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Progression of Class 3 HELLP Syndrome: Biochemical Indicators Among Women in Port Harcourt, South-south Nigeria

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Abstract: Background: Class 3 HELLP syndrome (c3HELLPs) is a mild transition stage of HELLP syndrome (HELLPs) with potential for rapid progression to more severe variants. Biochemical indicators of its progression are poorly understood. Hence, the current study evaluated the likely biochemical indicators of this progression among women in Port Harcourt, Nigeria. Methods: The current study was designed as a retrospective cross-sectional one and was conducted among women diagnosed with c3HELLPs in the University of Port Harcourt Teaching Hospital (UPTH) from 2011-2020. Relevant data from all eligible cases were abstracted from case notes, nurses' charts, laboratory, and medical records using well-structured research pro forma and analyzed using the Statistical Package for Social Sciences version 25. Results: During the study period, 84 cases of c3HELLPs presented; 58 progressed while 26 did not progress while on management. The progressed cases had higher mean and abnormal levels of plasma uric acid (UA), creatinine, but low and abnormal levels of plasma albumin compared to the non-progressed c3HELLPs cases ($p<0.05$). The abnormally high UA, creatinine, and abnormally low albumin levels were associated with increased risk of c3HELLPs progression on crude/adjusted logistic regression (LR) and ROC analysis. However, the UA had a superior LR (crude=OR: 4.097; 95%CI: 2.917-5.753; $p<0.001$; adjusted=OR: 4.723; 95%CI: 3.199-5.763; $p<0.001$) and ROC (AUC: 0.978; 95%CI: 0.887-1.000; <0.001) predictive potentials. Conclusion: The study showed that rising plasma UA, creatinine levels but falling plasma albumin levels may indicate an increased risk of c3HELLPs progression. This finding should be considered along with clinical features and other HELLP-defined laboratory markers during the management of c3HELLPs. However, we recommend further studies to evaluate conclusions from this study.

Keywords: HELLP, HELLP Syndrome, Class 3 HELLP Syndrome

1. Introduction

HELLP syndrome (HELLPs) is a rare complication of pregnancy that occurs in 0.5-0.9% of pregnancies and 10–20% of severe pre-eclampsia [1, 2] It is marked by three cardinal features: Hemolysis, Elevated Liver enzymes, and Low Platelet count, hence, its acronym HELLP [1-3]. The presence of all three characteristic features is regarded as complete HELLPs while the presence of one or two of these features in the presence of severe preeclampsia is regarded as partial HELLPs [2]. Though the syndrome is regarded as a severe variant of preeclampsia, it can still manifest in the absence of it in about 10% of cases [2-3].

The diagnosis of the syndrome is very challenging as most women present with nonspecific clinical features that may mimic other conditions and lead to misdiagnosis [2, 3]. In clinical practice, HELLPs is usually categorized into three major subclasses with decreasing severity from class 1 (mild variant), class 2 (moderate variant), and class 3 (mild variant) using the Mississippi triple-class classification [4-5].

However, the class 3 HELLP syndrome (c3HELLPs) is usually regarded as a transition stage of the syndrome with potential for rapid progression to the more severe variants (classes 1 and 2) which bring in adverse maternal and perinatal complications [6]. The transition of the c3HELLPs is usually preceded by rapid changes in the biochemical parameters usually determined at the initial suspicion and subsequent evaluation of cases of HELLPs [6, 7].

However, the biochemical determinants that underline the progression of c3HELLPs have not been documented among women at risk of the syndrome in our environment besides the traditional diagnostic markers. Hence, the current study evaluated the likely biochemical indicators of c3HELLPs progression among women in Port Harcourt, Nigeria.

2. Materials and Methods

2.1. Study Design and Site

This was a retrospective cross-sectional study carried out among Nigeria pregnant women who were diagnosed with c3HELLPs over ten years in the University of Port Harcourt Teaching Hospital (UPTH). The hospital is a tertiary public health facility located in Port Harcourt within the Southern zone of Nigeria. It serves as a major referral health center in Rivers State and the adjoining states within the sub-region.

2.2. Ethical Considerations

The study was approved by the Institutional Research Ethics Committee in the study center before the commencement of the study. All data was anonymized and treated with the utmost confidentiality. The conduct of the study was in tandem with institutional guidelines and in the principles embodied in the Helsinki declaration.

2.3. Study Instruments

The study utilized archived hospital data in the records and Pathology Departments of all eligible cases of c3HELLPs syndrome diagnosed and managed in the study center during the period under review.

2.4. Eligibility Criteria

The criteria for inclusion are as follows: data of all cases of c3HELLPs diagnosed and managed in UPTH over 10 years (1st January 2011 to the 31st December 2020).

Criteria for exclusion include antecedent or existing liver/hepatobiliary/gallbladder diseases, diabetes, thyroid disorders, chronic renal diseases, hemoglobinopathies, thrombotic microangiopathies, chronic and gestational hypertension, acute fatty liver disease of pregnancy, and those infected with HIV infection. Also excluded were: incomplete data, preeclampsia/eclampsia superimposed on chronic hypertension, renal transplant recipients, those diagnosed with drug-induced liver injury, and those diagnosed outside the study period.

2.5. Data Acquisition

Data was acquired anonymously without any distinguishing identifiers using trained research assistants. Key variables of which data was collected included the number of deliveries within the study period, the number of suspected HELLPs precursors (e.g. preeclampsia, etc), and the number of cases of HELLPs diagnosed within the study period. For each eligible case, all relevant socio-demographic, medical history review, clinical, gynecological, obstetric, biochemical, and hematological data were abstracted at the point of diagnosis.

2.6. Data Definitions

The HELLPs including the c3HELLPs was defined and categorized by the Mississippi triple-class classification as follows [8]:

Class 1: a. Total plasma bilirubin (TPB) ≥ 1.2mg/dl (20.5 µmol/L) or lactate dehydrogenase (LDH) activity ≥ 600 IU/L b. Plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity ≥ 70 IU/L c. PLT count <50 x 10^9/L.

Class 2: a. TPB ≥ 1.2mg/dl (20.5 µmol/L) or LDH of ≥ 600 IU/L b. Plasma AST and ALT activities ≥ 70 IU/L c. PLT count 50-100 x 10^9/L.

Class 3: a. TPB ≥ 1.2mg/dl (20.5 umol/L) or LDH of ≥ 600 IU/L b. Plasma AST and ALT activities ≥ 40 IU/L c. PLT count 100-150 x 10^9/L.

2.7. Data Stratification

Abnormal levels of plasma creatinine, uric acid, and albumin levels were arbitrarily defined as ≥97.2µmol/L, ≥0.5mmol/L, and ≤34g/L levels, respectively.

2.8. Specimen Acquisition and Laboratory Analysis

The acquisition of specimens for all laboratory analysis was conducted using standard protocols while observing universal safety precautions. The analysis was done using fully automated chemistry and hematological systems by well-experienced and trained analysts. To evaluate the analytical intra-assay and inter-assay coefficient of variations during analytical processes, at least two levels of commercially-produced quality control materials were used.

2.9. Data Management

Data was initially inputted into Statistical Package for Social Science software version 25. The distribution of continuous data was explored using the Shapiro-Wilk test. Continuous data with non-Gaussian distribution were all logarithmically transformed before analysis and presented as mean±standard deviation; comparison explored using the independent-samples t-test. The categorical data were presented as proportions in numbers/percentages; comparison was made using the Chi-square test. Crude and adjusted logistics regression was used to determine the degree of relationship of each indicator of c3HELLPs progression

(inclusion if alpha value is <0.05). Subsequently, the receiver operator characteristic (ROC) curve was employed to assess the predictive value of the significant indicators of C3HELLPs progression. The alpha value of ≤0.05 was chosen as the threshold for statistical significance.

3. Results

During the study period (2011-2020), a total of 298 pregnant women of Nigeria origin were diagnosed with HELLPs out of a total of 24,630 pregnancies who had presented in the hospital during the study period. Of the 298 diagnosed during the study period with HELLPs, 104 were of the class 3 HELLP syndrome (c3HELLPs) variants. However, 84 of these 104 cases of c3HELLPs met the inclusion criteria and were subsequently recruited for the study.

During the management of the 84 cases of c3HELLPs, 58 progressed from the c3HELLPs to more severe HELLPs variants (48 progressed to class 2 HELLP syndrome; 10 progressed to class 1 HELLP syndrome) while 26 did not progress (herein referred to as the non-progressed c3HELLPs in this study) during the management.

Table 1 depicts the descriptive characteristics of the non-categorical variables among the entire study cohorts (n=84), the progressed c3HELLPs (n=58), and the non-progressed c3HELLPs cases. The progressed c3HELLPs cases had higher mean plasma concentrations of uric acid (2.06±0.44vs.1.66±0.54), plasma creatinine (134.65±15.55 vs. 120.44±14.30) but lower albumin level (29.42±5.11 vs. 31.84±4.49) compared to the non-progressed c3HELLPs cases (p<0.05) (Table 1). Though the progressed c3HELLP cases also had a higher mean levels of the other demographic, obstetric, and laboratory parameters compared to the non-progressed c3HELLPs cases, no statistically significant difference was observed (p>0.05) (Table 1).

Depicted in Table 2, the progressed c3HELLPs cases had higher proportions of those with abnormally high levels of plasma uric acid, plasma creatinine but an abnormally lower levels of the plasma albumin compare to the non-progressed c3HELLPs cases (p<0.05).

Table 3 depicts the odd ratios (OR) of the risk of abnormally high/severe levels of plasma uric acid, plasma creatinine, and abnormally low albumin levels in predicting the progression of the c3HELLPs. All three abnormal parameters (plasma uric acid, plasma creatinine, and albumin) demonstrated statistically significant potentials (OR) to predict c3HELLPs progression on crude univariate logistic regression analysis (p<0.05) (Table 3; Item A).

Following adjustment for age, gestational age, gravidity, and parity (Table 3; Item B), the OR of the abnormally high creatinine level to predict c3HELLPs progression was attenuated but remained statistically significant while those of uric acid, and plasma albumin were amplified (p<0.005) (Table 3; Item B). Uric acid (OR: 4.097; 95% CI: 2.917-5.753; p<0.001) had the better likelihood of predicting progression on crude univariate logistic regression (Table 3; Item A) which was subsequently amplified on adjusted univariate logistic regression (OR: 4.723; 95% CI: 3.199-5.763;<0.001) (Table 3; Item B).

Using the ROC analysis as depicted in Table 4, the three abnormal parameters (higher plasma uric acid, higher plasma creatinine, and lower albumin) had significant ROC characteristics to predict progression of the c3HELLPs. However, plasma uric acid (AUC: 0.978; 95% CI: 0.887–1.000; p<0.001) still maintained superior ROC characteristics compared to the other two parameters.

Table 1. *Descriptive characteristics of the non-categorical data obtained at diagnosis.*

Variables	Total c3HELLPs cases, n = 84, M ± SD	Progressed c3HELLPs cases, n = 58, M ± SD	Non-progressed c3HELLPs cases, n = 26, M ± SD	p-value (Progressed vs. non-progressed)
Demographic				
Age (years)	31.04 ± 4.35	31.58 ± 3.40	29.84 ± 4.28	0.943
Obstetric				
Gravidity	3.14 ± 1.39	3.41 ± 1.39	2.53 ± 1.24	0.614
Parity	2.19 ± 1.42	2.27 ± 1.05	2.19 ± 0.97	0.800
GA at presentation, weeks	34.84 ± 1.42	34.80 ± 1.53	34.91 ± 1.94	0.402
GA at diagnosis, weeks	35.35 ± 1.21	35.30 ± 1.02	35.47 ± 1.60	0.578
Clinical				
SBP, mmHg	158.57 ± 9.72	157.24 ± 10.42	161.53 ± 11.13	0.053
DBP, mmHg	114.16 ± 7.23	110.69 ± 6.94	121.92 ± 7.12	0.250
Laboratory				
TPB, µmol/L	64.94 ± 7.71	65.11 ± 8.71	64.69 ± 9.82	0.115
AST activity, IU/L	212.14 ± 9.16	214.97 ± 9.79	207.95 ± 8.74	0.299
ALT activity, IU/L	315.71 ± 8.16	308.84 ± 7.92	304.84 ± 8.07	0.197
LDH activity, IU/L	892.14 ± 25.22	820.11 ± 29.22	830.84 ± 28.19	0.778
PLT count, x 10^9cell /L	95.23 ± 11.16	94.22 ± 10.20	96.15 ± 10.13	0.928
Plasma sodium, mmol/L	138.18 ± 4.43	136.73 ± 4.53	136.88 ± 4.03	0.291
Plasma potassium, mmol/L	4.95 ± 0.56	4.90 ± 0.56	4.86 ± 0.66	0.059
Plasma HCO_3, mmol/L	19.92 ± 2.12	20.06 ± 2.17	19.65 ± 2.07	0.192
Plasma urea, mmol/L	6.74 ± 2.05	6.40 ± 1.18	7.74 ± 2.22	0.114
Plasma creatinine, umol/L	124.53 ± 14.46	134.65 ± 15.55	120.44 ± 14.30	0.023*
Plasma uric acid, mmol/L	1.99.84 ± 0.58	2.06 ± 0.44	1.66 ± 0.54	<0.001*
Plasma total protein, g/L	60.76 ± 4.37	61.18 ± 4.30	60.14 ± 4.07	0.348
Plasma albumin, g/L	30.20 ± 5.52	29.42 ± 5.11	31.84 ± 4.49	<0.001*

Variables	Total c3HELLPs cases, n = 84, M ± SD	Progressed c3HELLPs cases, n = 58, M ± SD	Non-progressed c3HELLPs cases, n = 26, M ± SD	p-value (Progressed vs. non-progressed)
RPG, mmol/L	9.66 ± 1.15	9.92 ± 1.13	10.28 ± 1.08	0.753
QDP, +	3.60 ± 0.59	3.80 ± 0.40	3.68 ± 0.53	0.143

*Statistically significant; c3HELLPS: class 3 HELLP syndrome; M±SD: mean ± standard deviation; GA: gestation age; SBP: systolic blood pressure; DBP: diastolic blood pressure; mmHg: millimeter mercury; TPB: total plasma bilirubin; AST: aspartate aminotransferase enzyme; ALT: alanine aminotransferase enzyme; LDH: lactate dehydrogenase enzyme; PLT: platelet cell; HCO_3: bicarbonate; RPG: random plasma glucose; QDP: qualitative dipstick proteinuria.

Table 2. *Distribution of stratified significant laboratory data from Table 1 among the two study subgroups.*

Variables	Progressed c3HELLPs cases, n = 58, n (%)	Non-progressed c3HELLPs cases, n = 26, n (%)	p-value (progressed vs. non-progressed)
Plasma creatinine levels, µmol/L			
Normal (<97.2)	8 (13.8)	14 (53.8)	<0.001*
Abnormally high (≥97.2)	50 (86.2)	12 (47.2)	
Plasma uric acid, mmol/L			
Normal (<0.5)	10 (17.2)	15 (57.7)	<0.001*
Abnormally high (≥0.5)	48 (82.3)	11 (42.3)	
Plasma albumin levels, g/L			
Normal (>34)	15 (25.9)	10 (38.5)	0.001*
Abnormally low (≤34)	43 (74.1)	16 (61.5)	

*Statistically significant; c3HELLPs: class 3 HELLP syndrome.

Table 3. *Odd ratios of biochemical indicators of progression among the progressed class 3 HELLP syndrome cases.*

Variables	n	OR	95% CI		p-value
			Lower	Upper	
A. Univariate LR					
Plasma creatinine, umol/L					
Normal (<97.2)	8	1.0 (Ref)			
Abnormally high (≥97.2)	50	3.608	2.702	4.511	0.002*
Plasma uric acid, mmol/L					
Normal (<0.5)	10	1.0 (Ref)			
Abnormally high (≥0.5)	48	4.097	2.917	5.753	<0.001*
Plasma albumin, g/L					
Normal (>34)	15	1.0 (Ref)			
Abnormally low (≥34)	43	2.842	1.967	3.603	0.010*
B. Adjusted LR**					
Plasma creatinine, umol/L					
Normal (<97.2)	8	1.0 (Ref)			
Abnormally high (≥97.2)	50	2.564	1.966	4.078	0.013*
Plasma uric acid, mmol/L					
Normal (<0.5)	10	1.0 (Ref)			
Abnormally high (≥0.5)	48	4.723	3.199	5.763	<0.001*
Plasma albumin, g/L					
Normal (>34)	15	1.0 (Ref)			
Abnormally low (≤34)	43	3.416	2.855	4.789	<0.001*

*Statistically significant; OR: odd ratio; CI: confidence interval; Ref: reference; LR: logistic regression;
**Adjusted for age, gestational age, gravidity and parity.

Table 4. *ROC values of significant biomarkers of HELLP syndrome under evaluation among those with the complete HELLP syndrome.*

Variables	n	Sensitivity (%)	Specificity (%)	AUC	95% CI	p-value
Plasma creatinine ≥97.2µmol/L	50	94.3	82.6	0.842	0.788-0.948	0.010*
Plasma uric acid ≥0.5µmol/L	48	100	87.3	0.978	0.887-1.000	<0.001*
Plasma albumin ≤34g/L	43	96.6	89.6	0.829	0.884-0.936	<0.001*

*Statistically significant; AUC: area under the receiver operation characteristic curve; CI: confidence interval.

4. Discussion

The Mississippi class 3 HELLP syndrome (c3HELLPs) is a mild transition stage of HELLP syndrome (HELLPs) with the potential for rapid progression to more severe variants [6, 7]. However, the determinants of this progression are scarce in the literature and have not been reported around our environment to date. Hence, the current evaluated the likely biochemical predictors of the class 3 HELLP syndrome (c3HELLPs) progression among women in Port Harcourt, Nigeria.

The progressed c3HELLPs cases had higher mean and abnormal levels of plasma uric acid, creatinine but

abnormally low levels of plasma albumin compared to the non-progressed c3HELLPs cases. These characteristic findings may be indicative of the underlying pathophysiologic events that are usually associated with the transition of the HELLPs as vastly documented [9]. The rising plasma creatinine and uric acid and falling plasma albumin levels have also been associated with the worse maternal and perinatal consequences of HELLP syndrome [10-18]. Furthermore, this observed laboratory pattern usually parallel the adverse events that accompany the severe variants (Mississippi classes 1 and 2) of the HELLP syndrome beyond the Mississippi class 3 [6, 10-18].

Our finding was further strengthened by the fact that the abnormally high plasma uric acid, creatinine, and abnormally low albumin levels were likely predictors which increases the risk of c3HELLPs progression following logistic regression (LR) and ROC analysis. However, the plasma uric acid exhibited more superior characteristics on the LR and ROC analysis. Similar observations have been documented in the literature [19], but contrast with some others [20]. Increasing uric acid levels have been associated with several pathogenic pathways that underline pregnancy-related vascular events including HELLP syndrome [14, 19]. In support of our finding, a recent meta-analysis on the prognostic role of uric acid in HELLPs had observed that the increasing uric acid level significantly predicts HELLP syndrome progression [14].

The study has its shortcoming that requires reporting. First, its retrospectively designed structure may have led to under-estimation of the actual number of cases of HELLPs identified in the study. Secondly, as a single-centered and hospital-based study, its conclusions may not reflect the entire population in the studied region. Hence, the study conclusions should be interpreted with caution including its clinical application.

5. Conclusion

The current study evaluated the likely biochemical predictors of class 3 HELLP syndrome (c3HELLPs) progression. The progressed c3HELLPs cases had higher mean and abnormal levels of plasma uric acid (UA), creatinine, but abnormally low levels of plasma albumin compared to the non-progressed c3HELLPs cases. Abnormally high UA, creatinine, and abnormally low albumin levels were predictors of c3HELLPs progression on crude/adjusted logistic regression (LR) and ROC analysis. However, TPB had a more superior characteristic finding on the LR and ROC analysis. The rising UA, creatinine, and falling albumin levels may indicate c3HELLPs progression. Hence, to halt the c3HELLP progression during clinical management, the current study findings and conclusions should be considered along with clinical features and other HELLP-associated markers during the management of c3HELLPs.

Statement of Ethics

The ethical approval of the study was obtained from the Research Ethics Committee of UPTH following the review of the study protocols. The study was executed in compliance with the principles embodied in the Helsinki Declaration.

Disclosure Statement

The authors have no conflict of interest to declare.

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Author Contributions

All the authors were involved substantially in the concept and design of the study, data acquisition, analysis and interpretation of the data, drafting the article, revising the article critically for its intellectual content, and in the final approval of the version to be published.

Data Availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (CA) upon reasonable request.

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