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SERUM URIC ACID AND HOMOCYSTEINE AS PREDICTORS OF PRE-ECLAMPSIA

Biochemistry

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ABSTRACT

Objective: To estimate the serum homocysteine and uric acid levels in normal and pre-eclamptic patients and to find out any correlation between these parameters and pre-eclampsia Study design and setting: Cross-sectional study; Dept. of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, Patna Medical College and Hospital, Patna, Bihar. **Methods:** Data collected from 50 pre-eclamptic pregnant women and 25 normotensive pregnant women admitted in Antenatal ward, Department of Obstetrics and Gynaecology, PMCH, Patna. The blood samples were collected from these patients and analyzed for serum homocysteine and uric acid level. **Results:** The serum homocysteine and uric acid levels were found to be significantly higher in preeclamptic cases than in normal controls. A positive correlation was found between the serum uric acid level, homocysteine and blood pressure. Thus the study showed a strong association between increased uric acid, blood pressure and homocysteine levels.

KEYWORDS

Pre-eclampsia; Uric Acid; Homocysteine

INTRODUCTION

Hypertension is one of the common complications during pregnancy and contributes significantly to maternal and perinatal morbidity and mortality. Pre-eclampsia is a type of hypertensive disorder complicating pregnancy. It is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after the 20th week in a previously normotensive and non-proteinuric patient. Its pathophysiology is poorly understood but currently endothelial dysfunction is most popularly hypothesized to be a central pathophysiological feature of preeclampsia leading to altered vascular reactivity,loss of vascular integrity and activation of the coagulation cascade [1]. Uric acid (UA) is the major end-product of purine metabolism. The cause of hyperuricemia in pre-eclampsia has been attributed to either a decreased excretion or to an increased production of uric acid. Decreased uric acid clearance, reflected by altered tubular function has been documented, while in 1990 Fay proposed an increased breakdown of purines in the placenta as a possible explanation for the overproduction of uric acid [2]. Hyperuricemia is one of the most consistent and earliest detectable changes in pre-eclampsia and has been cited as a better predictor of fetal risk than blood pressure [3,4]. Homocysteine (Hcy), a thiol-containing amino acid, is the demethylated derivative of the essential amino acid methionine and thus an intermediate in the methionine cycle. Elevated homocysteine is a risk factor for endothelial dysfunction and vascular disease such as atherosclerosis and occlusive vascular disorders [5]. The mean homocysteine levels normally decrease with gestation either due to physiological response to the pregnancy, increase in estrogen, hemodilution from increased plasma volume or increased demand for methionine by both the mother and fetus [6]. The homocysteine-mediated vascular changes are similar to thoseassociated with preeclampsia; therefore, it has been postulated that hyperhomocysteinemia may be associated with this condition [7]. The present study was conducted to estimate the serum homocysteine and uric acid levels in pre-eclamptic indigeneous Manipuri women and to find out any correlation between these parameters and the disease.

Materials and Methods

A case control study was conducted to evaluate the level of serum homocysteine in preeclamptic patients (cases) and normal pregnant women (controls) admitted in the antenatal ward in the Department of Obstetrics and Gynaecology. It was done in the Department of Biochemistry in collaboration with the Department of Obstetrics and Gynaecology, PMCH,Patna. Patients who were diagnosed as preeclamptics were taken as the cases and normal pregnant women of comparable gestational age as the controls. Fifty pregnant women in the age group 18 to 45 years having blood pressure ≥ 140/90 mmHg and proteinuria ≥ 300 mg in a 24 hours urine collection after 20 weeks of gestation were recruited as preeclamptic cases. Another 25 normal pregnant women of similar age group and gestational age were also taken as controls. The study group and the control group were matched for age, weight and gestational age. All the cases and controls in the study were subjected to detailed history regarding age, parity, height and weight at the time of blood collection. Maternal education, religion, race, socioeconomic status, menstrual history, obstetric history was taken. General physical examinations and systemic examinations with special reference to oedema and blood pressure were carried out. And all the investigations were recorded in the proforma designed for the study. Those patients with preexisting hypertension, cardiovascular or renal diseases diabetes mellitus or chronic diseases and those patients on treatment with anti-folate drugs (antiepileptics, methotrexate) were excluded from the study. 5 ml of venous blood was drawn from anterior cubital vein after an overnite fast. The sample was centrifuged for 10 minutes and analysed for total serum homocysteine and uric acid in the Department of Biochemistry, PMCH, Patna. Total serum homocysteine was carried out by Enzyme Linked Immunosorbant Assay (ELISA) method [8] using Axis-homocysteine Enzyme Immunoassay (EIA) kit from Ranbaxy Diagnostic Ltd. India. Serum uric acid was analyzed by Uricase method (enzymatic-colorimetric test) modified by Human Co., Germany [9,10].

RESULTS

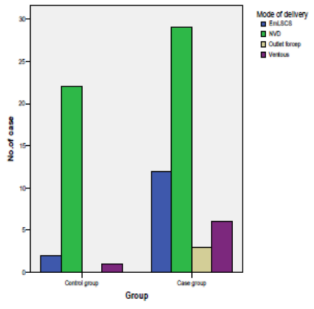
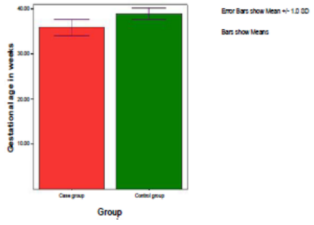


Figure 1: Comparison of mode of deliveries between the case and control group.



SD: Standard Deviation

Figure 2: Comparison of Mean ± SD of gestational age (weeks) at delivery between the case and control group.

The majority of women in the case group are Hindus (75%) whereas Muslims and Christian comprises of 20% and 5% respectively. In the control group Hindus comprises of 75% whereas Muslims and Christians comprises of 15% each. Majority of the women in the case group belong to the lowest socioeconomic group (70%) followed by women belonging to medium (15%) and high economic status (5%) respectively. It is seen that maximum number of cases (60%) occur in primiparas (P0+0),15% belong to P1+0, 15% belong to P2+0 and 10% belong to P3 and above. Maximum number of the cases occurs in the age group of 21-25 years. The women in control group have older age than that of the case group. However the difference is found to be insignificant at 5% probability level. It is observed that mean weight of women in the case group (52.46 ± 5.09 Kg) is more compared to that of control group (50.36 ± 3.55 Kg) but the difference is not significant at 5% level of significance. The haemoglobin concentration is more in the controls (11.20 ± 1.27 gm %) compared to cases (10.36 ± 0.82maximum number of cases (60%) and controls (90%) delivered by normal vaginal delivery (NVD) followed by caesarean section in 30% and 6% of the cases and controls respectively. Six percent of cases delivered by outlet forceps and the number of patients delivered by assisted ventouse are1 4% and 2% in the cases and controls respectively. However insignificant test value (p=0.068) suggests that the mode of deliveries in both the groups are almost alike. Figure 2 shows that the average gestational age at delivery for normal pregnant women (39.00 ± 1.19 weeks) is higher than of the cases (35.94 ± 1.83 weeks). The difference is very highly significant even at 0.1% probability level (p=0.000). The weights of the babies born to normal pregnant controls are more than those born to the cases. Mean ± SD (Kg) in the control group is 3.11 ± 0.36 compared to 2.80 ± 0.60 in the case group as is evident from figure 2. The difference is statistically significant at 5% probability level (p=0.023). 50 preeclamptic patients, 90% cases have no complications whilst 10% have intrauterine foetal dead (IUFD), 3% has abruptio placentae and 3% has congenital malformation. In the control group none has complications. The serum uric acid levels in the cases are higher than the controls (Figure 1). The mean ± SD (mg%) for the cases is 8.82 ± 1.68 whereas in the control group it is 4.06 ± 0.96. This difference in the values is very highly significant ($p \leq 0.001$). The level of serum homocysteine is higher in the case group compared to control group as evident in figure 2. The mean ± SD of homocysteine (µmol/l) in the case group is 10.32 ± 2.52 whereas the level in control is 3.55 ± 1.25. This variation is very highly significant as evident by very highly significant value of t=12.601 and p=0.0001. Table 10 shows the level of homocysteine levels in preeclamptic (PET) cases according to blood pressure. It has been observed that out of 50 cases of preeclampsia, 30 preeclamptic patients have blood pressure between 140/90 mm Hg and 160/110 mmHg and 20preeclamptic patients have blood pressure above 160/110 mmHg. In the mild preeclamptic cases majority has homocysteine level below 10 µmol/l whereas in the severe preeclamptic cases majority of them has level above 10 µmol/l. But the difference is not significant (p=0.148). In order to study the correlation among the parameters; serum homocysteine, blood pressure, and serum uric acid – Pearson correlation coefficient "r" is advocated and findings are shown in table 11. The analysis is based on the case group only. Table 11 highlights that there is a strong positive correlation between serum homocysteine with blood pressure (systolic and diastolic) which is highly significant. A positive correlation is also observed between serum serum uric acid and homocysteine.

DISCUSSION

The study shows that majority of the patients are Hindus (75%) followed by Muslims 15%) and Christians (5%). This pattern is observed in both the cases and controls and no significant difference (p=0.683) is found between them. The reason may be due the fact that the study is being conducted in the Hindu dominated area. In the case of socioeconomic status, women in the lowest status (70%) have the highest frequency followed by medium class (30%) and least number of cases belongs to high socioeconomic class (10%). The pattern is found to exist in both groups and no significant difference (p=0.114) is observed between the groups. Maximum number of cases is observed in the primigravida (55%) and only 5% of the cases are seen above third gravida. Ingec have also reported that preeclampsia occurs more commonly in primiparas compared to normal controls. In the present study maximum numbers of preeclamptic cases occur in the age group of 21-25 years (60%) and only 15% occurs at 36years and above. The women in the control group are older than women in the case group. However, the difference is found to be insignificant at 5% probability level. On comparison of weight and haemoglobin between the cases and controls, it has been observed that the weights of women belonging to the case group are heavier than the controls. Mean weight ± SD of the cases is 52.46 ± 5.50 kg compared to 50.36 ± 3.55 kg in control but the difference is not statistically significant (p=0.069). This finding is in agreement with that of Rajkovic et al. [11] who found in their study that the weights of the preeclamptic women were more than that of the normal pregnant controls. It is evident that maximum cases (75%) show the presence of both proteinuria and oedema whilst proteinuria and oedema alone are seen in 55% each. The study shows that out of the 50 preeclamptic cases, 45 (90%) cases have no complications, one case (3%) delivered a baby with congenital malformation, one case (3%) has abruptio placenta and another 6% have intrauterine foetal death . No complication is seen in the control group. The difference in complication between the cases and controls is highly significant (p=0.001). Our study shows blood pressure is higher in the cases compared to controls and the difference is highly significant. The serum uric acid level is higher in the cases than the controls (Figure 2) and the difference is highly significant. During pregnancy maternal serum uric acid levels initially falls, with a subsequent rise to prepregnancy levels near term [11]. The third –trimester rise in uric acid may be related to an increase in foetal uric acid production or a decrease in uric acid clearance [10]. Elevated serum uric acid levels due to decreased renal urate excretion are frequently found in women with preeclampsia [11]. Soluble uric acid impairs nitric oxide generation in endothelial cells inducing endothelial dysfunction [11]. Besides the reduced clearance hyperuricemia in pre-eclampsia may be due to increased uric acid production caused by trophoblast breakdown, cytokine release and ischemia. Uric acid can promote endothelial dysfunction, damage and inflammation, which leads to oxidation. So, pre-eclampsia, which is characterized by widespread endothelial dysfunction and inflammation, might be propagated by uric acid [11]. It has also been reported that rise in uric acid level in preeclampsia is secondary to placental damage leading to purine catabolism and production of uric acid. Besides the increased uric acid level in our cases a positive correlation is observed between serum uric acid and homocysteine . This supports the finding of Ingec et al. [11]. The serum homocysteine level in the case group is found to be highly significant compared to the control group (Figure 5). The findings are comparable to that reported by Rajkovic et al. [11], Sanchez et al. [8], Harma et al. [9] and Maruotti et al. [2,10]. A positive correlation isvascular disorders [2,3]. It has been suggested that the adverse vascular effects of high homocysteine are mediated by oxidative inactivation of nitric oxide, a powerful endogenous vasodilator released from endothelium [2,4]. The increased uric acid and homocysteine levels in our cases may be due to derangement in the metabolism that usually decreases their levels during pregnancy. Their increased levels might have led to endothelial dysfunction which eventually results in preeclampsia. The study also shows a strong association between hyperuricemia, hyperhomocysteinemia and preeclampsia.

CONCLUSION

The results of this study confirm the hypothesis that hyperuricemia and hyperhomocysteinemia are indirect risk factors for preeclampsia. Thus it can be concluded that hyperuricemia and hyperhomocysteinemia can be used as biomarkers for identifying women at risk of complications and adverse pregnancy outcomes. Several potential limitations of our study are worth mentioning. All the cases were preeclamptic before the measurement of serum uric acid and homocysteine levels and, so it cannot be determined whether the observed elevation in homocysteine and uric acid preceded the development of preeclampsia. Hyperhomocysteinemia and hyperuricemia in preeclampsia patients need to be confirmed in a design in which uric acid and homocysteine are measured before the development of preeclampsia or early in pregnancy in order to identify and monitor the patients at risk and thus provide the best prenatal care for these women and their babies.

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