NORMATIVE STUDY OF VISUAL EVOKED POTENTIAL IN DIFFERENT AGE GROUPS

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Abstracts: **Introduction:** Visual evoked potential (VEP) is a useful non-invasive, inexpensive diagnostic tool affected by certain physical and physiological parameters, age being the major of all. However, only few normative studies have been conducted in India. **Materials and Methods:** pattern reversal VEP (PRVEP) was carried out using a standard protocol in 158 subjects (58 females; 100males) in the age range of 1-75 years divided in five age groups. VEP recordings were done in strict accordance to the standardized methodology of IFCN and ISCEV and with RMS EMG EP MK II computerized software at EMG-NCV Lab., Department of Physiology, Govt. Medical College, Bhavnagar. Latencies of various waveforms were calculated and effects of age was studied. **Results:** Observations revealed normative VEP latencies in line with other studies. Difference observed with different age groups **Conclusion:** Normative VEP data of age, showed no ethnic variation.

Key Words: normative, latencies, visual evoked potential, waveforms

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Introduction:

Today, development in computerized devices provides High-quality amplifiers, smaller devices, perfect averaging techniques, multi-channel capability, quality filtration options (digital filter, adaptive filter, spectral analysis etc.), easy recording in any environment (e.g. operating room, bedside, or noisy environments), we can routinly use evoked potential recording in clinics. VEP (Visual Evoked Potential) records the latency and amplitude from different part of visual area. These latency varies with various physiological parameters like age, gender, head circumference, visual acuity, refraction, body temperature, mental activity etc., And technical parameters like type of stimulus, size of checker board, contrast, luminance, frequency of stimulus, type of monitor and also the illumination in room where the test is going on. By controlling these parameters rigidly, a clinical neurophysiology laboratory can obtain reproducible and reliable data of VEP to derive at normal values before using it as a diagnostic tool. VEPs can help in differentiate blindness from malingering and many prechiasmatic conditions[1,2]

In India very few normative data is available. To overcome these deficit in our area (west India) this study was conducted to prepare the normative data for our laboratory which will help us in interpreting various VEP anamalies. This study of VEP in normal subjects of different age groups is to prepare normative values for our Neurophysiology Laboratory in department of physiology, Government Medical College Bhavnagar.

The aims & objectives of this study were: To determine the normal average values of the VEP parameters in different age groups of the population in our area (west side of india). To record the latencies of N75, PI00 and N145, amplitude, inter-peak latencies and inter-ocular differences. Finally, to compare the normative values with other region, and set up a normative baseline data for our laboratory.

Material and Methods:

The present study was carried out at EMG-NCV LAB., Department of Physiology, Govt. Medical College, Bhavnagar, Gujarat, ,with prior approval of Institutional Review Board (IRB).

Sample Size and Subjects:

150 healthy people (male –female) of different age groups (1-75 yrs) were selected according to our inclusion and exclusion criteria. They were divided into 5 age groups of 1-15, 16-25, 26-40, 41-60, and 61-75 years. Each age group were having 30 subjects.

Selection of Subjects:

We selected the normal healthy volunteers from school, staff, medical students, and other who wished to participate in our study. Informed consent was taken. And thorough histories of each subject were taken to exclude any eye pathologies.

Inclusion criteria:

Both male and female subject with Visual acuity at least 6/6 (with or without corrective glasses) with normal pupillary size & reactions and agrees with rules of study.

Exclusion criteria:

History of any major chronic or Traumatic optic nerve/ophthalmic disease or Past history of serious visual problems. Any recent eye medications, cycloplegics prior to the test to be excluded.

Instrument and Method:

The present study was carried out by RMS EMG EP MK II computerized 4 channels instrument. With the help of inbuilt software it analyzes data according to standardize testing protocol. It analyzes the latencies and amplitudes. This machine uses negative up conventions.

The standardized methodology used was as recommended by the International Federation of Clinical Neurophysiology[3] (IFCN) Committee and International Society for Clinical Electrophysiology of Vision (ISCEV). We used prescribed settings by our software to avoid any calculation error by machine.[4]

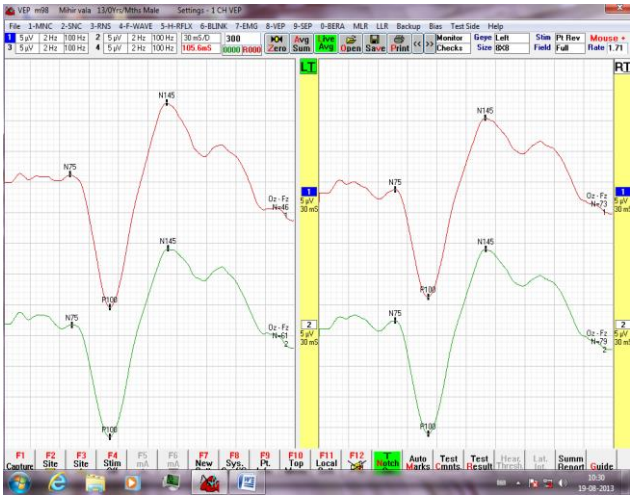
Procedure:

subjects were informed and explained about the procedure with full relaxation and desired co-operation. After the preparation subject has to close one eye with hand without any pressure on the eye and to fix another eye on a small red dot that appears at centre of the screen of the VEP monitor. The subject should avoid blinking or any mental activity to prevent artefacts during the recording. Recording was done in quiet, dimly lightened EMG-NCV Lab., The distance of 100cm was maintained from the screen of the VEP monitor.

Pattern-reversal VEPs are less variable in waveform and timing than the VEPs elicited by other stimuli. So Pattern reversal is the preferred stimulus for most clinical purposes, in which the black and white checker-board pattern is generated in full field and reversed. The fixation of the subjects was controlled by continuously observing the averaging VEP. Thus recording was done monocular for the left and the right eyes separately.

At least two reading for each eye were obtained to ensure reproducibility of the VEP pattern. VEP waveform consists of N75, P100, and N145 peaks. And amplitude of P100 from the preceding N75 peak was measured. The inter-ocular differences in the right eye and left eye stimulation were measured.

Figure: 1



STATISTICAL ANALYSIS:

Data were presented in Mean ± SD format and analyzed by ANNOVA and unpaired t test using Graph pad (trial version) and Microsoft excel 2007.

Result:

In this normative study of VEP there was 158 normal subjects (male and females)in different age groups from 1-75 years and recording was done on 316 eyes.

One symbolic representation of actual recording of VEPs is illustrated in Figure - 1. Recordings on the left of the graph are of the Left eye, and on the right side are of Right eye. Positive wave PI00 is plotted downwards as negative waves, N75 and N145 plotted upwards as positive waves in the graph as machine uses negative up conventions.

Table I : The mean ± SD of the age in years for males, females and total population in each groups.

Parameters Mean±Sd		Group A (1-15, n=35)	Group B (16-25, n=32)	Group C (26-40, n=30)	Group D (41-60, n=30)	Group E (61-75, n=31)
Age (years)	Male	9.75±2.71	19.40±1.96	30.29±3.77	45.74±3.74	67.71±4.74
	Female	10.53±2.85	20.24±1.82	27.67±3.57	49.00±8.00	65.64±4.43
	Total	10.09±2.76	19.84±1.90	29.50±3.85	46.07±4.24	66.77±4.65

Table II: VEP Parameters in Left eye of different Age Groups.

Parameters Mean±Sd		Group A (1-15, n=35)	Group B (16-25, n=32)	Group C (26-40, n=30)	Group D (41-60, n=30)	Group E (61-75, n=31)
N75 Latency (ms)	Male	75.50±7.53	76.80±9.96	77.00±9.78	77.90±9.09	71.41±10.64
	Female	74.58±8.87	77.03±7.64	75.59±6.67	67.38±5.88	74.01±7.71
	Total	75.10±8.02	76.92±8.65	76.58±8.87	76.85±9.31	72.58±9.37
P100 Latency (ms)	Male	106.61±8.61	114.38±5.99	110.76±11.40	108.52±8.29	109.66±10.21
	Female	108.11±9.54	110.72±4.60	107.29±9.81	103.37±11.48	109.63±8.14
	Total	107.25±8.91	112.44±5.53	109.72±10.90	108.01±8.56	109.65±9.18
P145 Latency (ms)	Male	161.45±14.07	160.69±13.35	160.63±8.57	145.91±9.12	158.45±9.24
	Female	161.43±10.65	154.31±14.74	147.02±16.79	141.07±15.89	154.45±9.53
	Total	161.44±12.54	157.30±14.25	156.55±12.99	145.43±9.70	156.64±9.43
P100 (Amp) µv	Male	11.83±8.28	5.75±2.87	5.58±3.62	4.17±2.27	2.62±1.78
	Female	9.51±4.09	6.09±3.46	5.59±3.51	10.31±10.19	4.90±2.31
	Total	10.84±6.82	5.93±3.15	5.58±3.53	4.78±3.91	3.65±2.31
P100 duration (ms)	Male	85.95±18.35	83.89±17.66	83.63±15.53	68.01±12.82	87.04±13.65
	Female	86.85±17.44	77.28±18.91	71.42±19.03	73.68±13.52	80.44±11.44
	Total	86.34±17.71	80.38±18.35	79.97±17.28	68.58±12.77	84.06±12.94

Table III: VEP Parameters in Right eye of different Age Groups.

Parameters Mean±Sd		Group A (1-15, n=35)	Group B (16-25, n=32)	Group C (26-40, n=30)	Group D (41-60, n=30)	Group E (61-75, n=31)
N75 Latency (ms)	Male	75.40±7.67	76.39±9.87	78.11±8.29	76.62±10.14	71.71±9.42
	Female	76.27±7.78	76.02±6.09	73.86±8.33	66.23±5.12	73.80±8.16
	Total	75.77±7.61	76.19±7.95	76.84±8.39	75.58±10.20	72.65±8.79
P100 Latency (ms)	Male	106.20±9.61	114.14±5.62	111.69±11.40	109.60±6.92	112.09±9.43
	Female	108.29±9.00	109.26±7.02	105.36±9.12	103.15±11.11	109.70±8.16
	Total	107.09±9.28	111.55±6.77	109.79±11.01	108.96±7.43	111.01±8.82
P145 Latency (ms)	Male	163.35±17.15	159.30±13.89	160.94±8.33	145.32±8.66	157.77±9.39
	Female	160.51±14.76	156.63±12.79	152.69±16.50	151.45±18.64	156.10±8.61
	Total	162.14±16.00	157.88±13.17	158.47±11.73	145.93±9.73	157.01±8.94
P100 (Amp) µv	Male	12.21±11.88	5.05±2.59	4.91±3.58	3.88±1.82	2.74±1.65
	Female	8.32±3.79	5.53±2.93	4.82±3.52	9.85±9.10	4.81±2.29
	Total	10.55±9.42	5.30±2.74	4.88±3.50	4.48±3.46	3.67±2.19
P100 duration (ms)	Male	87.96±21.82	82.90±17.80	82.83±13.30	68.70±14.75	86.06±15.16
	Female	84.24±19.88	80.61±14.80	78.83±13.98	85.22±14.05	82.30±11.16
	Total	86.36±20.79	81.69±16.04	81.63±13.39	70.35±15.30	84.36±13.42

Table IV: VEP Parameters for Inter ocular differences in different Age Groups.

ParametersMean±Sd		Group A (1-15, n=35)	Group B (16-25, n=32)	Group C (26-40, n=30)	Group D (41-60, n=30)	Group E (61-75, n=31)
N75 Latency (ms)	Male	2.54±2.33	4.21±5.81	4.13±4.89	4.48±6.16	2.92±3.40
	Female	1.97±4.08	4.74±3.73	4.09±4.99	1.15±1.99	2.29±2.62
	Total	2.30±3.16	4.49±4.74	4.12±4.84	4.15±5.94	2.64±3.04
P100 Latency (ms)	Male	1.60±2.76	2.12±2.69	2.55±2.56	3.72±6.83	2.75±6.35
	Female	1.21±1.95	2.94±5.20	3.13±2.93	0.22±0.38	0.73±0.87
	Total	1.43±2.42	2.56±4.17	2.73±2.64	3.37±6.56	1.84±4.78
P145 Latency (ms)	Male	3.53±8.96	4.41±4.91	4.13±3.92	1.47±1.75	2.25±4.61
	Female	2.56±5.42	5.25±5.22	7.46±16.00	11.25±14.67	3.14±5.17
	Total	3.11±7.56	4.86±5.01	5.13±9.14	2.45±5.15	2.65±4.81
P100 (Amp) µv	Male	1.88±3.90	1.10±1.18	0.86±0.92	0.72±0.78	0.44±0.37
	Female	1.26±1.75	1.15±1.13	1.39±1.33	0.71±0.91	0.34±0.38
	Total	1.61±3.14	1.13±1.14	1.02±1.06	0.72±0.78	0.39±0.37
P100 duration (ms)	Male	5.38±10.00	7.93±6.35	6.41±5.86	4.66±5.83	3.89±4.94
	Female	4.24±6.14	7.67±6.60	9.41±15.95	12.40±13.98	3.01±3.90
	Total	4.89±8.47	7.79±6.38	7.31±9.79	5.44±7.04	3.49±4.45

Table V: Comparison of various VEP parameters between different age Groups.

Comparison	N75	P100	N145	P100 amp	P100 duration
A vs B	P>0.05	P>0.05	P>0.05	P<0.001	P>0.05
Avs C	P>0.05	P>0.05	P>0.05	P<0.001	P>0.05
A vs D	P>0.05	P>0.05	P<0.001	P<0.001	P<0.001
A vs E	P>0.05	P>0.05	P>0.05	P<0.001	P>0.05
B vs C	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
B vs D	P>0.05	P>0.05	P<0.001	P>0.05	P<0.05
B vs E	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05
C vs D	P>0.05	P>0.05	P<0.01	P>0.05	P<0.05
C vs E	P>0.05	P>0 05	P>0.05	P>0.05	P>0.05
D vs E	P>0.05	P>0.05	P<0.01	P>0.05	P<0.01

Tables II, III and IV shows mean ± SD of the absolute latencies of positive wave P100 and the negative waves N75 & N145 and P100 amplitude which is measured from the peak of N75 to the trough of P100 (N75-P100) and its duration (inter-peak latency) between the peaks of N75 and N145 (N75-N145) in each eyes recordings along with their inter-ocular differences that were recorded in males and females in each for Group A, B, C, D and E.

Fig. 2: Mean latencies of P100 in Age Groups

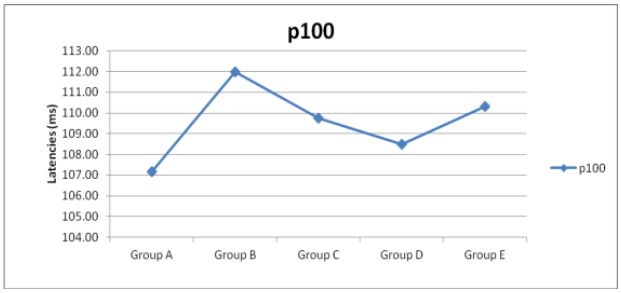
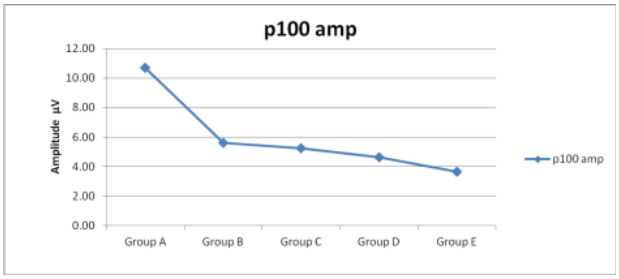


Fig. 3: P100 amplitude in Age Groups.



Discussion:

As VEP is a valuable tool to document subclinical especially pre-chiasmatic lesions of the central visual pathway and optic nerve. In case of multiple sclerosis even in era of MRI and CT-Scan VEP is useful tool. VEP latencies and amplitude (clinically important P100) component are dependents on the effects of various parameters of stimulation and recording. So it is necessary for each laboratory to establish its own normative values using its own stimulus and recording parameters. Further, Adult data cannot be generalized to pediatric or elderly populations.

For preparing a normal data for the laboratory, all possible sources of variation like, subject parameters, (age, gender, head circumference, etc.,) stimuli parameters, (check size, pattern reversal rate, luminance, contrast etc.,) and other factors like distance of the eye from the monitor, pupil size, visual acuity & state of the refraction of the subject and the montages used in the recording. All these parameters are to be rigidly controlled for a normative study. We tried our level best to maintain uniformity in present study.

The present study shows that the age-related changes in the VEPs are not uniform and full of complexities. This-is in accordance with the findings reported by other workers. Most of them have emphasized on the major positive wave P100 only. In the present study, we tried to analyze all the components.

Latency: The present study shows that there are certain age related changes in the latencies of all the three waveforms. We can see changes in N75, P100 and N145 with variations in age, out of these P100 latency is more useful. In present study we can see from childhood it increase with developmental age(107.17 to 111.99) and there after it slightly decreases (109.76 to 108.48) but in elderly people after 60 years of age it again increases(108.48 to 110.33). This can be explained by the gradual lengthening of the visual pathway with the growth of the child and increase in the head circumference Larsen JS [5]. There is change in mean of head circumference increases from Group A to Group B (50.43 to 57.47cm) thereafter it remains almost same. Latency also stabilizes in between age 25-60. After 60 years, it shows gradual prolongation may be explained by degenerative changes of aging. These findings are in line with those reported by previous workers.[6,7]

The mean latencies of the negative waves N75 and N145 as well as their inter-peak latency that gives the duration of P100 also show definite changes with age. As observed for P100, all three parameters increase from childhood till around 25 years of age and stabilize between 25 to 60 and again increase in later age. The changes in N145 latency and P100-duration appear to resemble each other closely. Both show high latencies in childhood and elderly age.

The changes in latency can be explained by study done by different researcher as follows:

Allison T et al[8] assumed that latency changes are a valid measure of the speed of axonal and synaptic conduction and the rise time of post synaptic potentials in sensory pathways and cortex. A decrease in latency with age reflects increasing conduction velocity or maturation of the nervous system. An increase in the latency with age reflects a decrease in conduction velocity or degenerative processes associated with aging. In growing children increase in latency probably reflect increase in length of the conduction pathway. Plonsey, 1969[9] suggested Impedance of the body is mainly resistive and changes with age in the conductive media surrounding the nervous system likely do not produce artifactual changes in latency. Balazsi AG et al, 1984[10]; Wisniewski and Terry, 1976[11] reported aging changes in the human brain particularly in the calcarine fissure and optic nerve & visual pathways like axonal dystrophy. Demyelination and defective myelin regeneration in the aging brain which may thereby reduce the conduction velocity in the visual pathways.' Vrabec F, 1965[12] reported degeneration of the retinal ganglion cells with increased deposit of lipofuscin and agyrophilic granules in the cell body, loss of dendrites and tortuosity of dendrites. McGeer, DI. and McGeer,P.1976[13]; Samorajaski T, 1977[14,] suggested a deranged metabolism and function of neurotransmitter in the aging brain leading to an increased synaptic delay. Ordy JM and Brizzee KR, 1979[15], and Devaney KO and Johnson, H.A,1980[16]. reported an age-related neuronal loss in the lateral geniculate and striate cortex.' Samuel et al, 1983[17] showed that vascular and biochemical changes

occurring in the elderly brain which may adversely affect various processing in the CNS.

Amplitude: The present study found a inverse relationship between age and the amplitude of P100. The maximum amplitude is found in the Group A(1-15yrs) with a mean of 10.69±8.03µV. It then shows a marked reduction of almost 50% to around 5 µV ($p<0.001$) and stabilizes till around 60 years alter which it again declines gradually to around 3.66 ± 2.66 µV in the 60-75 years Group E. The mean P100 amplitude observed here in present study (6.10±5.26 µV), is however in close agreement with those reported by O.P.Tandon [18] that is 6.53±2.44 µV. This changes in amplitude can be attributed to, At early age when neuronal density is highest in the human visual cortex, at 25-60 it reaches to adult level mental performance and in older ages due to degenerative changes in brain.

Nicholas R. Galloway[19] and Robert E.Dustman et al[20] in two different study observed the same age related changes in P100 amplitude as in present study. study was done separately on Flash VEP in 215 normal subjects(lmth-81 years) in 1969 and pattern VEP in 137 normal subjects (4-90 years) in1981. Robert Dustman et al[20] reported that the mean amplitude increased markedly from infancy to ages 5-6years followed by a rapid decline in amplitude until ages 13-14 and the amplitude in 5-6 year old was generally twice that of most adults. It stabilises from 15 years onwards but tended to decrease in older age groups. The high amplitude seen in children-may be due to activity of the brain from the occipital and central scalp reflecting more excitation and less inhibition in young adults. Due to lower levels of catecholamine, inhibitory function is reportedly reduced in children..

Inter-Ocular Asymmetry: The mean variation of Left- Right Differences/inter-ocular differences for N75 latency are 3.51ms, P100latency 2.35ms and for N145 latency 3.63. In the case of P100 amplitude, mean of inter-ocular difference was 0.99 µV while in case of P100 duration (inter-peak latency), it was 5.77 ms. The inter-ocular can be attributed to small differences in visual acuity, dominance of eye or changes in the alertness and eye movement and during the recording. These differences are small and should not affect the diagnosis.

Assclman ct al[21]**;** Halliday[22], suggested intraocular amplitude and peak latency analysis increases the sensitivity of the VEP to monocular diseases since each patient serves as his own control and may reveal abnormality not demonstrated by analysis of peak or inter-peak latency. **S**eyal, M et al[23], reported the disparities between the dominant and the non-dominant eyes seems to be the presence of lateralization in the Central Nervous System. Kurotwa Y et al[24], neuro-anatomic asymmetries of the human striate cortex. However, these differences in latencies and amplitude are small and should not affect the interpretation of VEPs obtained for clinical diagnostic purposes.

Most of observations in various VEP studies are of opinion that the relationships between VEP latency and age were more complex. Failure to take age and sex into account will thus have substantial effects on false-positive and false-negative rates.

Summary:

The present study shows that P100 latency-undergoes a gradual shortening from early childhood towards adulthood and then gradually increases with advancing age with a significant prolongation after 60 years of age. The P100 amplitude abruptly reduces to almost half the childhood value at around 15-16 years of age, remaining almost stable up to around 60 years after which it again shows a gradual reduction in the geriatric age group. Longer P100 latency in youngest subjects may be accounted for by the incomplete development of the brain, especially the association areas, ganglion cells of the retina and incomplete myelination of the optic nerve. Those in older subjects may be due to age related degenerative changes.

VEP could be a useful tool in determining the maturity of the CNS in children, checking the integrity and anomaly of the visual pathway at any age with standardized normal value for particular laboratory. Few Indian studies are also available (Tandon OP and Sharma KN, 1989[18]; Misra and Kalita, 1999[25]; Jayshree P 2008[26]) covering various age groups. Present study reflects normative values in western part of India and particularly for our laboratory.

Most available data are based on western subjects with very few on Indians The anthropometric

parameters and the rate of aging may be different in the western and Indian subjects so it is difficult to use same data. Thus it is necessary to establish a normative data in this part of the country to generate a baseline data for interpreting the various VEP**.**

The values of VEP parameter (especially P100 latency and amplitude) in present study were comparable to VEP studies done in other regions.

Limitations: The test is relatively inexpensive and reliable, but even larger sample size and strict adherence to stimuli and recording protocol can make the test more useful. It will always remain one of the simple, valuable tests to diagnose anomaly of the visual pathway at any age provided that one has a predetermined normative data.

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