Original Article

Event related evoked potentials in pregnancies complicated with preeclampsia

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Abstract

Background and Aim: Preeclampsia is the most significant cause of neurocognitive disturbances in pregnancy. These symptoms may persist for many years after the index pregnancy even if the somatic symptoms of preeclampsia disappear. In the present study, we have assessed the early cognitive changes in preeclamptic females with the help of event related evoked potentials (EREPs).

Methods: EREPs were recorded in 20 diagnosed patients of preeclampsia with the help of computerized evoked potential recorder using the standard auditory 'oddball' paradigm. An equal number of age and gestation matched healthy pregnant females served as controls. The latencies and amplitudes of different waves of EREPs in both the groups were analyzed by using student's unpaired T-test. Correlation of P3 (main tool for cognition assessment) with blood pressure parameters was done by using Pearson's correlation coefficient.

Results: Latencies of waves N_2 and P_3 from frontal, central and parietal (FzA_1A_2, CzA_1A_2, and PzA_1A_2 , respectively) were found to be significantly delayed in preeclamptic females when compared to their normal contemporizes. Neither latencies nor amplitudes of P_3 were found to be significantly correlated with systolic blood pressure, diastolic blood pressure, or mean arterial pressure.

Conclusion: Our results conclude that there are cognitive disturbances during the preeclamptic pregnancy. Prolonged latencies of EREP waves indicate that the cognitive functions such as information discrimination and reaction take longer time in preeclamptic patients when compared to their normal counterparts. This could be an electrophysiological manifestation of future memory loss in patients having preeclampsia.

Key words: Blood pressure, cognition, event related evoked potentials, preeclampsia

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INTRODUCTION

Preeclampsia is a multisystem disorder affecting approximately 3% of all pregnancies all over world with more incidence in developing countries.[1] Despite extensive study, this disorder remains enigmatic and a leading cause of maternal and neonatal morbidity and mortality.[1] Increasing evidences suggest that preeclampsia is the most significant cause of neurological symptoms in pregnancy. Although the somatic symptoms of preeclampsia such as hypertension and proteinuria disappear after delivery, formerly preeclamptic women complain of cognitive disturbances and memory loss as compared to women after uncomplicated pregnancies.[2-4] Children born to females with eclampsia or preeclampsia also have lower intelligence quotient.[5]

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Cognitive impairment in formerly eclamptic women has been documented by many researchers based on intelligence quotient (IQ) and memory tests.[3,6,7] Recently cerebral white matter lesions have also been demonstrated on imaging, following 6 weeks after index delivery.[8] Preeclampsia might be a risk marker for early cerebrovascular damage and for the development of cerebral white matter lesions.[9] Abnormal electroencephalograms (EEG) have already been

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reported in approximately 50% of preeclamptic patients which is totally reversible in most of the patients.[10] P1 latency of visual evoked potential was found to be positively correlated with blood pressure (BP) in preeclamptic pregnancy.[11] In our previous study, a delay in wave IV and V of brainstem auditory evoked potentials was found in preeclamptic females during their third trimester of pregnancy.[12]

Very few studies are available in preeclamptic females based on evoked potentials and we have not come across any study where cognition was tested with the help of event related evoked potentials (EREPs) in these females during the index pregnancy. EREPs are more sensitive and non-invasive method, which can detect any subclinical impairment of cognition at the earliest that may not be detected by the conventional methods of cognitive assessment.[11]

P300 component of EREPs has been a prominent tool to study cognitive psychology on information processing,[11] but the data in preeclamptic females is lacking. Moreover in most of the studies, neuropsychological tests were performed on these females few weeks to few months after the delivery[2-5] and we have not come across any study documenting cognitive abnormalities during the index pregnancy. If preeclampsia/eclampsia can deteriorate the cognitive functions so many weeks after the index pregnancy, then it should have some impact on brain functions even during the pregnancy and EREPs may pick up these early cognitive changes. Therefore, we planned this study to detect any early derangement of cognitive functions in preeclamptic females.

MATERIALS AND METHODS

Study design and patient population

Twenty diagnosed patients of preeclampsia of gestational age 32-40 weeks were selected from the out-patient department (OPD) and wards of Obstetrics and Gynaecology department of Lok Nayak Hospital for the present study. An equal number of age-matched healthy normotensive pregnant females were also recruited as controls. The EREP recordings were done in the Neurophysiology lab of the Department of Physiology, Maulana Azad Medical College, New Delhi. This study was approved by the Institutional ethics committee and no invasive procedure was done on the subjects.

The diagnosis of preeclampsia was done as per the norms of International society of the study of Hypertension in Pregnancy[13], that is systolic BP (SBP) ≥140 mmHg and diastolic BP (DBP) ≥90 mmHg or increase of ≥ 30 mmHg in SBP and increase of ≥15 mmHg in DBP over the pre-pregnancy state. Preeclampsia was diagnosed when any of these criteria was present at least on two occasions separated by an interval of 6 hours along with proteinuria and edema. Proteins in urine of ≥ 300 mg in 24 hours with no incidence of urinary tract infection was considered as criteria for proteinuria.[14]

Inclusion criteria for subjects

- BP ≥ 140/90 mmHg along with proteinuria and edema
- Mild to moderate degree of preeclampsia
- 32-40 gestational week
- Primigravida

Exclusion criteria for subjects

- Any history of essential hypertension, cardiovascular disease, seizures, epilepsy or any psychiatric disease
- Any history of metabolic or endocrinal disorder
- Incidence of urinary tract infection
- Hearing problems

Informed consent was taken from all the patients and controls. All the subjects were given a thorough ENT (ear, nose and throat) checkup to exclude any ear pathology.

Test procedure

EB Neuro machine (Evoked potential measuring system-Galileo NT by Firenze, Italy) was used to record the EREPs. The evoked potentials were recorded as per the guidelines of International Federation of Clinical Neurophysiologists (IFCN).[15] The examination was conducted under uniform conditions on all the subjects. The subjects assumed a comfortable and relaxed position in a standard audiometric, sound proof and air-conditioned room.

The scalp sites were first cleaned with a spirit swab to remove any oil from the skin. The site was then rubbed with an appropriate amount of "Neuprep skin prepping jelly" to abrade the skin for impedance reduction and the site was further cleaned with a dry piece of gauge. Ag/AgCl disc electrodes were affixed with collodion acccording to 10-20 international electrode placement system. The active electrodes were placed on frontal, parietal and central (Fz, Pz and Cz, respectively) sites, reference electrodes on earlobes and ground electrode was placed on forehead.[16] Electrode to skin impedance was kept below 5 Kohms. EREPs were measured by using standard "Odd-ball acoustic paradigm". 200 stimuli were presented to each ear separately. 80% of the tones were frequent or non-target (500 Hz stimuli) and 20% were rare or target (2000 Hz stimuli), randomly received by the patients. The Galileo NT settings were selected so as to filter the evoked responses to frequent and rare stimuli with a band pass of 0.1-20 Hz. The stimulus intensity of 70 dB sound pressure level was delivered binaurally at a rate of 1 Hz.

During the EREPs recording session, subject was instructed to fix her gaze on a particular spot on the ceiling in order to avoid artifacts due to eye movements and improve her concentration and attention to the target stimulus. She was also instructed to concentrate on rare stimuli and count them mentally. 40 responses of rare stimuli were averaged for measurement of different waves of event related potentials like N1, P2, N2, and P3. P3 or P300 wave was identified as the largest negative peak occurring around a latency of 300 ms after the N1-P2 and N2 complex. The latency and amplitude of the waveforms were recorded. P3 also has 2 components: P3a and P3b. Ideally, both the components should be measured but in clinical practice P3 measurements are done by measuring P3 from the point of maximum amplitude or by extrapolating these two to the point of intersection. In this study, we have followed the first method (i.e. from the point stimulus to the point of maximum amplitude of P3) to calculate the latencies for P3.

Statistical analysis of data

Recordings from both the ears were averaged and a mean of them was taken into consideration. Group wise descriptive statistics of parameters were computed as mean and standard deviation (SD). The data obtained from both the preeclamptic as well as normal pregnant females was analyzed for each variable by using unpaired student's *t*-test. $P < 0.05$ was considered significant. Pearson correlation coefficient was also used to assess the correlation of peak latencies or amplitudes of P_3 from FzA_1A_2, CzA_1A_2 and PzA_1A_2 with SBP, DBP or mean arterial pressure (MAP) in preeclamptic patients.

RESULTS

Demographic details of both the groups are depicted in Table 1. The mean ± SD of peak latencies of different components of EREPs that is, N1, P2, N2, P3 in preeclamptic and in normal pregnant females (controls) from 3 different (frontal, central and parietal) sites, are shown in Table 2. Unpaired student's T test on these two groups revealed significant delay in N2 and P3 component waves in preeclamptic females on all the 3 sites as compared to their normal contemporizes. N1 and P2 also showed a slight delay in their latencies but it was not statistically significant.

Mean ± SD of amplitudes of different EREP components in preeclamptic and normal pregnant females are given in Table 3. There was a trend of smaller amplitude of all the components of EREPs in preeclamptic females as compared to normal healthy pregnant females but was not statistically significant. There was no correlation found between latencies and amplitudes of P_3 wave from all the three sites with SBP, DBP or MAP in preeclamptic females during the index pregnancy [Table 4].

Table 1: Demographic details of study and control groups

Parameters	Study group (pregnant females with preeclampsia)	Control group (normal pregnant females)
No. of subjects	20	20
Mean age (years)	29.5±1.92	27.4±0.68
Gestational age (weeks)	31.92±1.48	32.15±1.16
Systolic blood pressure (mmHg)	148.2±3.99	120.8±4.21
Diastolic blood pressure (mmHg)	96.4±4.689	80.6±2.98
Mean arterial pressure (mmHg)	112.67±3.98	95.2±3.6
Proteinuria	≥300 mg/24 hours	Upto 150 mg/24 hours

Table 2: Mean latencies (in msec) of EREP components in females having preeclampsia (subjects) and in normal pregnant females (controls)

Parameters	Preeclampsia group (*n*=20)	Control group (*n*=20)	*P* values
FzA1A2			
N1	112.75±14.26	110.33±15.21	0.695
P2	166.23±12.02	164.42±14.71	0.586
N2	244.40±19.08	223.94±18.00	0.000*
P3	338.90±23.30	308.80±28.67	0.001*
CzA1A2			
N1	111.82±17.10	108.00±17.56	0.667
P2	163.00±11.98	162.77±12.51	0.810
N2	238.78±17.55	220.60±18.49	0.002*
P3	330.85±21.32	309.40±25.82	0.002*
PzA1A2			
N1	109.32±15.87	108.00±12.88	0.724.
P2	162.34±14.00	160.42±13.67	0.533
N2	240.66±16.87	216.31±19.40	0.001*
P3	334.8±24.85	311.30±22.52	0.000*

Data are expressed as mean±SD. *$P \leq 0.05$ were considered statistically significant. FzA1A2: Frontal site, CzA1A2: Central site, PzA1A2: Parietal site

Table 3: Mean amplitudes (in mV) of EREP components in females having preeclampsia (subjects) and in normal pregnant females (controls)

Parameters	Preeclampsia group (*n*=20)	Control group (*n*=20)	*P* values
FzA1A2			
N1	6.72±1.89	7.34±2.00	0.122
P2	3.44±1.20	3.98±1.27	0.455
N2	5.50±1.55	6.32±1.82	0.211
P3	9.26±2.95	10.27±2.97	0.291
CzA1A2			
N1	5.67±1.50	6.88±1.70	0.268
P2	4.60±1.34	5.42±1.61	0.196
N2	4.87±1.42	5.10±1.07	0.388
P3	9.15±3.06	11.10±3.51	0.118
PzA1A2			
N1	4.56±1.41	5.29±1.06	0.267
P2	4.00±0.99	4.75±1.46	0.504
N2	5.21±1.11	5.88±2.02	0.652
P3	9.45±2.64	11.41±3.81	0.070

Data are expressed as mean±SD. $P \leq 0.05$ were considered statistically significant. FzA1A2: Frontal site, CzA1A2: Central site, PzA1A2: Parietal site

DISCUSSION

In the present study, we found a significant delay in the latencies of N_2 and P_3 components of EREPs picked up from all the three sites (FzA_1A_2, CzA_1A_2, and PzA_1A_2) in preeclamptic females compared to the normal pregnant females [Table 2 and Figures 1 and 2]. Slight decrease in amplitudes of all the waves of EREPs in preeclamptic women was also noticed although it was not statistically significant [Table 3 and Figures 1 and 2]. N_2 reflects attention shift, detection of novelty or mismatch to the attended stimuli while P_3 reflects discrimination of stimulus events.[16] The P_3 wave is believed to reflect cognitive processes underlying attention allocation and memory updating evoked by an unexpected stimulus and reflects the updating of working memory. N_2 is a negative going wave just before P_3 which reflects attentional shift, overcoming stereotypical responses and detection of novelty or mismatch to the attended stimuli. P_2 may reflect general neural processes that occur when a sensory input is compared with an internal representation or expectation in memory or language context. N1 may be sensitive to predictability of an auditoy stimulus. Changes occurring during preeclamptic pregnancy may interact with the neural generators of P_3 or N_2 which are located in the frontal, temporal and parietal lobes of cerebral cortex and limbic area such as anterior cingulate cortex and hippocampus.[17] P_3 and N_2 are also often researched together as they both are sensitive to similar manipulations and represent a connection of mental mechanisms that work together to interpret the changing environment.

Table 4: Correlation of latencies and amplitudes of P-3 with SBP, DBP and MAP

	SBP		DBP		MAP	
	r	*P*	*r*	*P*	*r*	*P*
Latencies (msec)						
FzA1A2	0.075	0.752	0.164	0.490	0.204	0.388
CzA1A2	0.096	0.686	0.215	0.363	0.340	0.142
PzA1A2	0.029	0.905	0.034	0.887	0.228	0.334
Amplitudes (mV)						
FzA1A2	0.325	0.140	0.210	0.389	0.221	0.352
CzA1A2	0.289	0.302	0.254	0.327	0.205	0.380
PzA1A2	0.310	0.164	0.225	0.355	0.204	0.384

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, $P \leq 0.05$ were considered statistically significant. FzA1A2: Frontal site, CzA1A2: Central site, PzA1A2: Parietal site

Our findings suggest that discrimination of rare to frequent auditory stimuli was harder and took longer time in preeclamptic females. Shifting attention from one stimulus to other also took longer time. Reduction in amplitudes of EREP waves may suggest a decrease in alertness or attention related to task relevance of eliciting events in these females. P3 amplitude is directly related to the amount of uncertainty that is reduced by a stimulus

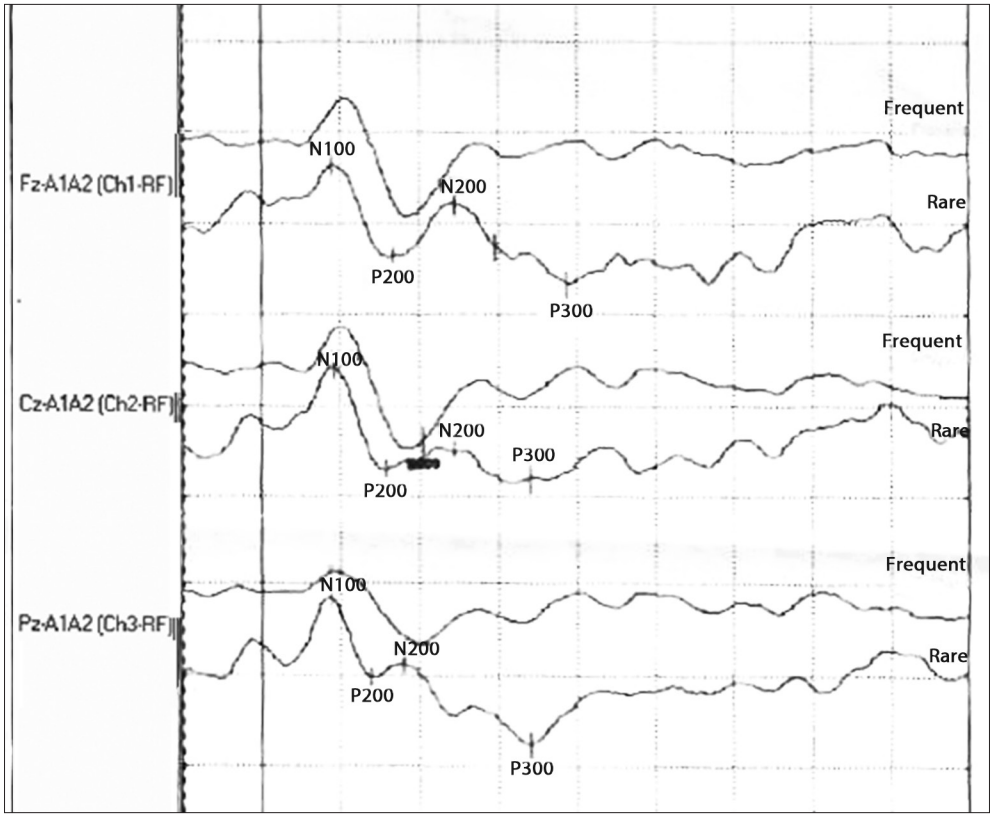

Figure 1: Event related evoked potential recording in preeclamptic patient. FzA1A2: Frontal site, CzA1A2: Central site, PzA1A2: Parietal site

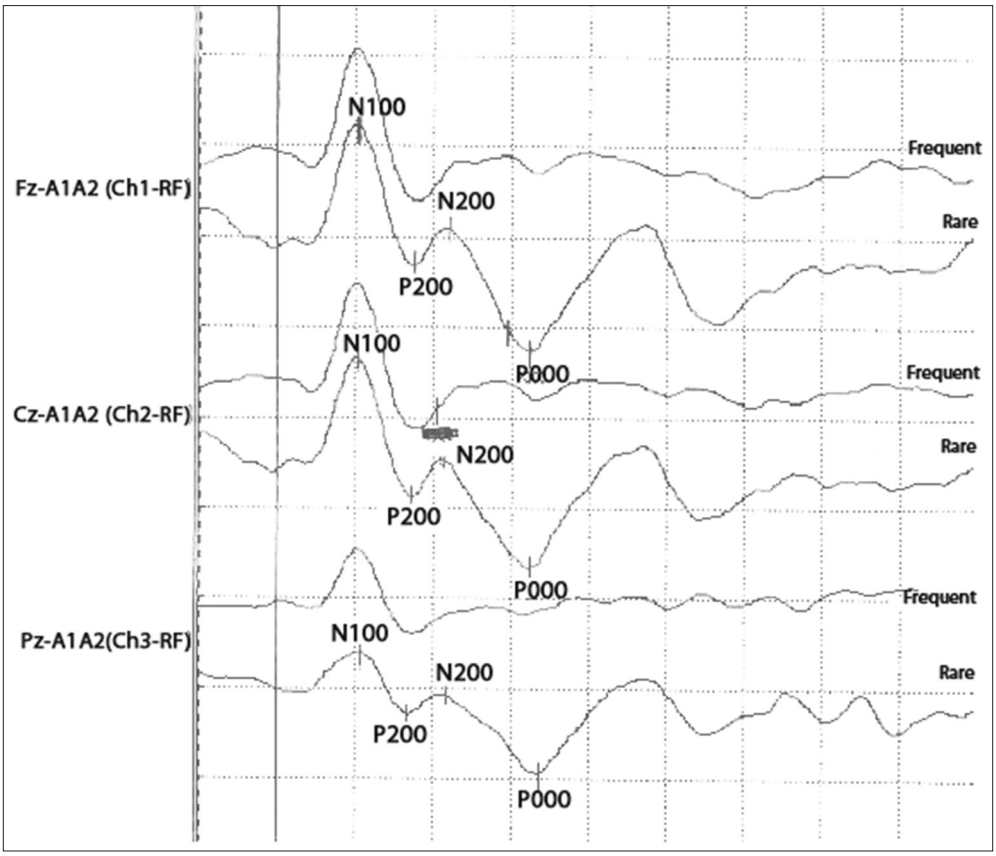

Figure 2: Event related evoked potential recording in healthy pregnant female. FzA1A2: Frontal site, CzA1A2: Central site, PzA1A2: Parietal site

so when the stimulus is harder to discriminate or perceive its amplitude is lower.

Neither latencies nor amplitudes of P_3 wave from all the three sites were found to be correlated with SBP, DBP, or MAP in preeclamptic females in our study [Table 4]. Therefore, cognitive functions in females with preeclampsia are not seemed to be influenced by an increase in BP. Many studies also indicate that pathologic and pathophysiologic changes in preeclamptic women are not secondary to increase in BP.[18] Autopsy findings in women died due to eclampsia were best explained by end organ hypoperfusion rather than by elevated BP.[19] Hypoxia-reperfusion injury also adds to the pathologic change in these patients.[20] However, there are studies showing positive correlation of SBP with P_3 and N_2 latencies in primary hypertensive patients.[21,22] Therefore, the exact interaction between vasomotor mechanisms controlling BP in preeclamptic females and the higher cortical areas concerned with cognitive functions need to be explored.

Preeclampsia is considered as endothelial cell disorder with activation of coagulation cascade and increased sensitivity to pressor agents.[19] Most of the researchers have already documented an increase in the production of various oxidants like superoxide anion, lipid peroxides and thiobarbituric acid reactive substances (TBARS) and decrease in various antioxidants such as Superoxide-desmutase (SOD), catalase and vitamin C and E in preeclamptic maternal blood for the endothelial derangement.[23-25] Thus, preeclampsia is a multisystem disorder whose etiology is also multifactorial and not just high BP.

To the best of our knowledge, this is the first study which documents an early derangement in cognitive functions in preeclamptic pregnancy, using EREP recodings. Cognitive functions start deteriorating from second or third trimester of index pregnancy and continue many years after the delivery although other symptoms of preeclampsia disappear. Hence, we suggest that preeclampsia has a major impact on brain functions, especially on documentation of memory.

Limitations of the study

Due to small sample size (n = 20), multiple regression analysis between P3 and SBP, DBP, or MAP, to link the altered cerebral function without the rise in BP has not been studied. Moreover, due to technical constraints body mass index and assessment of memory loss were not done in these patients and controls.

CONCLUSION

We conclude that cognitive functions deteriorate in preeclamptic pregnancy as compared to normal pregnancy. Though the exact mechanism is not clear, it may be due to a complex interaction of neural generators of EREPs and various structural or functional changes in body caused by preeclampsia. This could be an electrophysiological manifestation of future memory loss in patients having preeclampsia. Further research on a large number of subjects may provide more insight into understanding the cognitive aspects of preeclampsia.

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