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Amplitude and latency of visual evoked potential are un-correlated variables: A revelation from normative laboratory database of eastern India

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ABSTRACT

Aims: To establish normative database and investigate whether VEP amplitude and latency have any correlation between them.

Materials and Methods: Institution based cross-sectional observational study done in Electrophysiology of Vision Laboratory at a tertiary centre in Eastern India. 126 subjects of age group between 20 and 59 years of either sex with best corrected visual acuity 6/6 in both eyes and no other eye ailments (except error of refraction) on examination with informed consent were included. PVEP with pattern reversal stimulus with check element size 1° (60') was recorded with Retimax "Advanced" machine (manufactured by CSO s.r.l., (Firenze) Italy) and standard silver-silver chloride disc electrodes. The test parameters were customized in the machine by the manufacturer and designated to measure the N75-P100 amplitude and P100 latency.

Results: Normative values were established for our laboratory. Only the most reliable parameters for clinically significant alterations of visual pathway i.e. N75-P100 amplitude and P100 latency were included in the analysis. Results of uniocular, age group-wise and gender-wise values were obtained by descriptive statistics as per ISCEV guidelines. No linear co-relationship (ascertained by Spearman's rho Correlation Coefficient) was found between N75-P100 amplitude and P100 latency, in either of the eyes.

Conclusions: PVEP amplitude and latency are uncorrelated variables. To the best of our knowledge, our study was the first study in literature on correlation between amplitude and latency of PVEP.

1. Introduction

Visual evoked potentials (VEPs) are signals extracted from the electroencephalographic activity of the visual cortex in response to visual stimuli. As visual cortex is activated primarily by the central visual field, VEPs depend upon functional integrity of central vision at all level of the visual pathway from eye, retina, optic nerve, optic radiations right up to the occipital cortex.[1] However, the ISCEV standard VEP protocols are defined for a single recording channel with a midline occipital active electrode for assessment of the eye and / or optic nerves anterior to the optic chiasm. Extended, multi-channel protocols are required to evaluate post-chiasmal lesions.[2] VEP testing although primarily an applied tool, may be useful to corroborate findings discovered in basic vision research.

There has been sporadic attempts in literature to segregate retinal and optic nerve elements in abnormal VEP recordings. S Ryan et al. (1988) showed that abnormally long delay in VEP in some cases of diabetic retinopathy was due to retinal disease rather than optic nerve disease.[3] Celesia GG (1986) et al. enumerated in multiple sclerosis patients four types of combination of amplitude and latency changes in concomitantly performed PVEP AND PERG, with corresponding sole or combined damage of retina/optic

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nerve/ ganglion cell (retrograde) / central vision in each type.[4] Deak K et al. (2016) found, for screening of subclinical retinal or optic nerve involvement in diabetic patients, simultaneous use of PVEP and PERG helped them to differentiate abnormal VEPs of purely optic nerve origin from those reflecting retinal involvement.[5] Prescosolido N et al. (2015) recommended that flash and pattern electroretinogram (PERG) should be done to assist PVEP, in order to confirm the existence / co-existence of an involvement of the outer retina and therefore exclude a direct involvement of the optic nerve elements (ganglion cells/ retinal nerve fibre layer/ pre-chiasmatic optic nerve).[6] Therefore interpretation of VEP abnormalities is not straight forward and in this scenario a study of correlation between amplitude and latency of PVEP in normal subjects, which was never done before, may throw some more light to the existing knowledge particularly in relation to investigating whether PVEP reading alone without the aid of PERG can accurately differentiate optic nerve disease from retinal disease.

2. Materials and Methods

This Institution based cross-sectional observational study was conducted in Electrophysiology of vision laboratory at a tertiary centre in Eastern India. Normal volunteers between 20 and 59 years of either sex with best corrected visual acuity of 6/6 in both eyes with informed consent were included in this study. Following were the exclusion criteria

1. Subjects with abnormality detected on ocular examination like fundoscopy using direct ophthalmoscope, field of view using confrontation test and Amsler Grid, color vision using Ishihara color card, 2. Systemic diseases like Diabetes, Thyroid disease, Kidney disease, Epilepsy. 3. History of intracranial neurological disorder. Data collection was done after noting subject particulars, clinical examination to rule out any ocular morbidities and performing pattern VEP on individual subjects. RETIMAX Advance system manufactured by C.S.O srl (Firenze) Italy was used for PVEP examination. Electrodes used in our laboratory were 24 mm adhesive Ag/AgCl electrode with push button which have the advantage of lowest impedance, maximum skin penetrability and best waveform reproducibility. Amplifier, stimulator and acquisition parameters were as follows: Amplifier: Gain-50000, L.P. Filter-30Hz, H.P. Filter-1Hz, Stimulator: Spatial form- Checkerboard, Spatial frequency-9.74 min, Temporal form- Reverse, Temporal frequency-2.00 Hz, Contrast-10%. Distance- 114cm Acquisition: Acquisition Time: 300 ms, Number of Events- 100. Electrode placement:

The scalp electrodes were placed relative to bony landmarks, in proportion to the size of the head according to the International 10/20 system.[7] The active electrode was placed at the highest point of the occiput, which lies over the visual cortex. The reference and ground electrodes were placed at the forehead just above the nasion and vertex respectively. Clinical protocol[8]: PVEP was tested in subjects fitted with standard electrodes and seated comfortably 114 cm from the checkerboard in a quiet dark room. He/she was optimally refracted for the stimulus distance, and with glasses worn he/she would be able to view the centre of the pattern field. No mydriatic was instilled. Monocular stimulation was done at a time with other eye covered with an opaque eye-shield.

Procedure: The recording was done in a dark room with quiet surrounding as stated. Visual stimulation was done with a checkerboard pattern generated on the monitor using the software installed, which consisted of black and white checks whose phase was reversed (black to white and white to black) at a fixed rate of two reversals per second.

3. Results and Analysis

The mean age (mean±s.d.) of study sample was 37.2154± 9.88 yrs. We found that, 37 (29.7%) subjects were between 20-29 years, 31 (24.6%) were between 30-39 years, 50 (39.68%) were between 40-49 years old, and 8 (6.35%) were between 50-59 years.

In our study, 45 (35.71%) subjects were female and 81 (64.29%) patients were male. The study samples were age and sex matched (Tables 1 and 2).

Only the most reliable parameters for clinically significant alterations of visual pathway i.e. N75-P100 amplitude and P100 latency[6] were included in the analysis. Right and left eye data were subjected to Shapiro- Wilk test and found to be non-normal ($P< 0.001$). This finding of our study corroborates with ISCEV guidelines.[2]

Normative values of were found out in all subjects in right and left eyes, and no statistically significant difference in N75-P100 amplitudes was found between the two eyes ($P= 0.900$). But P100 latency showed interocular asymmetry ($P = 0.001$).(Table 3)

Decade-wise age -group based (Table 4) and gender based (Table 5) normative database were also established.

No correlation between N75-P100 amplitude and P100 latency was found in Spearman's rho Correlation Coefficient [Right: $r(124) = .10$, $p=.263$, Left: $r(124) = .06$, $p= .452$].(Table 3).

Values of P100 latency (mSec) were plotted in Y-axis against the values of N75-P100 amplitude (μV) in X-axis for both the eyes. In the graph, the values of latency were found to be distributed in a straight line parallel to x-axis for both the eyes. This implied N75-P100 amplitude of PVEP did not have any linear correlationship with P100 latency. Spearman's rho Correlation Coefficient (r) for Right eye 0 .10, for Left eye 0.06.

Table 1: Showing age groups for both right and left eyes were matched

		Eye No.(%)		Total	p Value	Significance
		Right	Left			
Age (Years)	20-29	37(29.37)	37(29.37)	74(29.37)	1.000	Not Significant
	30-39	31(24.6)	31(24.6)	62(24.6)		
	40-49	50(39.68)	50(39.68)	100(39.68)		
	50-59	8(6.35)	8(6.35)	16(6.35)		
Total		126(100)	126(100)	252(100)		

Table 2: The study sample was sex matched

		Eye No.(%)		Total	p Value	Significance
		Right	Left			
Sex	Female	45(35.71)	45(35.71)	90(35.71)	1.000	Not Significant
	Male	81(64.29)	81(64.29)	162(64.29)		
Total		126(100)	126(100)	252(100)		

Table 3: Normative values of N75-P100 amplitude and P100 latency and correlation between them

Eye (N)	Percentile	Amplitude N75-P100 (μV)	P-value	Latency P100 (mSec)	P-value	Spearman rho Correlation Coefficient between N75-P100 Amplitude and P100 Latency
Right (126)	Q1	8.05	0.900 (Not Statistically significant)	95.51	0.001 (Statistically significant)	0.101(No correlation)
	Median	11.81		98.44		
	Q3	15.32		99.61		
Left (126)	Q1	8.48		97.27		0.068 (No correlation)
	Median	12.64		98.72		
	Q3	14.63		102.54		

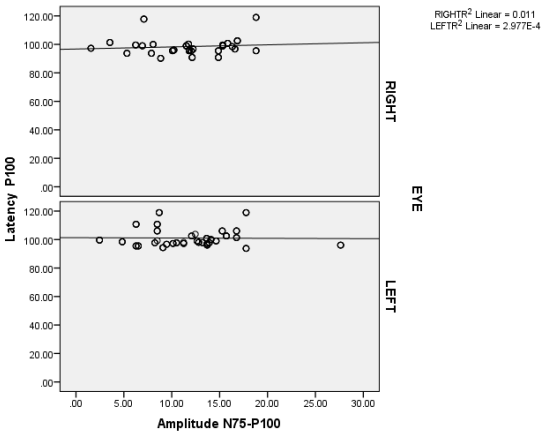

Fig. 1: Values of P100 latency (mSec) were plotted in Y-axis against the values of N75-P100 amplitude (μV) in X-axis for both the eyes. In the graph, the values of latency were found to be distributed in a straight line parallel to x-axis for both the eyes. This implied N75-P100 amplitude of PVEP did not have any linear correlationship with P100 latency. Spearman's rho Correlation Coefficient (r) for Right eye 0 .10, for Left eye 0.06

4. Discussion

In this present study our objective was to establish normative database and investigate whether VEP amplitude and latency have any correlation between them. As a first step to reach our objective, normative values of the two most reliable and clinically relevant parameters i.e. N75-P100 amplitude and P100 latency were found out for our laboratory and compared with other studies.(Table 6)

In our study, the interocular P100 latencies between two eyes of the same individual revealed statistically significant difference. This finding corroborates with studies of Mahjoob et al. (2019)[8] who documented interocular difference in P100 latencies between two eyes. We also found statistically significant left- right asymmetry in latency in females. Therefore, interocular difference of P100 latency of all male-female group might be contributed by female components, as in both instances latency being longer in left eye.

The value N75-P100 amplitude was found to be statistical-significantly higher in male gender in our study.

The difference in results across laboratories could be due to the different machine being used for PVEP in different laboratories, difference in electrodes, sample size, check size,[8] luminance. Also, difference in head circumference,[14] asymmetry of optic nerve length may cause variation in the values of amplitudes and latencies across the globe.

Table 4: Age-group -wise analysis of PVEP parameters

Age-group	Eye	Percentile	Amplitude N75-P100 (μV)	P value	Latency P100 (mSec)	P value
20-29	Right	Q1	9.46	0.254	95.51	0.051
		Median	12.03		98.44	
		Q3	15.32		99.61	
	Left	Q1	11.66		97.27	
		Median	13.70		98.99	
		Q3	15.49		102.52	
30-39	Right	Q1	8.05	0.300	95.51	0.192
		Median	11.81		97.27	
		Q3	15.32		99.61	
	Left	Q1	10.13		96.09	
		Median	13.64		98.02	
		Q3	16.76		101.37	
40-49	Right	Q1	7.68	0.428	95.51	0.017 Statistically significant
		Median	11.75		98.44	
		Q3	15.32		100.00	
	Left	Q1	6.51		97.27	
		Median	9.80		99.32	
		Q3	13.91		106.05	
50-59	Right	Q1	11.59	0.046 Statistically significant	95.51	0.369
		Median	13.55		97.90	
		Q3	15.32		99.02	
	Left	Q1	8.54		96.95	
		Median	9.98		97.80	
		Q3	12.92		101.81	

Table 5: Gender-wise analysis of PVEP parameters

Gender	Eye	Percentile	Amplitude N75-P100 (μV)	P value	Latency P100 (mSec)	P value
Female	Right	Q1	6.23	0.300	95.51	**<0.001** Statistically significant
		Median	11.81		96.09	
		Q3	14.87		99.02	
	Left	Q1	8.36		97.27	
		Median	12.81		98.99	
		Q3	15.70		102.54	
Male	Right	Q1	8.84	0.547	95.51	0.105
		Median	11.81		99.02	
		Q3	15.84		100.49	
	Left	Q1	8.59		97.27	
		Median	12.45		98.44	
		Q3	14.09		103.16	

Table 6: Comparison between values of PVEP parameters of the present study with other studies

Study	Place	Number of eyes	Number of patients/subjects	Latency P100	P value (Latency P100)	Amplitude N75-P100	P value (amplitude N75-P100)
Gregori et al (2006)[9]	England	108	54	89.75±2.32	P<0.001		
Sharma et al (2015)[10]	Patiala	200	100	86±3.32	P<0.001	13.31±5.57	P<0.001
Mahjoob et al (2019)[8]	Iran	118	59	101±7.54	P=0.002	11.56±6.34	P= 0.199
Tandon et al (1997)[11]	Delhi	78	39	99.45±7.89	P=0.433	11.32±2.21	P=0.035
Agrawal et al (2019)[12]	Central India	120	60	98.79±5.75	P=0.015	7.45±1.14	P<0.001
Gupta S et al (2016)[13]	North India	240	120	100.78±2.21	P=0.011	11.34±3.37	P= 0.041
Present study	West Bengal	252	126	99.76±6.29		11.93±4.57	

Next we have compared our mean values with studies done around the world where we have got statistically significant difference with almost all studies- Gregori et al. (2006),[9] Sharma et al. (2015),[10] Mahjoob et al. (2019),[8] Agrawal et al. (2019),[12] Gupta S et al. (2016).[13] However our study results by and large corroborated with that of with Tandon et al. (1997).[11]

The main factor arising in these studies is the head circumference difference[14] which is leading to different values across the globe thus highlighting the racial difference which exists in the PVEP parameters. The values have been demonstrated in the Table 6.

As was discussed above that our primary objective was to see whether there was any correlation between N75-P100 amplitude and P100 latency in the backdrop of our discussion in "Introduction section", that PVEP reading is not straightforward and retino-optic differentiation is difficult from PVEP reading alone without the aid of PERG. Having established our laboratory values, we now looked into our primary objective to find out whether there was any correlation between N75-P100 amplitude and P100 latency. No correlation between N75-P100 amplitude and P100 latency was found in Spearman's rho Correlation Coefficient [Right: r(124) = .10, p=.263, Left: r(124) = .06, p= .452]. (Table 3). This has probably opened up many possibilities of further research as discussed in "Conclusion" section.

The present study established our laboratory's own normative data and was developed as a compliance to ISCEV guidelines.[1,2,15] The other clinical applications of this study might be highly significant. Un-correlated VEP amplitude and latency, both in health (as established in this present study) and in disease (preliminary findings in retinal disease are encouraging)[16] would mean, even minimal threshold level functional retina would be able to elicit full conduction. Therefore, within the ALL range (expressed in amplitude, μV) of functional retina, the conduction (latency, ms) do not change. However, when the retina was severely damaged, amplitude fails to reach threshold level, and NO conduction of electrical potential would take place and VEP would show extinguished response. This is what is known as "All or None" phenomenon of nerve conduction which is to be investigated further.

5. Conclusion

We can conclude from the study that:

1. To the best of our knowledge, this is the first report on normative laboratory database of PVEP from Eastern India.
2. There exists a statistically significant difference in the VEP parameters of different populations around the world. These intracontinental and intercontinental differences can be owing to the difference in head circumference and other anatomical variations which highlight the existence of racial differences.
3. PVEP amplitude and latency are uncorrelated variables.
4. Study outcome that the amplitude and latency are uncorrelated variable is unique in nature and to the best of our knowledge was discovered for the first time in literature. This has probably opened up following possibilities of further research like,
   (a) Whether this independent behavior of amplitude and latency of PVEP might be an expression of 'All or None phenomenon' of nerve tissue conduction.
   (b) Whether differential diagnosis of retinal and optic nerve disorders can be done by performing VEP test only. This may be helpful for those centres who have machine to perform VEP only, not ERG.

6. Source of Funding

None.

7. Conflict of Interest

None.

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