Original Article

Blood Uric Acid Level as a Marker of Increased Risk of Eclampsia in Severe Pre-Eclamptic Patients: A Cross-Sectional Study in Two Tertiary Hospitals of Yaoundé, Cameroon

L'uricémie comme marqueur de la survenue d'une crise d'éclampsie en cas de preéclampsie sévère : une étude transversale dans deux hôpitaux de Yaoundé

Félix Essiben[1], Olivier Itembe[2], Pascal Foumane[1], Marcelle Tsafack de Nguefack[2], Filbert Eko Eko[2]

[1]Faculty of Medicine and Biomedical Sciences– University of Yaoundé I
[2]Higher Institute of medical Technology, Yaoundé Cameroon
Corresponding author: Félix Essiben. Email: essibenx@yahoo.com

ABSTRACT

BACKGROUND. Eclampsia is the most dangerous maternal complication in hypertensive disorders of pregnancy (HDP). Hyperuricemia is a sign of poor prognosis for both the mother and the fetus. We investigated the relationship between uricemia and the occurrence of eclampsia in cases of severe pre-eclampsia.

MATERIALS AND METHODS. This was a three-month' cross-sectional study carried out in two tertiary hospitals in the city of Yaoundé, Cameroon. All patients attending the hospitals with evidence of severe pre-eclampsia or eclampsia and willing to participate in the study were enrolled. Socio-epidemiology data and blood were collected as soon as the diagnosis was made; uricemia were measured using a spectrophotometric method. Statistical analyses were performed using SPSS 18.0 and significance was observed when *P* was <0.05.

RESULTS. Ninety five pregnant women, aged between 15 to 41 years, with evidence of severe pre-eclampsia (60) or eclampsia (35) were enrolled during the months of January to march 2015. While age below 20 years increased the risk of eclampsia (OR=4.2; IC= [1.2-15]; *P* =0.002), marital status, parity, educational level, gestational age at time of diagnosis, the timing with respect to labor, and blood pressure values did not influence significantly the risk of developing eclampsia. Interestedly, we found that hyperuricemia is significantly increased in eclamptic patients (OR=3.1; IC= [1.2-8.2]; P=0.001).

CONCLUSION. This study suggests that blood uric acid levels are greater in eclamptic patients especially in younger ones.

KEYS WORDS. Severe preeclampsia, eclampsia, hyperuricemia, eclamptic seizures, Yaoundé, Cameroon.

RÉSUMÉ

INTRODUCTION. L'éclampsie est une des complications maternelles les plus redoutées en cas de toxémie gravidique. L'élévation de l'uricémie est un signe de mauvais pronostic materno-fœtal. Le but de l'étude était de rechercher s'il existe une corrélation entre l'uricémie et la survenue de crises convulsives en cas de pré éclampsie sévère.

MÉTHODOLOGIE. Nous avons réalisé une étude prospective analytique comparative dans 02 formations sanitaires de la ville de Yaoundé sur une période de trois mois. Toutes les patientes ayant présenté une pré-éclampsie sévère ou une éclampsie étaient recrutées et un dosage sanguin de l'acide urique était réalisé. Les données collectées étaient analysées à l'aide des logiciels SPSS version 18.0 et Epi info version 7. Le test de Chi carré a permis de comparer les variables d'intérêt entre les deux groupes avec un seuil de significativité P<0,05.

RÉSULTATS. Au total, 95 cas ont été recrutés soit 60 cas de pré-éclampsie sévère et 35 cas d'éclampsie. L'âge <20 ans augmentait le risque d'éclampsie (OR=4,2 ; IC= [1,2-15] ; P=0,0). Le statut matrimonial, la parité, le niveau d'instruction, l'âge gestationnel au moment du diagnostic, le moment de survenue de la maladie par rapport au travail, de même que le niveau des chiffres tensionnels n'ont pas influencé pas de façon significative la survenue des crises convulsives. L'hyperuricémie était augmentée de façon significative en cas d'éclampsie (OR=3,1 ; IC= [1,2-8,2] ; P=0,001).

CONCLUSION. Nous avons pu établir que l'hyperuricémie était plus élevée en cas d'éclampsie surtout chez les jeunes femmes.

MOTS CLÉS. Preéclampsie sévère, éclampsie, hyperuricémie, crises d'éclampsie, Yaoundé, Cameroun.

INTRODUCTION

Eclampsia is the development of convulsions and/or neurologic disorder in a context of preeclampsia that is not attributed to any other cause. It occurs in 0.2 to 1% of all pregnancies in Africa [1- 3]. Hypertensive disorders of pregnancy (HDP) are common and a major cause of maternal and perinatal morbidity and mortality. Its complications are ranked within the three major causes of maternal mortality in our setting [4, 5]. In a recent study, Mboudou and al [6] investigating this pathology amongst 1629 deliveries found a prevalence 8.2% and 10.6% of cases presented evidence of HDP complications.

In most of the cases, these complications are severe such as abruptio placentae, premature delivery and intra uterine fetal death [6]. Even though many of them are reversible, the materno-foetal prognosis can be affected [1, 9]. Eclampsia is a paroxystic complication of HDP and highly associated to maternal and perinatal morbidity and mortality [1, 7, 8]. Data on the indicators of severity of this pathology are crucial for the management as they can allow anticipation of complications which might be deadly to the mother and fetus.

It has been shown that high blood pressure and proteinuria or albuminuria, as indicators for the diagnosis of the disease, can also be used to appreciate the severity of the disease without predicting the risk of developing eclampsia. However, no direct evidence of the role of albuminuria in eclampsia has been found [1].

The role of uric acid in the pathogenesis of preeclampsia has been highlighted by some authors [9, 10] but this role is still controversial [11]. An increased blood level of uric acid in preeclampsia is usually consider as a prognostic factor for the fetus and the presence of hyperuricemia in cases of severe preeclampsia a criteria for fetal extraction. Changes in the metabolism of uric acid start early in the pregnancy and continue throughout [12]. Hyperuricemia in preeclamptic women is associated to adverse outcomes such as preterm birth and growth retardation [13] and is used for decision-taking during the management of the HDP [9]. The existence of a relationship between levels of blood uric acid and eclampsia in severe preeclampsia has not yet been established.

The objective of the study was therefore to find out if the level of blood uric acid in severe pre-eclampsia can predict the occurrence of convulsions.

MATERIALS AND METHODS

This was a cross sectional analytic study carried out in two hospitals in the Yaoundé city of Cameroon; the Central Hospital and the Gyneco-obstetric and Pediatric Hospital. We chose these two hospitals because of their patient's diversity and number and also their geographical accessibility.

The study was approved by the institutional ethic committees of the University of Douala and different hospitals. Participation in the study was voluntary. All study participants gave a verbal consent and for unconscious patients, the consent was given by the accompanying person. Women who had convulsions from other causes were excluded. Patient information was obtained from clerking patients and filling in a pre-conceived questionnaire. The variables studied included parity, marital status, level of education, Timing of diagnosis with respect to onset of labour, age, uricemia, systolic and diastolic blood pressure at the time of diagnosis and gestational age at time of diagnosis.

The study spanned a period of three months from March to May 2015. The sampling was consecutive and exhaustive.

All patients with severe preeclampsia or eclampsia were included and divided into two groups. Group 1 comprised patients with severe preeclampsia While Group 2 comprised patients with eclampsia. Severe preeclampsia was defined as a presence of systolic blood pressure ≥160mmHg and/or a diastolic pressure ≥110mmHg associated to a massive proteinuria of 5g/24h or a 3+ proteinuria on dip stick urinalysis or oliguria of less than 100ml/24h.

Eclampsia was defined as the occurrence of convulsive crisis in a context of preeclampsia and/or anomaly of consciousness.

Five milliliters of venous blood was collected in a dry tube as soon as the diagnosis was done and sent to the laboratory for the testing of uric acid using a colorimetric assay. The blood was centrifuged and 500 µl of serum was used for the test using UA2 Uric acid ver.2 reagent with COBAS C111 automat analyzer. The reference values were 24 – 57 mg/l.

The variables studied were parity, marital status, level of education, Timing of diagnosis with respect to onset of labour, age, uricemia, systolic and diastolic blood pressure at the time of diagnosis and gestational age at time of diagnosis.

The two groups were compared according to the variables in question. The software SPSS 18.0 was used for the analysis of the variables. Pearson's Chi square and Student test were used to compare quantitative and qualitative variables respectively. The Odds ratio (OR) and its 95% confidence interval (CI) were calculated to assess the association between variables.

RESULTS

We included 95 patients amongst whom 35 had eclampsia and 60 had severe preeclampsia. Age varied from 15 to 40 years. Sixty two patients (65.3%) were married. More than half patients (53.7%) have a secondary level education. Fifty nine (51.6%) patients were primigravida. Eclamptic patients were younger than pre eclamptic patients. There were no significant differences in clinical or demographic characteristics between the two groups except that the risk of convulsion was greater in patients within the age group of 15 to 19 years (OR=4.2; CI= [1.2-15]; *P*=0.022 and table 1).

Table1. Comparison of the socio demographic data between the group with eclamptic crisis (group 1; *n* = 35) and the group with severe pre eclampsia without eclamptic crisis (group 2; *n* = 60).

Variables	Eclamptic patients N = 35 n (%)	Sévère Pre-eclamptic Patients. N = 60 n (%)	Odds Ratio (95% *CI)	P value
Maternal age (years)				
[15- 20[	08 (22.9)	4 (6.7)	**4.15 (1.15-15)**	**0.022**
[20- 30[	16 (45.7.6)	32 (53.3)	0.74 (0.32-1.71)	0.475
> 35	11(31.4)	24 (40.0.7)	0.69 (0.29-1.67)	0.403
Marital status				
Married	20 (57.1)	42 (70.0)	0.57 (0.24-1.36)	0.204
Single	15 (42.9)	18 (30.0)	1.75 (0.73-4.17)	
Level of education				
Primary level	3 (8.6)	7 (11.7)	0.71 (0.17-2.94)	0.639
Secondary level	21 (60.0)	30 (50.0)	1.5 (0.64-3.49)	0.345
Higher level	11 (31.4)	23 (38.3)	0.74 (0.31-1.79)	0.498
Parity				
Primiparous	19 (54.3)	30 (50.0)	1.19 (0.52-2.74)	
Multiparous	16 (45.7)	30 (50.0)	0.84 (0.36-1.94)	0.687

Marital status, level of education and parity did not influence the occurrence of convulsive crisis (table 1). Gestational age at time of diagnosis was comparable in both groups. The diagnosis of severe preeclampsia during labour did not influence the progress to eclampsia (OR= 0,8 ; CI= [0,31-2,15]; *P*= 0.680 and table 2). The systolic blood pressures at the time of diagnosis were similar in the two groups (OR=0.54; CI= [0.19-1.54]; *P*=0.251 and table 2) as well as diastolic blood pressures (*P*=0.46; CI= [0.19-1.13]; *P*=0.092 and table2). Hyperuricemia is more increased in eclamptic patients (OR= 3.14; CI= [1.32- 7.47]; *P*=0.009).
Independent associated variable after logistic regression was the age < 20 years (p=0,02).

Table2. Comparison of clinical and paraclinical data between the group with eclamptic crisis (group 1; *n* = 35) and the group with severe pre eclampsia without eclamptic crisis (group 2; *n* = 60).

Variables	Eclamptic patients N=35 (%)	Severe Pre eclamptic patients N=60 (%)	Odds ratio (95% CI)	P value
Gestationnal age at the time of the diagnosis				
< 36	15 (42.9)	32 (53.3)	0.66 (0.28 -1.53)	0.325
≥ 36	13 (37.1)	20 (33.3)	1.18 (0.49 -2.82)	0.708
Post partum period	7 (20.0)	8 (13.3)	1.63 (5.54 -4.96)	0.390
Antepartum	21 (60.0)	35 (58.3)	1.7 (0.46-2.5)	0.862
Per partum	8 (22.9)	16 (26.7)	0.8 (0.31-2.15)	0.680
Post partum	6 (17.1)	9 (15.0)	1.17 (0.38-3.62)	0.777
[140-159]	6 (17.1)	16 (27.6)	0.54 (0.19-1.54)	0.251
≥ 160	29 (82.9)	42 (72.4)	1.84 (0.64-5.26)	
Diastolic blood pressure at the time of the diagnosis				
[90-109]	10 (29.4)	27 (47.4)	0.46 (0.19-1.13)	0.092
≥ 110	24 (70.6)	30 (52.6)	2.16 (0.88-5.33)	
[25-60[(normale)	13 (37.1)	38 (63.3)	0.34 (0.14-0.81)	**0.014**
≥ 60(hyperuricemia)	22 (62.9)	22 (36.7)	**2.92 (1.23-6.93)**	

DISCUSSION

We found out that uric acid levels were often higher in patients presenting with convulsive crises. Also, patients aged less than 20years often had eclampsia complicating pre-eclampsia.

Eclampsia is a severe complication of HDP. It is the most frequent complication of preeclampsia [9] and is responsible of severe materno-fetal morbidities when it does not result to death of mother or fetus. Several studies have found a very high maternal and fetal mortality associated to eclampsia [1, 7, 8]. Preeclampsia and its complications can occur anytime during pregnancy, labour or after delivery. Early detection of the deterioration of the maternal state is primordial for the management of this disease.

Several risk and aggravating factors for preeclampsia and eclampsia are described in literature [1, 7]. For instance, young age had been identified as a risk factor in several studies [1, 3, 7]. We also found that the younger the patient was the greater the risk was to develop eclamptic crisis. The mean age for eclamptic patients is smaller than pre eclamptic patients. The peak maternal age of occurrence of eclampsia was different to that of pre eclampsia. The eclamptic patients in our series were found to be younger than those of other African series [1, 14]. Age less than 20 years was at higher risk of developing eclampsia. We can speculate that the occurrence of eclampsia in younger individuals may be due to the incapacity of the young maternal body to adapt to the hemodynamic and renal changes as well as uterine hypoplasia. The absence of convulsions in severe preeclampsia could be explained as either unnoticed essential hypertension or resistance to acute accidents in HDP.

Convulsive crisis is usually due to cerebral vasospasm which leads to cerebral suffering and consequently results in cerebral oedema. Hypertensive encephalopathy is another hypothesis especially for cerebrovascular accidents [15].

Nulliparity is a known risk factor for preeclampsia [1] but this did not increase the risk for eclampsia in our study. Blood pressure values higher than 160/110mmHg didn't increase eclampsia risk contrary to some authors [1].

We found 62% of eclampsia cases with high uric acid values. The pathogenesis of uric acid in preeclampsia has been well described by some authors [9, 16]. A correlation has been established between the concentration of uric acid and the severity of HDP [17, 18]. Uric acid is a reliable predictive marker for increased blood pressure in preeclampsia [19] but uric acid concentration during pregnancy is influenced also by protein-rich diet, alcohol consumption and renal failure. It drops in early pregnancy under the influence of estrogen [20] and then increases gradually to attain non-pregnant values at term [21].

There still exists a controversy on the role of uric acid in the pathogenesis of preeclampsia and its clinical benefit in diagnosis and management. Practically, one third of the eclamptic cases had normal uric acid values in the study performed by Roberts and collaborators [18] and an increase in uric acid level in the blood precedes clinical manifestations of preeclampsia. The diagnosis of preeclampsia with hyperuricemia is associated to poor maternal outcome [22]. Considering our results, there was a positive correlation between eclampsia and hyperuricemia. The risk of eclampsia is as higher as uric acid concentration is important. Mayi-tsonga et al [1]. did not find hyperuricemia as a risk factor for eclampsia. A majority of the study participants in their study had normal uric acid values [1]. This is contrary to the findings of Ben Salem [23] et al. Normal blood uric acid values in pre eclamptic and eclamptic patients could be explained by the presence of hypouricemic factors like high protein diet, physical effort, alcohol consumption, altered renal function even some drugs intake [12]. Those factors are usually not systematically checked for. Furthermore, difficulties in seting normal values in pregnancy owing to individual variability caused by physiologic modifications of pregnancy can also explain normal uric acid values.

Nonetheless our study had some limitations. Uric acid was dosed within 24 hours for all subjects but at different periods. In our subjects, we neither evaluated renal function nor feeding habits both of which could influence uric acid levels in one way or the other. We also could not come out with a threshold value for serum uric acid beyond which convulsions became inevitable. We cannot now conclude that hyperuricemia is a risk factor for eclampsia because of the design of our study.

CONCLUSION

Eclampsia is a common complication of preeclampsia associated to high perinatal and maternal morbidity and mortality. Hyperuricemia highly correlates with eclampsia in pre eclamptic patients. We recommended that clinicians may look at blood uric acid level earlier in pregnancy in order to anticipate eclampsia particularly in young patients.

CONFLICT OF INTEREST

The authors declare no conflict of interests

AUTHORS' CONTRIBUTIONS

Essiben F, Itembe O and Foumane P conceived the study, participated in the study design, data collection, and drafting and editing of the manuscript. Tsafack de Nguefack MA participated in data collection and analysis. Nana PN and Eko Eko F participated to the review of the article. Mboudou TE supervised the study. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors are grateful to Dr. Marcel Tongo (University of Cape Town) and Dr Dohvoma Viola (Yaoundé Central Hospital) for helpful discussion and critical review of the manuscript.

REFERENCES

[1] Mayi-Tsonga S, Akouo L, Ngou-Mve-Ngou JP, Meye JF. Risk factors for eclampsia in Libreville (Gabon): A case-control study. Sante (Montrouge, France).2006 ; 16(3):197-200. doi:10.1684/san.2006.0026.

[2] Faye A, Picaud A, Ogowet-igumu N, Nlome, Nzé RA, Nicolas PH. Eclampsia in Libreville central hospital. 53 cases in 41.285 deliveries in 1985-1989. Rev Fr Gynecol Obst. 1991; 86: 503-10.

[3] Pambou O, Ekoundzola JR, Malanda JP, Buambo S. management and prognosis of eclampsia in the university teaching hospital in Brazzaville: a retrospective study of 100 cases. Med Afr Noire. 1999; 46: 508-512.

[4] Mbu RE, Dempouo, Nana PN, Tonye RN, Ako S, Eteki NT, Leke RI. The materno-fœtal outcome of eclamptic women who give birth by caesarean or vaginal route in 3 tertiary hospitals in Yaoundé. Clinics Mother Child Health.2006; 3(2): 555-62.

[5] Yakana NI. Evolution of maternal mortality after reorganisation of the obstetric service: the case of the Central maternity in Yaoundé [thesis] (2003): Faculty of Medecine and Biomedical Sciences. University of Yaoundé I

[6] Mboudou ET, Foumane P, Belley PE, Dohbit J, Ze MJ, Nkengafac WM, Doh AS. Hypertension during pregnancy: epidemiological and clinical aspects at the Gyneco-Obstetric and Pédiatric Hospital of Yaoundé, Cameroon. Clin Mother Child Health 2009; 6 (2): 1087-93.

[7] Buambo-Bamanga SF; Ngbale R; Makoumbou P, Ekoundzola JR. Eclampsia in the university teaching hospital in Brazzaville, Congo. Clin mother child health. 2009; 6 (2): 1129-33.

[8] Coulibaly KT , Abhé CM , Ouattara A, Yapi N , Assa NL , Binlin-Dadié RY. the complications of preeclampsia in resuscitation's department of the teaching hospital of Cocody (Abidjan - RCI). Rev Afr Anesth Med Urgence. 2014; 19 (1). http://saranf.net/Les-complications-de-la-pre.html

[9] Kang DH, Finch J, Nakagawa T, Karumanchi SA, Kanellis J, Granger J, Johnson RJ. Uric acid, endothelial dysfunction and pre-eclampsia: searching for a pathogenetic link. J Hypertens. 2004; 22(2) : 229-35.

[10] Lam C, Lim KH, Kang DH, Karumanchi SA. Uric acid and preeclampsia. Semin Nephrol. 2005; 25(1) : 56-60.

[11] Chen Q, Lau S, Tong M, Wei J, Shen F, Zhao J, Zhao M. Serum uric acid may not be involved in the development of preeclampsia. J Hum Hypertens. 2016; 30, 136-40.doi: 10.1038/jhh.2015.47. [Epub ahead of print]

[12] Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003; 41:1183–90.

[13] Bainbridge SA., Roberts JM. Uric Acid as a Pathogenic Factor in Preeclampsia. Placenta. 2008; 29: 67–72.

[14] Tchaou BA , Tshabu-Aguèmon C , Hounkponou FM , Brouh Y , Aguémon AR, Chobli M. Serious obstetric morbidity in intensive care unit in the the University Teaching Hospital of Parakou (Benin) about 69 cases. Rev Afr Anesth Med Urgence. 2013; 18 (1). http://saranf.net/Morbidites-obstetricales-graves-en.html

[15] Baeta S, Tete KVS, Noutsougan YM, Nya-me AN, Akpadza KS. Eclampsia in CHU in Lomé (Togo): risk factors, maternal and perinatal prognosis. SAGO Journal 2002 ; 1 : 1-6

[16] Masoura S, Makedou K, Theodoridis T, Kourtis A, Zepiridis L, Athanasiadis A. The Involvement of Uric Acid in the Pathogenesis of Preeclampsia. Curr Hypertens Rev. 2015;11(2):110-5.

[17] Voto LS, Illia R, Darbon-Grosso HA, Imaz FU, Margulies M. Uric acid levels: a useful index of the severity of preeclampsia and perinatal prognosis. J Perinat Med. 1988;16: 123-6.

[18] Roberts JM, Bodnar LM, Lain KY, Hubel CA, Markovic N, Ness RB, Powers RW. Uric acid is as important as proteinuria in identifying fetal risk in women with gestational hypertension. Hypertension. 2005;46:1263-9.

[19] Elmas O, Elmas O, Aliciguzel Y, Simsek T. The relationship between hypertension and plasma allantoin, uric acid, xanthine oxidase activity and nitrite, and their predictive capacity in severe preeclampsia. J Obstet Gynaecol. 2015 Sep ; 14:1-5.

[20] Carter J, Child A. Serum uric acid levels in normal pregnancy. Aust N Z J Obstet Gynaecol. 1989; 29:313-4.

[21] Powers RW, Bodnar LM, Ness RB, Cooper KM, Gallaher MJ, Frank MP, Daftary AR, Roberts JM. Uric acid concentrations in early pregnancy among preeclamptic women with gestational hyperuricemia at delivery. Am J Obstet Gynecol. 2006; 194:160

[22] Cicero AF, Degli Esposti D, Immordino V, Morbini M, Baronio C, Rosticci M, Borghi C. Independent Determinants of Maternal and Fetal Outcomes in a Sample of Pregnant Outpatients with normal blood pressure, Chronic Hypertension, Gestational Hypertension, and Preeclampsia. J Clin Hypertens. 2015; 17:777-82.

[23] Ben Salem F, Ben Salem K, Grati L, et al. Risk factors of eclampsia: a case-control study. Ann Fr Anesth Rea. 2003. 22: 865-9