinnitus in 39.2% (Table 2). The paraclinical variables found that 70.3% had schistocytes at the time of performing the peripheral blood smear and 90.7% of these patients presented LDH above 600 I/U with a mean of 768.1, the systolic pressure of most of the patients (40.5%) was between 141 and 160 mm/Hg, and 56.1% had a diastolic pressure between 91 and 110 mm/Hg. In 63.5%, the platelets were below 100,000 mm^3. 63.5% presented TGP for above 70 IU/I; 13.5% indirect bilirubin values above 1.2 mg/dl; and hemoglobin was found in 62.8% of the patients with values between 7 and 11 mg/dl (Table 3).

Table 2: Distribution of clinical variables in patients with HELLP Syndrome, period 2011-2021. Absolute figures and percentages.

Clinical Alterations	Frequency	Percentage
1. Epigastralgia		
Yes	84	56.8
No	54	43.2
2. Exalted Reflexes		
Yes	94	63.5
No	54	36.5
3. Headache		
Yes	111	75.0
No	37	25.0
4. Phosphenes		
Yes	68	45.9
No	80	54.1
5. Tinnitus		
Yes	58	39.2
No	90	60.8

Source: Collection instrument based on the clinical records with HELLP Syndrome from IAHULA, period 2011- 2021; own calculations.

Table 3: Distribution of paraclinical variables in patients with HELLP Syndrome, period 2011-2021. Absolute figures and percentages.

	Paraclinical Alterations	Frequency	Percentage
Schistocytes in Peripheral Blood	Yes	104	70.3
Smear	No	44	29.7
LDH cut-off point IU/l	Greater than 600	49	36.7
Systolic Tension	Below 140	41	27.7
mm/Hg	From 141 to 160	60	40.5
	Above 160	46	31.1
Diastolic tension	Below 90	41	27.7
mm/Hg	From 91 to 110	83	56.1
	Above 110	23	15.5
Platelets mm^3	Below 100,000	94	63.5
	Above 100,000	54	36.5
TGP IU/l	Below 70	54	36.5
	Above 70	94	63.5
Indirect Bilirubin	Below 1.2	116	78.4
mg/dl	Above 1.2	20	13.5
Hemoglobin mg/dl	Under 7	1	0.7
	Between 7 and 11	93	62.8
	Over 11	49	33.1

Source: Collection instrument based on the clinical records with HELLP Syndrome from IAHULA, period 2011-2021, own calculations.

As it was a longitudinal study, the approximation to risk was determined utilizing the Odds Ratio (OR) and the relationship between LDH levels and the presence of schistocytes in peripheral blood smear in patients with HELLP syndrome. It was determined if the levels of LDH with a cut-off point of 600 IU/l, was a risk factor in patients with HELLP syndrome with schistocytes as a confirmatory parameter of hemolysis.

The results showed that for obstetric patients, being exposed to levels of Lactate Dehydrogenase equal to or above 600 IU/l, there is a risk factor, whit 6.9 times more likely to present a peripheral blood smear with schistocytes (Table 4).

Relationship between LDH Levels and the presence of schistocytes in peripheral blood smears in patients with HELLP syndrome

Statistically significant different levels were found for TGP, LDH, IB, and Hb, among patients who had the presence of schistocytes compared to those who did not present this parameter; indicating that in patients with hemolytic syndrome, the laboratory values were significantly elevated; however, this was not the case with the platelet level whose difference was not statistically significant (Table 5).

The direct association between LDH and clinical alterations such as epigastric pain, exalted osteotendinous reflexes, headache, phosphenes, and tinnitus was analyzed in patients with HELLP syndrome. We utilized the Chi-Square test based on Fisher's exact statistic, with a significance level of 0.05, for determine if the presence of this symptomatology was associated with LDH levels. For such patients, it was observed that those with epigastric pain, headache, phosphenes, and tinnitus had over 2, 5 times more possibilities to have LDH above 600 IU/l. This association was statistically significant, and did not occur with the exalted osteotendinous reflexes, which, when altered showed no relationship with LDH in this group of patients (Table 6).

Discussion

The present study interpreted the value of the enzyme lactate dehydrogenase and its association with the presence of schistocytes in peripheral blood smear as an indicator of hemolysis and its relationship with

Table 4: Distribution of Schistocytes according to the level of LDH IU/L in Patients with HELLP Syndrome, period 2011-2021.

LDH level IU/L	Presence of Schistocytes	Absence of Schistocytes	Total
Greater than 600	49	5	54
	(90.7%)	(9.3%)	(100%)
Less than or equal to 600	55	39	94
	(58.5 %)	(41.5%)	(100%)
Total	104	44	148
	(70.3%)	(29.7%)	(100%)

Chi-Square statistic χ^2 = 17.05 P = 0.000 OR = 6.94; 95% CI (2.5-19.0) Very Significant. Source: Collection instrument based on the clinical records with HELLP Syndrome from IAHULA, period 2011-2021, own calculations.

Table 5: Paraclinical variables according to the presence of schistocytes in patients with HELLP syndrome, period 2011-2021. Results of the Student's t-test for independent samples.

Paraclinical variables	Presence/Absence Schistocytes	Mean Paraclinical Variables	P
1. TGO	Yes	227.3	0.002*
	No	95.6	
2. TGP	Yes	162.0	0.0001*
	No	57.3	
3. Platelets	Yes	90.076	0.007
	No	101.431	
4. LDH	Yes	768.1	0.001*
	No	250.0	
5. Indirect bilirubin	Yes	0.86	0.001*
	No	0.43	
6. Hemoglobin	Yes	10.55	0.01*
	No	11.15	

*P < 0.05 Significant Source. Collection instrument based on the clinical records with HELLP Syndrome from IAHULA, period 2011-2021, own calculations.

Table 6: Clinical Alterations vs. Categorized LDH. Period 2011-2021.

Clinical alteration	χ^2	P	OR	95% CI
1. Epigastralgia- LDH	18.12	0.001*	5.05	(2.32-10.9)
2. Exalted reflexes-LDH	2.78	0.009	1.84	(0.89-3.8)
3. Headache- LDH	4.70	0.03*	2.5	(1.07-6.1)
4. Phosphenes- LDH	9.91	0.002*	3.0	(1.4-6.0)
5. Tinnitus-LDH	11.84	0.001*	3.34	(1.6-6.7)

Chi-Square, Odds Ratio, and Confidence Interval at 95%. *P < 0.05 Significant. Source: Collection instrument based on the clinical records with HELLP Syndrome from IAHULA, period 2011-2021; calculations own.

clinical alterations and other paraclinical parameters in obstetric patients diagnosed with HELLP syndrome.

From 148 patients who met the inclusion criteria for this study, it was found an average of 27 years of age, with 39.9% of patients between 26 and 35 years, which corresponds with the results obtained in the study carried out by López [12], who found the most age group between 18 to 35-years-old (81.8%), and with the work of Castano and Rico [13], where the majority, 76.5% were between 20 and 35-years-old. However, it is possible to find this pathology in groups of extreme ages, more than 36 years and younger than 15 years, where would be expected to see more significant associated comorbidity.

Primary education, married marital status, and urban origin were registered as predominant, which coincides with De Jesús, et al. [14]. Regarding the clinical findings, the symptoms most common found were epigastralgia, exalted tendon reflexes, headache, phosphenes, and tinnitus, where the headache was the most common, which points to neurological and systemic involvement, matching with the studies by Tijerino, et al. [8] and Otero [15], whose main symptom was a headache.

At the time of performing the peripheral blood smear, most patients with HELLP syndrome presented schistocytes. Most of the patients had blood pressure between 140/90-160/110 mm/Hg and were diagnosed with mild preeclampsia, requiring antihypertensive therapy; however, there was 27.7% whose blood pressure was within normal limits, a feature that is possible to find in this syndrome, coinciding with the reports in the literature by Reyes, et al. [16] where 10 to 20% of patients with HELLP syndrome are not associated with hypertensive disorders of the pregnancy.

Regarding the mean values in the paraclinical, the platelet level was below 100,000 mm^3. The high TGP transaminase value supported the diagnosis for this syndrome, coinciding with the work of Castano and Rico [13], reporting values above 70 mg/dl. Also, it agreed with the results of Reyna, et al. [17], concluding that elevated transaminases are adverse parameters of organ damage in HELLP syndrome.

In the presence of schistocytes the mean value of the LDH above 600 I/U was 768.1, object of this study, which agreed with the bibliography consulted according to Altamirano, et al. [6], who found LDH values above 600 IU/l as a hemolysis indicator. The presence of schistocytes found in 90.7% of patients, matched with the results of Castano and Rico [13] who establish an association between LDH and paraclinical alterations.

Also, it was observed that the LDH value was associated with clinical parameters such as epigastralgia, headache, phosphenes, and tinnitus; this coincided with the results of the work of Altamirano and Egüez [6], where they attributed epigastric pain as one of the most important factors in developing HELLP syndrome.

The indirect bilirubin was found in most cases below 1.2 mg/dl. Regarding the hemoglobin levels, most of the patients presented mild to moderate anemia, coinciding with Otero [15], whose mean was 9 mg/dl, despite showing schistocytes in peripheral blood. This indicates that these paraclinical parameters did not behave as indicators of early stages of hemolysis in this study, which could be attributed to factors such as the placement of blood transfusion or performing the blood smear in the early stages of the onset of the syndrome with little impact in all paraclinical parameters.

Conclusions

In the context of a patient with HELLP syndrome, it was found that in obstetric patients who have Lactate Dehydrogenase levels above 600 IU/l, there is more chance of having a peripheral blood smear with schistocytes, as well as more probability of having epigastric pain, headache, phosphenes, and tinnitus. Elevated LDH is an indicator of maternal morbidity, which, when is high in pregnancy, indicates that the patient could be experiencing HELLP syndrome.

It is concluded that LDH should be quantified in every obstetric patient with hypertensive disorder, which at elevated levels above 600 IU/l and associated with symptoms such as headache, epigastric pain, heightened reflexes, phosphenes or tinnitus, alert about a possible hemolytic picture before reaching more advanced stages with worse repercussions on the mother-fetus binomial.

Recommendations

- Guarantee access to information through

promotional campaigns on the importance of good prenatal care.

- Request to all obstetric patients with hypertensive disorders of pregnancy and symptoms like epigastralgia, headache, phosphenes or tinnitus, serial paraclinical where complete blood count, liver profile, and LDH, should be included looking for early alterations that shows that the patient is presenting HELLP syndrome.

What is known about the Subject

Hemolysis increases in preeclampsia with severe features, independent of elevated liver enzymes and low platelet count. Lactate dehydrogenase levels (≥ 600 IU/l) are associated with adverse maternal and neonatal outcomes.

What this Study Contributes

Lactate dehydrogenase levels may be helpful to guide clinical management in women with hypertensive disorders of pregnancy. Hemolysis, determined by lactate dehydrogenase levels ≥ 1.6 times the normal, can be considered a severe feature of preeclampsia.

Conflict of Interests

The authors declare that they have no competing interests.

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