Improving the understanding about Immune Profile before the HELLP Syndrome Onset: A Case Report.

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Abstract

The term HELLP refers to the acronym characterized by Hemolysis, Elevated Liver enzymes and Low Platelets count. The aim of this study was to evaluate the immune profile of a pregnant woman that later developed HELLP syndrome in comparison to gestational age-matching healthy pregnant. We have determined multiple plasma biomarkers, including chemokines, pro-inflammatory/regulatory cytokines and growth factors in a pregnant woman (19th+4 week of gestation) 12 days before HELLP syndrome onset. An overproduction of CXCL10, CCL2, CCL11, CXCL8, IFN-→ and IL-13, besides a pronounced deficiency of IL-6, G-CSF, IL-5, IL-10 and IL-12 was obtained in the studied pregnant woman comparing to controls. Our pioneer findings of pro-inflammatory increasing and insufficient regulatory mediators may support future strategies to clarify the early events associated with the HELLP syndrome pathophysiology. Furthermore, these data could be a powerful tool for providing disease early biomarkers, as well as perspectives for precise therapeutic intervention.

Keywords: HELLP syndrome, Systemic immune profile, Chemokines, Cytokines, Growth Factors.

Introduction

The HELLP syndrome is a very severe gestational complication that may lead to mother and/or fetus death. The term HELLP refers to the acronym characterized by Hemolysis, Elevated Liver enzymes and Low Platelets count. More than 40 years later the indefatigable efforts of Weinstein to characterize HELLP syndrome there is still a lack for many questions to be elucidated related to this syndrome [1, 2]. It is still unclear whether it is in fact an outcome of preeclampsia [2, 3]. As this syndrome occurs suddenly, as far as we know, in all the studies involving HELLP syndrome, the pregnant women already showed the clinical and laboratory signs of the disease when they were studied. Thus, few or nothing is known about systemic alterations that occur before the syndrome clinical onset. We had the lucky chance to collect a blood sample of a pregnant woman 12 days before the HELLP syndrome onset because she was enrolled in a longitudinal study conducted by our group (which aims to evaluate inflammatory and haemostatic biomarkers of pregnant women with risk factor for preeclampsia).

The aim of this study was to evaluate the immune profile of a pregnant woman that subsequently developed HELLP syndrome in comparison to gestational age-matching healthy pregnant women, in order to improve understanding of inflammation in this challenged syndrome.

Case Report

A 37-year-old non-caucasian pregnant woman at the 21st+2 gestational week was admitted at a Brazilian Public Hospital, reporting severe epigastralgia that started two days before and worsened gradually even after venous analgesia. The woman did not complain of headache, scotoma or other symptom, but presented intense legs edema.

Medical prenatal records showed laboratorial data at the 13th+2 and 17th+1 gestational week (Table 1). Besides, an ultrasound at 16th gestational week revealed increased resistance of the uteroplacental circulation. At 18th gestational week she had a moderate edema in legs without other symptoms. She reported two previous miscarriages and one gestation interrupted at

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***Received:** 14-Jul-2023, Manuscript No. AAICR-23-106390; **Editor assigned:** 18-Jul-2023, PreQC No. AAICR-23-106390(PQ); **Reviewed:** 31-Jul-2023, QC No. AAICR-23-106390; **Revised:** 04-Aug-2023, Manuscript No. AAICR-23-106390(R); **Published:** 11-Aug-2023, DOI:10.35841/aaicr-6.4.156*

***Citation:** Dusse L. Improving the understanding about Immune Profile before the HELLP Syndrome Onset: A Case Report. Immunol Case Rep. 2023; 6(4):156*

Table 1: *Laboratorial data.*

PARAMETERS	13th+3 week	17th+1 week	19th+4 week	21st+2 week (Admission and partum day)	2 days (after partum)	5 days (after partum)	3 months (after partum)	4 months (after partum)
RBC (x 106/mm³)	3,86				3,35	-	-	4,21
		-		3,69				
	12,2				10,76		-	12,47
Hb g/dL				11,9		10,41		
	34,5				29,98		-	36,4
Hct %		-		33,4		29,92		
	89,4			90,5	89	-	-	87
MCV fL		-						
	13,3				12,12	-	-	10,9
RDW %		-		11,38				
	7,180				12,920		-	6,220
Leukocytes /mm³		-		12,700		10,720		
	77,2				78,4	-	-	61
Neutrophils %		-		86,9				
	14,8					-	-	28,5
Lymphocytes %		-		5,9	12,6			
Platelets mm³	254				70,2		-	
(x 103/mm³)		-						238,5
				45,9		133,6		
				7,9		-	-	
MPV	-	-			9,7			6,4
	-				82		23	-
AST U/L		-		365		84		
	-				216		27	-
ALT U/L		-		384		149		
	-				-		0.3	-
Total Bilirubin mg/dL		-		0.74		0.3		
	-				-		0.1	-
Conjugated Bilirubin mg/dL		-		0.13		0.1		
	-				-		0.2	-
Unconjugated Bilirubin mg/dL		-		0.61		0.2		
	-				711		-	-
LDH U/L		-		1094		647		
Glycemia mg/dL	67	-						
	-	-			-		-	-
Uric Acid mg/dL				6		5		
	-			-	22	-	-	-
Urea mg/dL		27						
	-				0.7		-	-
Creatinine mg/dL		0.62		0.8		0.7		
Proteinuria	-			2.738	-	-	-	-
mg/2.500 mL/24 hours		-						

Blood collection for immune profile assessment

VDRL	NR	-	Blood collection for immune profile assessment	-	-	-	-	-
Hep.B/HBsAg		-		-	-	-	-	-
	NR							
Toxoplasmosis	IgM - NR	-		-	-	-	-	-
	IgG - Reagent							
Anti-HIV		NR						
Anti-HTLV I/II		NR						
D-Dimer (ng/dL)	-	495.1		-	-	-	-	-
C-PR (mg/L)	-	<5		-	-	-	-	-

32th week due to eclampsia followed by HELLP syndrome 12 years before.

At admission and partum day, there were no abdominal organs painless on palpation and absence of visceromegaly. Her blood pressure was 140/90mmHg and the body weight 90Kg. The laboratorial records displayed low platelet count (45,9x103/µL), signal of hemolysis (LDH=1.094U/L), and elevated liver enzymes (AST=365U/L, ALT=384U/mL), as showed on Table 1. Altogether these data allowed the HELLP syndrome diagnosis. She was under use of methyldopa (500mg per oral every 8 hours), which was maintained and also received anlodipin (5mg per oral every 12 hours) and magnesium sulphate (loading dose of 4g per infusion pump over 20-30minutes, followed by a maintenance dose of 1g per hour as a continuous intravenous infusion) for seizures' prophylaxis. The vaginal delivery was induced with misoprostol (eight 200µg tablets) inserted in the posterior vaginal fornix at a dosage of 1 tablet every 6 hours. Magnesium sulphate was maintained by 24 hours. The stillborn baby weighed 245g and was born without vital signs. Methyldopa and anlodipin were maintained after delivery.

Short-term follow-up revealed progressive improvement of clinical and laboratorial records and five days later she was discharged with better laboratorial results: Platelets= 133,6x103/µL, Hemoglobin=10,41g/dL, Hematocrit= 29.9%, Leukocytes= 10,72x103/µL, AST= 84U/L, ALT= 149U/L, LDH= 647U/L, Bilirrubin Total/Conjugated/Unconjugated= 0.3/0.2/0.1mg/dL, Creatinine= 0.7mg/dL, Uric Acid= 5.0mg/dL (Table 1). Her blood pressure was 136/80mmHg and methyldopa and anlodipin were maintained. Long-term follow-up at 3 and 4 months after delivery showed clear return of blood pressure and laboratorial parameters to normal ranges (Table 1).

Methods

Ethical Statement and Biological Sampling

A blood sample was collected of the studied pregnant woman 12 days before the HELLP syndrome onset (at 19th+4 week of gestation) because lucky she was participating of a longitudinal study conducted by our group, which was previously approved by the Ethical Committee at Federal University of Minas Gerais/Brazil (#CAAE-69371517.5.0000.5149). Fifteen healthy pregnant women from 18-42 years old (enrolled in the same longitudinal study) that kept normotensive and healthy were enrolled as control. Following the consent form signature by all pregnant women, 5mL venous blood sample was collected in EDTA. Samples were centrifuged and the plasma aliquots were stored at -80oC until immune profile determination. Case and controls were gestational age-matched (13-26 weeks, mean=18.6 weeks).

Plasma Biomarker Measurements

A high-performance magnetic beads Bio-Plex array (Bio-Rad, Hercules-CA,USA) was employed for detection and quantification of chemokines: CXCL8 (IL-8), CCL11 (Eotaxin), CCL3 (MIP-1α), CCL4 (MIP-1β), CCL2 (MCP-1), CCL5 (RANTES) and CXCL10 (IP-10); pro-inflammatory cytokines: IL-1β, IL-6, TNF-α, IL-12, IFN-γ, IL-17; regulatory cytokines: IL-1Ra (IL-1 receptor antagonist), IL-4, IL-5, IL-9, IL-10 and IL-13; and growth factors: FGF-basic, PDGF, VEGF, G-CSF and GM-CSF. The analysis of soluble immunological mediators was carried out using a blood sample collected at 12 days (19th+4 week of gestation) before the clinical onset of HELLP Syndrome.

Data Analysis

Data analysis was performed considering statistical significance when the biomarker levels of the studied pregnant were outside of the 95%CI of those observed in healthy pregnant women (Controls). Additional analysis was performed considering the baseline fold changes, calculated as the ratio between the biomarker levels found in studied pregnant divided by the mean level observed in controls.

Results

Systemic Profile of Soluble Immunological Mediators

HELLP syndrome pregnant woman exhibited increased levels of most chemokines (CXCL8, CCL11, CCL4, CCL2, CCL5 and CXCL10). Moreover, enhanced levels of IFN-□ along with IL-1Ra, IL9 and IL-13 were also observed. Increased levels of GM-CSF were also documented. The levels of CCL3, IL-1□□□TNF-□□ IL-17, IL-4, FGF-basic, PDGF and VEGF were within the reference range (95%CI of mean values) found for gestational age-matching healthy pregnant women (controls). Furthermore, lower levels of IL-6, IL-12, IL-5, IL-10 and G-CSF were observed in HELLP syndrome as compared to controls (Figure 1A). The overlaid analysis of biomarker profile further illustrated these findings (Figure 1B).

Additional analysis of fold changes in biomarker levels observed in the HELLP syndrome pregnant in comparison to mean levels detected in controls, demonstrated a mean increase of 2.6 times, with values ranging from 1.2 times for IL-4 to

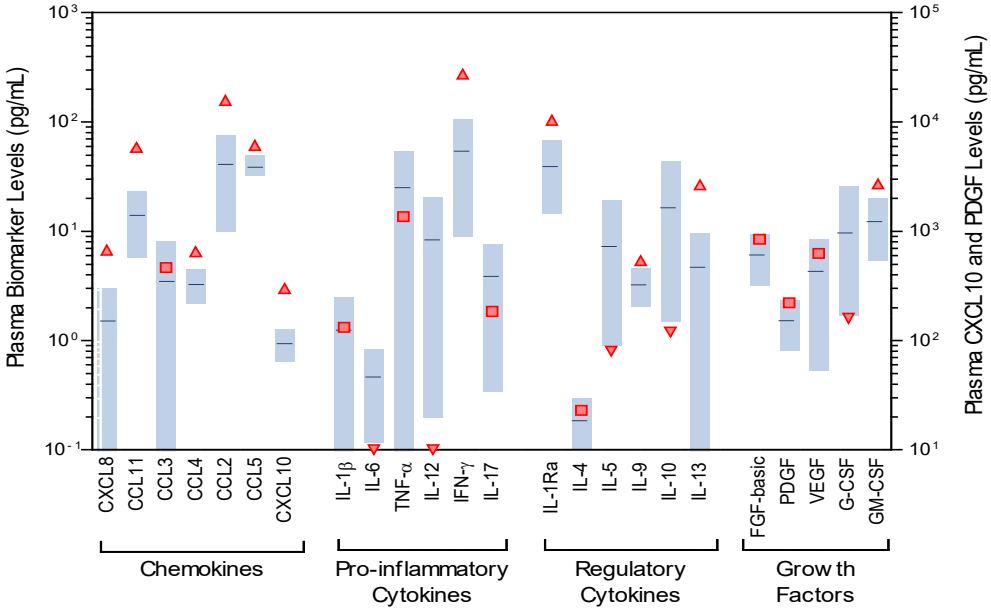

Figure 1A. *Biomarker levels in a case of HELLP syndrome as compared to healthy pregnant women at matching gestational age. Levels of chemokines (CXCL8 /IL-8; CCL11/Eotaxin; CCL3/MIP-1α; CCL4/MIP-1β; CCL2/MCP-1; CCL-5/RANTES and CXCL10/IP-10), pro-inflammatory (IL1-β; IL-6; TNF-α; IL-12; IFN-□ and IL-17) and regulatory cytokines (IL-1Ra; IL-4; IL-5; IL-9; IL-10 and IL-13) as well as growth factors (FGF-basic; PDGF; VEGF; G-CSF and GM-CSF) were measured by high performance microbeads 27-plex assay. Data are expressed as plasma levels of each biomarker (pg/mL) and the confidence interval (95%CI) found for healthy pregnant women at matching gestational age (background blue boxes). Up right and down-right triangle symbols represent, respectively, the increase or decrease in the biomarker levels observed in the HELLP syndrome patient as compared to the 95%CI of controls. Square symbol underscores the biomarkers with unaltered levels as compared to the 95%CI of controls.*

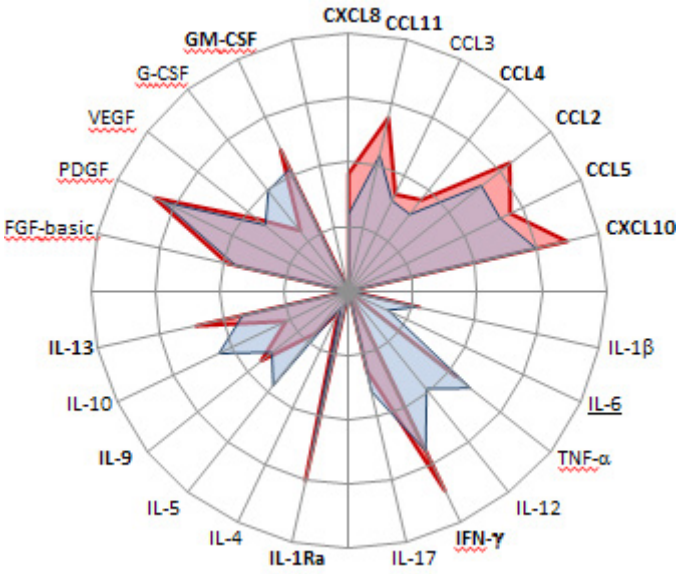

Figure 1B. *Overlaid biomarker profile further illustrates the major differences between the biomarker levels observed in HELLP syndrome as compared to the mean levels found in healthy pregnant women at matching gestational age. Data are displayed in radar chart of plasma levels of each biomarker (pg/mL). Biomarkers displaying increased levels in the HELLP syndrome patient as compared to the 95%CI of controls were underscored by bold format and those biomarkers displaying decreased levels were assigned by underline format.*

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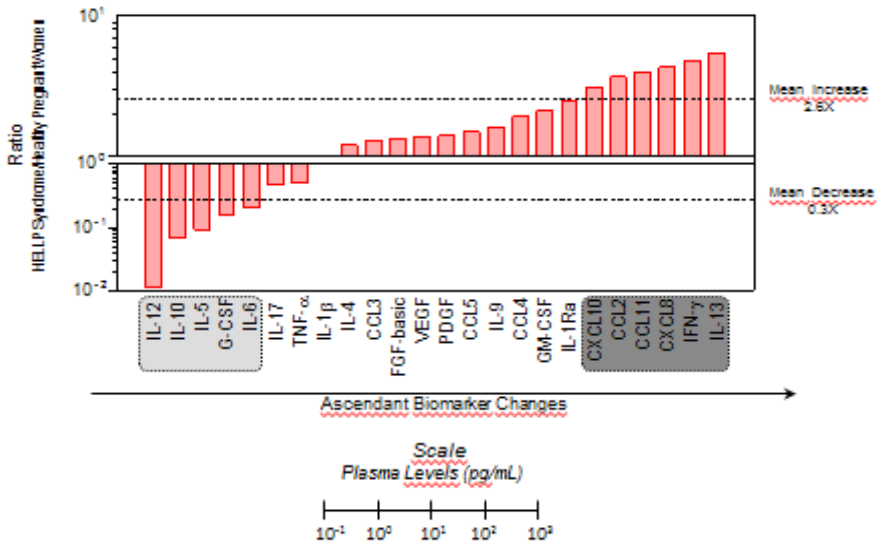

Figure 1C. *Fold changes in biomarker levels in HELLP syndrome according to mean levels observed in healthy pregnant women. Plasma levels of chemokines, pro-inflammatory and regulatory cytokines as well as growth factors are expressed as baseline fold changes, calculated as the ratio between the biomarker levels found in HELLP syndrome divided by the mean level observed in healthy pregnant women at matching gestational age. Mean increase and decrease in biomarker levels are provided in the Figure.*

5.5 times for IL-13. The biomarkers with fold changes above the mean increase ratio included: CXCL10, CCL2, CCL11, CXCL8, IFN-□ and IL-13. Conversely a mean decrease of 0.3 folds was observed for a set of biomarkers, with values ranging from 0.5 folds for TNF-□ to 0.01 folds for IL-12. The biomarkers with fold changes below the mean decrease ratio included: IL-6, G-CSF, IL-5, IL-10 and IL-12 (Figure 1C).

Laboratorial Records

The short-term follow-up carried out at 2 and 5 days after delivery the laboratorial records showed a progressive decrease of LDH (711 and 647U/L, respectively) and liver enzymes (AST=82 and 84U/L; ALT=216 and 149U/L, respectively) with a gradual recovery in platelets (70,2 and 133,6x103/µL, respectively). D-Dimer and C-Reactive Protein (C-RP) were determined at the 17th+1 gestational week excluding thrombosis or erysipelas, since she was presenting moderate edema in the legs. Uric acid, urea and creatinine results were unaltered. VDRL, hepatitis B antigen, anti-HIV and anti-HTLV were non-reagent, as well as Toxoplasmosis IgM, while IgG was reagent. The blood pressure 5 days after partum was 136/80mmHg. The long-term follow-up records at 3 and 4 months postpartum demonstrated a clear return of laboratorial parameters and blood pressure to normal ranges (Table 1).

Discussion

A fine-tuning control of immunological interactions among the immune, angiogenic and hemostatic systems is required to guarantee a healthy pregnancy outcome [4, 5]. Unbalanced interaction amongst these systems may lead to relevant pregnancy-associated disorders, such as preeclampsia and its outcome, eclampsia, HELLP syndrome or disseminated intravascular coagulation [6]. In fact our group and others showed a greater inflammation in preeclamptic women comparing to normotensive pregnant [7, 8]. We also observed a compromised microenvironment, resulting from an unbalanced angiogenic and anti-angiogenic factors, which has been considered to play a role in preeclampsia pathogenesis [9, 10]. In addition, a link between hemostasis and inflammation in preeclampsia were previously discussed by our group [11]. Furthermore, we have recently demonstrated a systemic overproduction of leukotriene B4 comparing to resolvin and maresin, which suggest that these lipid mediators may be involved with the preeclampsia pathogenesis [12]. It is known that HELLP syndrome pregnant women may have signs and symptoms that are not characteristic of preeclampsia. Therefore, it has been questionable whether HELLP syndrome is a distinct entity. However, the changes that occur specifically in this syndrome remain an under studied field [2, 13].

Our pioneer data revealed a clear unbalanced profile of immune biomarkers at 12 days before the clinical onset of HELLP syndrome. An outstanding overproduction of CXCL10, CCL2, CXCL11, IFN-□, CXCL8 and IL-13 was observed, reaching mean increase of 2.6 times over the reference values observed in controls (Figure 1). Besides, a pronounced deficiency IL-6, G-CSF, IL-5, IL-10 and IL-12 was also obtained.

It is known that he CXC chemokine family comprises two subfamilies, depending on the presence of a Glu-Leu-Arg sequence (ELR motif), referred as: CXC ELR+ (promote angiogenesis), and CXC ELR- (inhibit angiogenesis). Amongst the CXC ELR+, the CXCL8 has been considered a potent angiogenic promoter, while CXC ELR-, such as CXCL11 and CXCL10 are involved in anti-angiogenic mechanisms [14]. Our data demonstrated that the HELLP syndrome pregnant presented an increase in angiogenic CXCL8, as well as enhanced anti-angiogenic factors CXCL10 and CXCL11 levels, suggesting a balanced angiogenesis before the clinical onset.

Boij et al [15] previously demonstrated increased anti-angiogenic CXCL10 and CXCL11 levels in preeclampsia. Besides, this group showed significantly increase of CXCL11

in preeclamptic women in which the onset occurred before 34 weeks of gestation (early preeclampsia) comparing to healthy controls. Gotsch et al [16] admitted that the higher CXCL10 levels in preeclampsia likely to reflect an anti-angiogenic state as well as an enhanced systemic inflammatory response in preeclamptic women.

We found increased IFN-γ levels, a powerful pro-inflammatory mediator, in the HELLP syndrome pregnant, confirming a pro-inflammatory state. Moreover, an enhanced of GM-CSF was also found. The GM-CSF is known to regulate the differentiation of both macrophages and dendritic cells in human decidua as well as in a preeclampsia mouse model [17]. It has been reported in preeclampsia experimental model that the decidua displayed higher levels of GM-CSF along with increased numbers of macrophages and dendritic cells as compared to control animals, suggesting that this growth factor plays a role in the preeclampsia pathogenesis.

The classic marker of systemic vascular inflammation: IL-6 and C-RP were not increased before HELLP syndrome onset. IL-6 has been considered an essential pro-inflammatory cytokine produced by a broad variety of cells. Moreover, the C-RP is the main downstream mediator derived from IL-6–dependent hepatic biosynthesis in most acute inflammatory diseases [18]. Previous studies showed that C-RP and IL-6, in addition to other inflammatory markers are significantly increased during the HELLP syndrome onset [19-21]. Our findings of unaltered C-RP and IL-6 levels reinforce that the studied pregnant woman did not present inflammation before the HELLP syndrome occurrence.

HELLP syndrome shares several characteristics with other diseases such as viral hepatitis, cholangitis, systemic lupus erythematosus, thrombotic microangiopathies (thrombotic thrombocytopenic purpura and hemolytic uremic syndrome) or acute fatty liver of pregnancy [22, 23]. Although the studied pregnant woman had early manifested the classic symptoms of the HELLP syndrome at 21st+2 week (it usually occurs between 27 and 37 weeks) [1, 3], there was no doubt regarding the diagnosis, especially due to classic symptom of epigastric pain, the absence of jaundice, and prompt clinical improvement after pregnancy interruption and removal of the placenta, as well as the recovery of circulating platelets and liver function.

In conclusion, our pioneer findings of pro-inflammatory increasing and insufficient regulatory mediators may support future strategies to clarify the early events associated with the HELLP syndrome pathophysiology. Furthermore, these data could be a powerful tool for providing disease early biomarkers, as well as perspectives for precise therapeutic intervention.

Conflicts of Interest

The authors declare no conflict of interest.

Funding Statement

This study was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq #404353/2016-9); Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG #00764-16) and Fundação Oswaldo Cruz (FIOCRUZ).

Acknowledgment

The authors thank the program for technological development in tools for health-PDTIS-FIOCRUZ for the use of its facilities. ATC, LMSD and OAMF thank the CNPq for the PQ fellowships program. OAMF is a research fellow from FAPEAM (PVN-II, PRÓ-ESTADO Program #005/2019).

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