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Visual and Brainstem Auditory Evoked Potentials in Neurology

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1. Introduction

Historically, Richard Caton (1875) discovered evoked potentials and the electroencephalogram (EEG) at the same time. The evoked potentials provided a useful tool for neurophysiological research (Shagass, 1976).

Evoked potentials are the voltage changes generated in the brain, the sense organ and the pathway leading to the brain in response to an external stimulus. This stimulus has to be somewhat above its subjective detection threshold so as to be clearly discernible, as well as to be of abrupt onset and /or offset so, that discrete volley is set up in the afferent pathway, hence capable of eliciting distinct cortical potential changes (Kriss, 1980).

Chiappa et al., 1987 defined an evoked potential as the record of the electrical activity produced by groups of neurons within the spinal cord, brain stem, thalamus or cerebral hemispheres following stimulation of one or another specific system by means of visual, auditory, or somatosensory input.

EEG recording may be obtained in a relatively direct manner by amplifying and displaying the activity picked up by electrodes placed on the scalp (Shagass, 1976), but most evoked potential (EP) activity due to their low amplitude, 0.1-20 microvolts relative to the normal background activity of EEG, their activity can not be clearly displayed, however with the development of micro-computers in the seventies (special signal averaging process) helping the extraction of the evoked potential from the EEG activity which is of much greater amplitude leading to their widespread clinical use (Kimura, 1985).

2. Visual evoked potentials (VEPs)

2.1 Introduction

The visual evoked potentials (VEPs) result from change of brain activity following application of intermittent visual stimulus to the visual system. They provide a quantitative measure of the functional integrity of the visual pathways (Celesia, 1988). The function measured includes that of the optic nerve, through the optic chiasma and tract, to the lateral geniculate bodies and the geniculocalcarine projection to the visual cortex "area 17" (Yiannikas and Walsh, 1983).

Since the VEP measures the pathway from the retina to area 17, a normal P100 does not exclude lesions of the visual pathway beyond area 17. For this reason, the VEP may be normal in patients with the diagnosis of cortical blindness. The usefulness of VEP is limited in

malingering and hysterical visual loss (Bodis-Wollner et al., 1977). It is useful when a normal VEP is recorded, but abnormal responses are of limited diagnostic value in such cases.
The most important fact to consider is that, although the axons from the nasal half of the retina decussate at the optic chiasm, the temporal axons do not. Therefore, retrochiasmatic lesions may not be detected by full-field checkerboard stimulation. VEPs are most useful in testing optic nerve function and less useful in postchiasmatic disorders. In retrochiasmatic lesions, the MRI is a more useful test. Partial-field studies may be useful in retrochiasmatic lesions; however, they are not performed routinely in clinical settings (Chiappa, 1990).
Recordings of this evoked potential are recognized as a reliable diagnostic procedure in the investigation of lesions of the anterior visual pathway (Halliday et al., 1976). However, it is not specific with regard to etiology. A tumor compressing the optic nerve, an ischemic disturbance, or a demyelinating disease may cause delay in the P100; only additional clinical history and, often, MRI are needed to uncover the etiology (Leslie et al., 2002).

2.2 Normal components of pattern reversal visual evoked potential (PRVEP) (Figure 1)

The cerebral pattern reversal evoked potential to full field stimulation consists of three peaks in normal subjects. The peak polarities are negative, positive and negative (NPN) and the mean peak latencies are 70, 100 and 145 milliseconds (msec) respectively. The first negative wave (N1 or N70) may be difficult to identify in some normal subjects and many patients likewise, the second negative peak (N2 or N145) is too inconsistent in latency and amplitude to be of clinical value. Thus, waveform identification in the pattern shift visual evoked potential consists of the large positive peak (P1 or P100). Depending on the stimulating device in use, and the presence or absence of abnormalities, it may be found any where from 90 to 250 msec (chiappa, 1982).

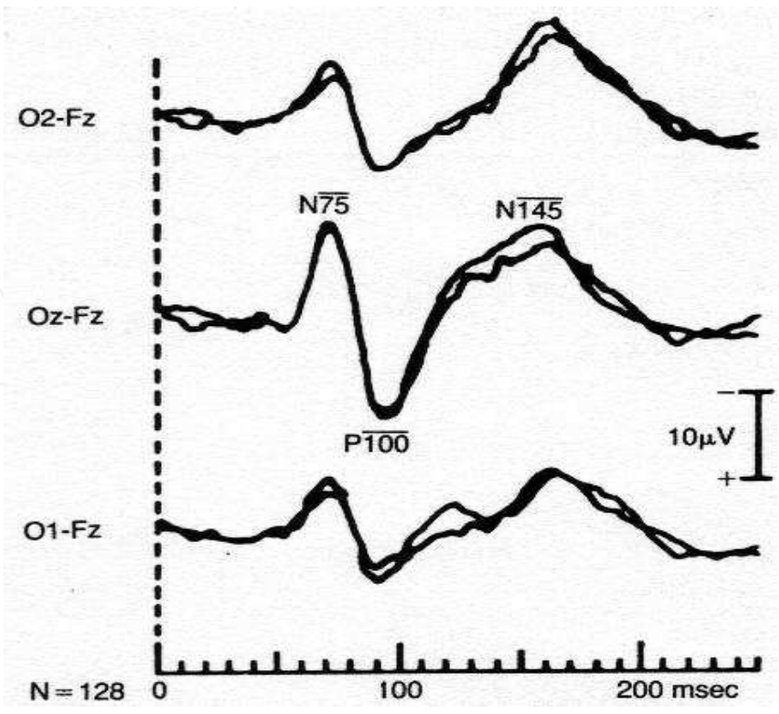

Fig. 1. Normal Visual Evoked Potential (VEP) (Poon's, 2003a).

	Latency (msec.)	R-L Difference	Amplitude (μV)	R-L Difference
N70	71.1 (<81.8)	9.4	3.8 (>0.1)	5.1
P100	95.8 (<112.0)	9.3	10.1 (>1.8)	7.0
Steady state P1	95.5 (<118.1)	21.0	8.3 (>6.1)	6.1

Table 1. Visual Evoked Potential Normative Data From Celesia (1985).

	Full field VEP			
	Mean	**Range**	**SD**	**Mean + 3 SD**
P100 latency	102.3 msec.	89-114	5.1	117.6
L-R difference	1.3 msec.	0-6	2.0	7.3
P100 amplitude	10.1 uV	3-21	4.2	22.7
P100 amp. Diff.	1.6 uV	0-5.5	1.4	5.8

Table 2. Visual Evoked Potential Normative Data From Chiappa (1990).

Check size	**VEP Check Size Effects**						
	Latency (msec.)				**Amplitude (uV)**		
	Latency Mean (SD) (Range)	**Latency ULN**	**L-R Diff Mean (SD) (Range)**	**L-R Diff ULN**	**Amplitude Mean (SD) (Range)**	**L-R Diff Mean (SD) (Range)**	**L-R Diff ULN**
17"	106.8 (6.4) (96.7-128.8)	126.0	2.73 (2.32) (0-8.80)	9.7	8.34 (3.71) (1.6-18.7)	1.48 (1.19) (0.2-5.2)	5.1
35"	102.9 (7.4) (88.6-121.4)	125.1	2.53 (2.91) (0-13.4)	11.3	7.13 (3.68) (1.0-19.8)	1.69 (2.00) (0-8.6)	7.7
70"	103.8 (6.9) (88.2-122.5)	124.5	2.18 (2.59) (0-12.7)	10.0	7.95 (3.64) (1.8-19.8)	1.29 (1.16) (0-4.8)	4.8
144"	107.3 (8.8) (91.1-130.6)	133.7	2.44 (2.55) (0-12)	10.1	7.72 (2.95) (1.5-16.1)	1.36 (1.22) (0-5.4)	5.0
288"	113.5 (11.8) (91.4 -142)	148.9	3.95 (4.03) (0 -15.2)	16.0	7.31 (2.74) (2.6 -14)	1.10 (1.05) (0 -3.9)	4.3

ULN = Upper Limit of Normal (Mean + 3 SD) *(Chiappa, 1990).*

Table 3. Check size 25.8" *(Chiappa, 1990)*.

P100 is usually seen in all normal subjects and has a variability small enough to make it reliable in clinical practice, in addition to measuring the absolute latency of P100, determining the inter-ocular latency difference, amplitude, inter-ocular amplitude difference ratio and duration of P100 has increased the diagnostic yield of the test (chiappa, 1983).

The "W" morphology is most often an individual variation, although decreasing the stimulation frequency from 2 Hz to 1 Hz usually converts the W shape into a conventional P100 peak. Check size and alternation rate are factors in this; the responses can be manipulated to a "W" or a conventional P100 response by changing these parameters. Large checks tend to produce VEPs similar to those produced by flash stimulation (Leslie et al., 2002).

Blumhardt and Halliday, (1979) noted that the ipsilateral hemisphere evoked potential was actually a series of waves with negative components preceding and following P100 wave at latencies of approximately 75, 145 msec respectively. The contralateral hemisphere response consists of a triphasic complex occurring synchronously but of opposite polarity with a major negativity at about 100 msec and smaller positive deflections at 75 and 145 msec.
Maximum value for P100 is 115 msec in patients younger than 60 years; it rises to 120 msec thereafter in females and 125 msec in males. Even though published norms are available in the medical literature, each individual laboratory should have its own norms to control for lab-to-lab variability in technique **(Leslie et al., 2002).**

2.3 Generator source of pattern reversal visual evoked potential (PRVEP)

In relation to the generator sources of PRVEP Chiappa,(1983) claimed that P100 is generated in the striate and pre-striate occipital cortex as a result of both primary activation and subsequent thalamocortical volleys. However, the exact sources of P100 are not well defined. Positron tomographic mapping of human cerebral metabolism during reversal checkerboard stimulation revealed strong activation of both primary and association visual cortical areas (Phelps et at., 1981).
Ikeda et al., 1998 studied generators of VEP by dipole tracing in the human occipital cortex. Current source generators (dipoles) of human VEP to pattern-onset stimuli were investigated. A visual stimulus, a checkerboard pattern, was presented for 250 ms in each of the 8 quadrants. Central and peripheral parts of each of the 4 quadrant fields were evaluated. The results from these analyses of VEP indicated topographic localization of the dipoles around the calcarine fissure.

2.4 Principles of recording of VEP

2.4.1 Technical details (Leslie et al., 2002)

Dark room; Patient seated 70-100 cm from the screen; Corrective lenses used if necessary (acuity check prior to commencement of VEP); Pupil size and any abnormality should be noted(The pupils should not be dilated by mydriatics to prevent interference with accommodation); Sedation should not be used, and note should be taken of medications that the patient is taking regularly; Checkerboard pattern is used as stimulation; Check size of approximately 30 seconds of visual angle; Contrast between 50-80 percent; Stimulus rates of 1-2 Hz are recommended (producing a reversal every 500 msec); Filter setting should be 1 to 200 Hz bandwidth (outside limit is 0.2-300 Hz); The recommended recording time window (i.e. sweep length) is 250 ms; 50-200 responses are to be averaged; A minimum of 2 trials should be given.

2.4.2 Stimulation procedures

There are two general types of visual stimuli that are most often used to elicit visual evoked potential. These are the un-patterned flashing lights and the patterned stimuli which in clinical laboratories are usually checkerboards (Sokol, 1980).
Unpatterned flashing stimuli can be produced with a photo stimulator similar to that used in EEG recordings for photic driving. The intensity, color and rate of stimulation of the flash light can be varied. But, the variability in amplitude and latency of the evoked potential is much greater than in patterned stimuli (Halliday, 1982).
Patterned stimuli can be presented in three ways. These are the flashing patterned stimulus, the pattern onset, offset and the pattern reversal. A flashing patterned stimulus is produced

by placing a photo stimulator behind a large photographic transparency of black and white checks (Harter and White, 1968). In pattern onset, offset the checks appear for discrete amount of time (500 msec) and then disappear. While, in the pattern reversal stimulation, checks are visible all the time. In order to maintain a constant luminance level, one half of the checks increases in luminance, while the other half decreases. This can be accomplished electronically by using T.V. monitor to generate the checks (Arden et al., 1977b).
Checkerboard pattern reversal are the most frequently used stimuli in clinical investigations of the visual pathway as they evoke relatively large potentials (Halliday et al.,1987 and Chiappa, 1988) with variability in latency less than in flash stimuli and it is more sensitive to the presence of conduction defects in the visual pathway (Chiappa, 1982). The fovea is estimated to generate 65% of the pattern-reversal response; flash stimuli, in contrast, tend to generate response from the peripheral retina as well. The insensitivity of flash VEPs, particularly in retrochiasmatic lesions, has been based on diagnostic studies in which patient recordings must differ from normative population data by 2 standard deviations (SDs) to be considered abnormal (Berson, 1994).

Characteristics of pattern reversal stimulation

Erwin, 1980 outlined seven basic characteristics of pattern-reversal stimulation:
1-The rate of pattern-reversal is the number of times that the pattern changes within a second. The direction of pattern reversal is not considered since usually all the pattern reversal responses are averaged together. 2-The reversal time is the total time taken to change from one pattern to its opposite. 3-Stimulus luminance is an essential attribute for visual stimulus. 4-The type of the pattern is obviously important. The most commonly used stimulus is a checkerboard. 5-Vertical-horizontal orientation of the pattern evokes larger responses than oblique orientation. 6-The size of the pattern elements can be described in two ways. The visual angle subtended by each element can be measured. As well, the spatial frequency (the number of intensity cycles through light and dark per degree of visual field) can be used. Another aspect of the stimulus related to the spatial extent of the pattern elements is the spatial rate of luminance change. 7-Two of the most important aspects of the stimulus are its field size and relationship to fixation.

2.4.3 Electrode montage

Responses are collected over Oz, O1, and O2 and with hemifield studies at T5 and T6 electrodes using the standard EEG electrode placement. Scalp electrodes are positioned as follows:

a. Electrode number one: 5 cms above the inion posteriorly in the middle line (Oz).
b. Electrodes number two and three: 5 cms lateral on either side of electrode one (O1, O2).
c. Two additional electrodes: 10 cms away on each side from the middle electrode (T5, T6). Optional to be used in hemifield studies.
d. Reference electrode: is usually FZ. (e) Ground electrode: over the ear lobule (Halliday, 1982).

Both eyes are tested at first, then each eye is tested at a time, (while the other is covered with an eye patch) to avoid masking of a unilateral conduction abnormality. The subject is instructed to gaze at a dot in the center of the pattern during display. The pattern stimulator is operated at about two reversals per second. Patient having field defects or amblyopia may shift their center of gaze into the good visual field. So in order to offset this, a 1˚ to 2˚ blank strip may be inserted on either side of the fixation point during partial field stimulation (Chiappa, 1983).

2.4.4 Interpretation

Abnormalities of VEPs have been described in many disorders of the optic nerve, chiasma and retrochiasmatic visual pathways. The VEP is considered abnormal when the latency of P100 wave is outside the boundaries established for normals, or the P100 is absent. The most frequent abnormality is characterized by normal amplitude but prolonged latency of N70 and P100, but a prolonged latency may sometimes be associated with decreased amplitude. The most sever abnormality is an absent VEP (Celesia and Tobimatsu, 1990).

Monocular VEP abnormality

This abnormality suggests a conduction defect in the left/right visual pathway anterior to the optic chiasm. Although demyelinating disease is the most common aetiology for such a finding, various other possibilities cannot be excluded e.g. retinal disease and compressive lesions of the optic nerve (Poon's, 2003a).

In patients with small monocular delays in N70 and P100, it is useful to look at the intereye latency difference. A latency difference between the two eyes greater than 10 msec is clearly indicative of pathology on the side with the longer latency (Celesia and Tobimatsu, 1990).

Binocular VEP abnormality

These abnormalities suggest conduction defects in the visual pathways bilaterally. However, because of the binocular nature of the findings, the lesion location (retina, optic nerve, tracts or radiations) cannot be determined (Poon's, 2003a).

2.4.5 Pitfalls

Check size of 27 seconds of visual angle may result in normal P100 latency in a patient with cortical blindness; smaller checks (i.e. 20 seconds of visual angle or less) should be used to demonstrate the abnormality. If cortical blindness is suspected, large checks should not be used (Bodis-Wollner, 1977).

In conditions such as retinal disease or refractory errors, the amplitude may be smaller and, at very small check sizes, the latency may increase. For this reason proper refraction is of great importance (Chiappa, 1990).

2.5 Factors affecting VEP

Factors which affect VEP are either technical and / or subject factors.

2.5.1 Technical factors

2.5.1.1 Screen luminance

A decrease in brightness results in delaying P100 i.e. increase in its latency (Halliday et al., 1973). Stochard et al., 1979 showed that the pupillary diameter has an effect on retinal illumination and thus also on P100 latency.

2.5.1.2 Degree of contrast

Reduction in the degree of contrast between the black and white squares of checkerboard pattern increases P100 latency and reduces the amplitude (Mackay and Jeffreys, 1973).

2.5.1.3 Size of the stimulating pattern

A decrease of the size of the stimulating pattern (degree of visual angle) results in a reduction of the amplitude of the response (Asselman et al., 1975).

2.5.1.4 Check size

Smaller checks give the highest amplitude responses (Leserve and Romand, 1972).

2.5.1.5 Electrode placement

Ipata et al., 1997 assessed interhemispheric visual transfer of information in humans. Estimates of interhemispheric transfer time ranged between 5.77 and 12.54 msec, depending upon the type of component and the location of the electrode sites. More anterior locations yielded shorter values and overall transfer time tended to be 7 msec shorter for the N70 component than for the P100 component.

2.5.1.6 Stimulus rate

When the rate of pattern reversal is increased, changes in P100 latency is noticed. Increasing the rate beyond 8 per second transforms the evoked responses into a steady state evoked potential (a long train of repetitive wave with a sinusoidal appearance) (Stockord et al., 1979).

2.5.2 Subject factors

2.5.2.1 Age

There is an increase in the latency for subjects of ages starting from the end of the second decade onwards. This increase amounts to 2 msec per decade (Celesia and Daly, 1977). However, Stochard et al., 1979 found no change in P100 latency for subjects of age until the fifth decade. Then, the latency increases at a rate of 2 msec per decade.

2.5.2.2 Sex

Females have usually shorter P100 latency than males. This may be due to difference in the head size (Stockard et al., 1979). However, Shearer and Dustman, (1980) reported no such difference.

2.5.2.3 Visual acuity

Changes in visual acuity markedly affect P100 amplitude. In visual acuity lower than 6 / 18, no latency changes is observed but the amplitude is reduced (Fitzgerald et al., 1980). Diminution of visual acuity has a greater effect on latency using smaller checks (giving visual angle 12) than larger checks (giving visual angle 48). (Sokol et al., 1981).

2.5.2.4 Body temperature

No significant change in P100 latency results by raising body temperature in normals (Matthews et al., 1979). Also, little effect on P100 latency is noticed in patients having multiple sclerosis.

2.5.2.5 Physiological changes of serum glucose level

Sannita et al., 1995 evaluated the correlation between amplitude and latencies of the pattern-reversal VEP and serum glucose level in healthy volunteers. Pattern VEP and serum glucose levels were obtained at 2-hour intervals during an 8-hour experimental session. At serum glucose concentrations within the physiological range of variability (55-103 mg/dL), the P100 latency increased with increasing serum glucose level, with a 6.9% estimated latency difference between lower and higher glucose concentrations.

2.5.2.6 Medications

2.5.2.6.1 Carbamazepine

Certain drugs, such as carbamazepine, prolong VEPs. The effects of carbamazepine monotherapy on VEPs were studied in epileptic children by Yuksel et al., 1995. Pattern-reversal VEPs were determined before administration of the antiepileptic drugs and after 1 year of therapy. The VEP amplitude showed no consistent changes after 1 year of therapy, but VEP P100 latencies were significantly prolonged after 1 year of carbamazepine therapy. The conclusion was that carbamazepine slows down central impulse conduction.

2.5.2.6.2 Lithium

Previous reports in the literature have suggested that lithium medication does not affect the VEP to flash stimulation. It was predicted that this would not be true for pattern reversal stimulation. Seven patients had their pattern evoked potential measured using a 42' check to fractional pattern displacement of 1/4, 1/2, 3/4 and Full Square. The VEP was measured before, 1 week after and 5 weeks after the commencement of lithium medication. The results show that there is a significant increase in both the N70-P100 and P100-N145 amplitudes when the 'before lithium' sessions are compared to 'after lithium.' Seven normal subjects matched for the age and sex of the patient group were tested twice, once as a 'control' and a further 5 weeks after this. No significant differences were found in the 'control' sessions between patient and normal groups although a significant difference in both the N70-P100 and P100-N145 amplitude after the treatment of the patient group with lithium was found (Fenwick and Robertson, 1983).

2.5.2.6.3 Levodopa

Pattern visual evoked potentials (PVEPs) were recorded at three luminance levels and five different check sizes in a group of 16 control subjects before and after the oral administration of levodopa. At the lower luminance levels, significant decrease in PVEP latencies were found. For PVEPs the latency changes occurred only at small check sizes. No changes were observed in control experiments without levodopa administration. These results are in agreement with a VEP delay found in Parkinson's disease and with a VEP latency increase in rats after dopamine depletion (Gottlob et al., 1989).

2.6 Clinical applications of VEP

Clinical usefulness of VEPs includes the following

- More sensitive than MRI or physical examination in prechiasmatic lesions.
- Objective and reproducible test for optic nerve function.
- Abnormality persists over long periods of time.
- Inexpensive as compared with to MRI.
- Under certain circumstances, may be helpful to positively establish optic nerve function in patients with subjective complaint of visual loss; normal VEP excludes significant optic nerve or anterior chiasmatic lesion (Leslie et al., 2002).

With abnormal VEP, some of the differential diagnostic considerations are as follows

- Optic neuropathy.
- Optic neuritis.

- Toxic amblyopia.
- Glaucoma.
- Leber's hereditary optic neuropathy.
- Retrobulbar neuritis.
- Ischemic optic neuropathy.
- Multiple sclerosis.
- Tumors compressing the optic nerve e.g. Optic nerve gliomas, meningiomas, craniopharyngiomas, giant aneurysms and pituitary tumors (Andrew et al., 2002).

2.6.1 VEP in Optic neuritis

Prolongation of P100 latency is the most common abnormality and usually represents an optic nerve dysfunction. VEP is clearly more sensitive than physical examination in detecting optic neuritis. Elvin et al., 1998 used Doppler ultrasonography, MRI and VEP measurements to study abnormal optic nerve function. VEP assessments were performed in 16 patients. Patients with impairment of visual acuity and a prolonged VEP initially had a more swollen nerve and increased flow resistance in the affected optic nerve. Statistically significant side-to-side differences were found in the optic nerve diameter and in the resistance to flow in the central retinal artery between the affected and unaffected eyes.

2.6.2 VEP in Multiple Sclerosis

Visual evoked potentials have become widely accepted in diagnostic schemes for the assessment of multiple sclerosis. It has been shown that a deviation in latency is a better criterion than a deviation in amplitude, since amplitude varies widely among subjects, whereas evoked potential latency remains restricted rather to a narrow range (McDonald and Brans, 1992).

VEPs has the ability to reveal the presence of a clinically silent lesion in the visual pathway in a patient having signs of demyelination evident in other parts of the CNS, thus confirming the diagnosis of multiple sclerosis (Russel et al., 1991).

In multiple sclerosis, P100 absolute latency may be increased unilaterally or a significant interocular difference may occur (Cutler et al., 1985). Moreover, broad response of P100 latency and abnormal shape of NPN was found in majority of multiple sclerosis patients (Glaser, 1990).

In a review of 180 patients with multiple sclerosis 73 % had abnormal VEPs; more importantly, VEPs were abnormal in 54 % of patients without any symptoms or signs referable to the visual system. Such patients are often in the early stages of the disease, when diagnosis is difficult even with modern neuroimaging techniques (Halliday et al., 1977). MRI demonstrated high-signal lesions in 84-88 % of symptomatic patients, whereas VEPs were abnormal in 100% of cases (Kojima et al., 1990).

Brigell et al., 1994 described the pattern VEP using standardized techniques. They concluded that the peak latency of pattern-reversal VEP is a sensitive measure of conduction delay in the optic nerve caused by demyelination. Pattern-reversal VEPs were recorded from 64 healthy subjects and 15 patients with resolved optic neuritis. The results showed that the N70 and P100 peak latencies and N70-P100 interocular amplitude difference were sensitive measures of resolved optic neuritis.

2.6.3 Flash VEP in Cerebral stroke

Ipata et al., 1997 studied left-right asymmetry of flash VEPs in patients after stroke. The VEP amplitude was smaller over the ischemic hemisphere than over the intact hemisphere. This finding indicates that the left-right asymmetry in VEPs of patients after brain damage may be a result of changes in the conductivity of the volume conductor, due to the ischemic region between the source and the electrodes.

2.6.4 Pattern-reversal VEP in classic and common migraine

Shibata et al., 1997 recorded pattern-reversal VEP to transient checkerboard stimulus in 19 patients with migraine with visual aura (i.e. classic migraine), 14 patients with migraine without aura (i.e. common migraine) in the interictal period, and 43 healthy subjects. Latencies and amplitudes of pattern-reversal VEPs in each group were analyzed. In patients with classic migraine, P100 amplitude was significantly higher than in healthy subjects, whereas latencies of pattern-reversal VEPs did not differ significantly. No significant differences were noted in latency between the common migraine group and healthy subjects or in latencies and amplitudes of pattern-reversal VEP between the classic migraine and common migraine groups. These results suggest that patients with classic migraine may have hyperexcitability in the visual pathway during interictal periods and that the increased amplitude of pattern-reversal VEPs after attacks may be due to cortical spreading depression.

2.6.5 VEP in adrenoleukodystrophy

Adrenoleukodystrophy is an X-linked metabolic disorder with very long-chain fatty acid (VLCFA) accumulation and multifocal nervous system demyelination, often with early involvement of the visual pathways. Kaplan et al., 1993 found that pattern-reversal VEPs were abnormal in 17% of patients with adrenoleukodystrophy; no evidence indicated that reduction of VLCFA levels improved or retarded visual pathway demyelination.

2.6.6 functional disorders

In malingering and hysterical visual loss normal VEP usually suggests continuity of the visual pathways ruling out disease up until area 17 but does not exclude fully cortical blindness in such cases (Bodis-Wollner, 1977).

2.6.7 VEPs in retinopathies and maculopathies

Diseases of the retina, especially diseases affecting the macular region, are associated with abnormal VEPs. In maculopathies, simultaneous recording of pattern Electroretinogram (ERG) and VEPs may be diagnostically useful in differentiating between involvement of the macula and optic nerve. In maculopathies and retinopathies involving the macular region, pattern ERG are absent or have a prolonged b-wave latency. The retinocortical time remains within the normal boundaries, indicating that the P100 delay occurs at the retinal level. In optic nerve diseases VEPs may be absent or prolonged, but pattern ERG are normal; the retinocortical time is thus prolonged, indicating that the pathology is postretinal (Celesia and Kaufman, 1985).

In patients with retinopathies the latency of P100 was found to be prolonged by a mean of 19.6 msec with a range of 6 to 39 msec. Delays in latency that exceeded the limits of normality by more than 45 msec usually indicate optic nerve dysfunction especially in multiple sclerosis (Lennerstrand, 1982).

3. Brainstem Auditory Evoked Potentials (BAEPs)

3.1 Introduction

On applying auditory stimulus to one ear, activation of peripheral and central auditory pathways occurs. Brain stem auditory evoked potentials (BAEPs) are the electrical activities resulting from the activation of the eighth nerve, cochlear nucleus, tracts and nuclei of the lateral lemniscus and inferior colliculus (Chiappa, 1983).

Brain stem auditory evoked potential recording is a physiological technique which can be used to evaluate the auditory pathway. It has the advantage of not requiring a voluntary response by the patient and occurring during sleep (Stephen, 1983).

3.2 Description and origin of BAEPs (Figure 2,3)

Clinical stimuli delivered to one or both ears evoke seven submicrovolt vertex-positive waves that appear at the human scalp in the first 10 msec after each stimulus (Picton et al., 1974). They are named according to their sequence in roman letters (from I to VII) (Chiappa et al., 1978).

Wave (I)

This wave is generated from the auditory portion of the eighth cranial nerve, probably from the proximal portion of that nerve just lateral to the brain stem in contact with the spiral ganglia. It is a prominent initial upgoing peak in the ipsilateral ear recording channel. It is important as a reference point for interwave latency measurement (Rowe III, 1978). Patients who have only central nervous system problems should have a preserved wave I. Conversely, patients who have a significant peripheral hearing impairment may have a very poor formed or absent wave I, but may have relatively normal waves II-V (Nuwer et al., 1994).

Wave I can sometimes be seen to have two separate components. The first, earlier component is present and higher in amplitude especially during high intensity, high pitched stimulation. This component should be used for scoring whenever it is present. The second, slightly later lower amplitude component of wave I, is present at a more wide range of stimulus intensities and pitch (Matsuoka et al., 1994).

Waves (II)

This wave may be generated near or at the cochlear nucleus (Row III, 1978). A portion of it can come from the eighth nerve fibers around the cochlear nucleus, and this part of II can be preserved despite brain stem death. Wave II is poorly defined in some adults and most neonates. It sometimes appears as a small peak along the downgoing slope of the wave I. At other times, it merges into the upgoing slope of wave III. It is more often prominent on the contralateral channel recording, where it has a slightly prolonged latency compared to the ipsilateral channel, sometimes fusing with wave III into an M-shaped II-III complex (Aminoff et al., 1994).

Wave (III)

This wave is probably generated from the lower pons as the pathway travels through the superior olive and trapezoidal body (Row III, 1978). The nuclei or fiber tracts that are most responsible for generating this potential are unknown and may be multiple.

Wave III is usually a prominent peak and is followed by a prominent III trough. In the contralateral channel wave III often appears smaller and earlier than on the ipsilateral channel, because its amplitude is similar at the vertex and contralateral ear (Goodin et al., 1994).

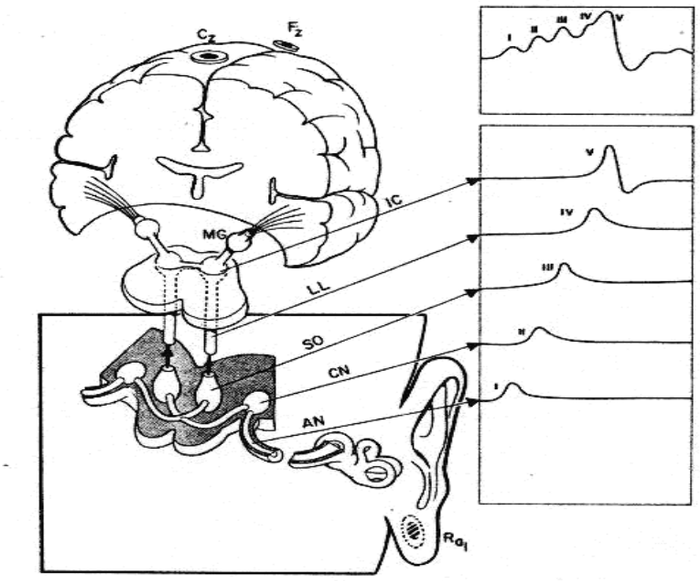

Figure 93. **Auditory evoked response studies. AN = auditory nerves; CN = cochlear nuclei; SO = superior olives; LI = lateral lemnisci; IC = inferior colliculi; MG = medial geniculates.**

Fig. 2. Anatomical-electrophysiological correlation of BAEP *(Poon's, 2003b).*

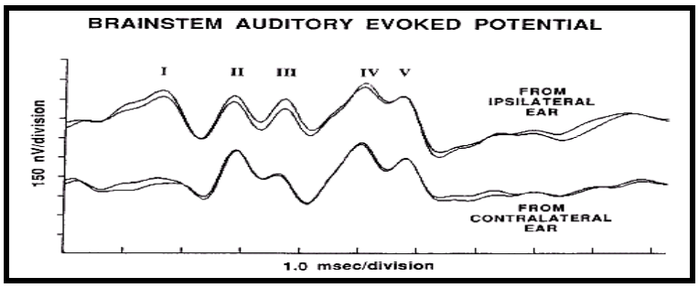

Fig. 3. Normal components of BAEP *(Nuwer et al., 1994).*

Waves (IV) and (V)

Contribution to these two potentials probably includes generators in the upper pons or lower midbrain, in the lateral lemniscus and the inferior colliculus. There are conflicting reports about whether these peaks are generated in the ipsilateral or contralateral brain stem, but the preponderance of evidence favors a contralateral brain stem generator site for wave V (Starr et al., 1994).

These peaks may fuse together into a IV-V complex on the ipsilateral recording channel. This complex can vary between: (a) two peaks which are close but still visibly separate, and (b) a single peak which is completely fused as a tall and wide pyramid. There are also various intermediate stages of trapezoid-shaped figures which represent the partial fusion of the two peaks. On the contralateral recording channel the IV and V peaks tend to be separated more from each other with wave IV being slightly earlier and wave V being slightly later. Comparison of ipsilateral and contralateral peaks can be helpful for distinguishing which peak or shoulder to score as wave V. The wave V is generally followed by a large V trough. Sometimes wave VI appears before the bottom of this trough, and then wave VI can be confused with wave V if the reader is not careful. The fusion of wave VI into

a IV-V-VI complex occurs more often when a 10-30 Hz low filter is used for recording (Nuwer et al., 1994).
The typical IV-V complex has a shape of a somewhat inflated pyramid or trapezoid. The base of this complex should be more than 1.5 msec across. A peak narrower than this is usually a wave IV alone. Wave V is usually most prominent at an intermediate intensity of stimulation. As this stimulus intensity increases further beyond that point, the identification of wave V can actually become more difficult. It is often helpful to have the technician reduce the intensity of stimulation to identify wave V. Wave V is a robust peak that is present despite moderately low intensities of stimulation (and often even despite high frequency hearing impairment, or other types of peripheral auditory changes). Wave V and especially the V trough are often the last deflections to disappear when the stimulus intensity is gradually decreased to threshold (Matsuoka et al., 1994).
Overall there are several ways to help identify wave V when its identity is unclear: the typical contralateral splitting of the IV-V complex; the wide base of a IV-V complex and the preservation of wave V at lower stimulus intensities (Aminoff et al., 1994).

Waves (VI) and (VII)

Are not found in all normal subjects. They are generated in medial geniculate body and auditory radiation from the thalamus to temporal cortex respectively (Row, 1980).
The most constant and most important waves, from the clinical point of view, are waves I, III, V (Rosenhall et al., 1985). Their measurements include absolute latency (stimulus to peak) and interpeak latency (time interval between the peaks). The clinical interpretation is based on the interpeak latencies. Absolute amplitudes are extremely variable in normal subjects (Chiappa, 1983).

3.3 Normal limits and the clinical correlation of changes

There are 5 principle features used to assess routine BAEPs

3.3.1 I-V interpeak interval

This is the primary feature for most BAEP interpretations. It represents conduction from the proximal eighth nerve through pons and into the midbrain. It can be slowed in a variety of disorders, including focal damage (demyelination, ischemia, tumors), or diffuse problems (degenerative disorders, post-hypoxic damage, etc.) (Starr et al., 1994).
A typical upper limit of normal for the I-V interpeak interval is 4.5 msec. That limit is slightly lower for young women and slightly higher for older men. Normal right-left asymmetries for the I-V interpeak interval should be at most 0.5 msec. For full-term infants, the I-V interpeak interval should be less than 5.4 msec (Goodin et al., 1994).

3.3.2 I-III interpeak interval

This interpeak interval represents conduction from the eighth nerve across the subarachnoid space, into the core of the lower pons. The I-III interpeak interval can be increased in any diffuse process that affects the whole I-V interpeak interval. This I-III portion of the pathway is susceptible to a tumor, inflammation or other disorders especially affecting the proximal portion of the eighth nerve, or the ponto-medullary junction where the eighth nerve enters the brain-stem, or impairments in the lower pons around the superior olive or trapezoidal body. Acoustic neuromas or other cerebello-pontine angle tumors can cause a delay at the juncture. Infarction can cause an interruption or a delay here too, although the classical

Wallenberg syndrome is usually too caudal to affect this segment. Inflammation in the subarachnoid space can also increase this I-III interpeak interval (subarachnoid hemorrhage, meningitis and Guillain-Barre syndrome) (Aminoff et al., 1994).
The upper limit of normal for the I-III interpeak interval is about 2.5 msec. The acceptable right-left asymmetry of this interval is less than 0.5msec. An excessively long interpeak interval I-III cannot be considered unless there is an accompanying prolongation of the I-V interpeak interval (Matsuoka et al., 1994).

3.3.3 III-V interval

This interval reflects conduction from the lower to the upper pons and possibly into the midbrain. There is not yet complete agreement about whether this III-V interpeak interval represents conduction along the ipsilateral or contralateral brain-stem, compared to which ear is stimulated. The preponderance of evidence favors a contralateral brain-stem site (Nuwer et al., 1994).
The typical upper limit of normal for a III-V interpeak interval is about 2.4 msec. A right-left asymmetry for these intervals should be less than 0.5 msec. An excessively long III-V interpeak interval is not considered abnormal unless either the I-V interval or the V/I amplitude ratio is also abnormal (Goodin et al., 1994).

3.3.4 V/I amplitude ratio

Absolute amplitudes of BAEP peaks vary widely among normal subjects. In addition, several technical factors influence the absolute amplitudes of BAEP peaks. To reduce this normal intersubject variability, a ratio of amplitudes is usually calculated. For this ratio, the amplitude of IV-V complex is divided by the amplitude of the wave I. The IV-V complex is measured from the highest point of the complex to the trough of the V peak. When V is completely separated from IV, the V amplitude is used In place of the IV-V amplitude. When wave VI is found lying part way down the descending slope of wave V, then the amplitude is measured to the trough following wave VI. The wave I amplitude is measured from the top of the highest part of wave I to the bottom of the trough of I. If wave II is riding on the descending slope of I, then wave I amplitude is measured to the succeeding trough of the wave II (Starr et al., 1994).
The amplitude ratio should be between 50% and 300%. These numbers vary between laboratories and they are especially affected by filter setting changes. When the V/I amplitude ratio is less than 50%, then the IV-V peaks are too small. In that case, suspicion is raised of some central impairment which has diminished the amplitude of the IV-V even if it may have not increased I-V interpeak interval. This is useful criterion for abnormality, especially when the IV-V peaks are so low that they are difficult to distinguish from background noise. Then the record may be interpreted as abnormal because of such low amplitude central peaks, even if the latencies cannot be precisely defined. For full-term infants, the lower limit for V/I is 30% (Goodin et al., 1994).
When the V/I amplitude ratio is greater than 300%, wave I is usually considered to be too small. This raises the suspicion of some peripheral hearing impairment, especially of a high frequency or a sensorineural hearing loss (Aminoff et al., 1994).

3.3.5 Presence of wave I-V

The wave I-V all are seen in most normal individuals. Occasional normal subjects have a wave IV that is so merged into a IV-V complex that it cannot be distinguished as a separate

peak, unless extra traces are run at different stimulus rates and intensities. Such a merging of wave IV into a IV-V complex is considered to be a normal variant. Wave II can also be difficult to distinguish when testing some normal subjects. Upon changing stimulus intensities, rates and phase, wave II can be distinguished in essentially all normal subjects. However wave II can appear to be missing at the specific rates and intensities used for simple clinical BAEPs, and this would be considered a normal variant (Matsuoka et al., 1994).

When all waves I-V are absent the BAEP is abnormal, although the cause is usually peripheral (Technical problems must also be considered). It is also abnormal to record a wave I, but not succeeding waves. Finally, it is abnormal if wave I and III are present but IV-V is absent. These roles for the absence of peaks are predicted upon the assumption that technically good quality records have been obtained. The record should be considered technically unsatisfactory if moderate or large amount of background noise are present in the tracing, rather than being interpreted as showing an absence of important peaks (Nuwer et al., 1994).

Waves VI, VII, VIII can normally be present or absent or asymmetrical in latency or amplitude, without any apparent clinical correlation. The main reason for knowing their existence is to prevent confusion with the earlier important waves (Starr et al., 1994).

3.3.6 Absolute latency measurements

The absolute latency measurements of wave I, III and V can be occasionally of clinical value. This is particularly so when some peaks are absent. For example, the absolute latency of wave V can be compared against normal limits when there is no waves I-IV. The absolute latency of wave V is normally less than 6.4 msec. The right-left asymmetry of the wave V absolute latency is normally 0.5 msec or less. Absence of waves I-IV with delayed wave V may be due to a hearing loss. When waves I, III and V are all present, the standard means of interpretation is by the interpeak intervals (Goodin et al., 1994).

The absolute latency of wave I can be used as part of the assessment of hearing. The wave I is often seen around 1.75 msec, but may be seen up to 2.2 msec in some normal subjects. The right-left asymmetry of the wave I absolute latencies is normally 0.4 msec or less. Wave I latency delays or asymmetry suggest a hearing impairment, rather than brain-stem dysfunction (Aminoff et al., 1994).

3.3.7 Reference Values of BAEP (Tandon and Krishna, 1990)

Wave	Mean	Range
Wave I	1.62	1.26-1.98
Wave II	2.80	2.23-3.37
Wave III	3.75	3.24-4.26
Wave IV	4.84	4.15-5.53
Wave IV/V	5.27	4.61-5.93
Wave V	5.62	4.93-6.31
I-III	2.63	
III-V	2.31	
I-IV/V	4.32	

3.4 Principles of recording of BAEPs

3.4.1 Technical details

The test can be performed under sedation or under general anesthesia; Filter band pass 100-3000 Hz; Standard broadband click stimulation is used on the ear tested; Monoaural stimulation is used; The click intensity should be 60-70 dB above click perception threshold;

The contralateral ear receives masking noise of 30- to 40-dB lesser intensity; The first 10 ms are averaged, and 2-4000 responses may be averaged; At least 2 separate trials should be performed (Leslie et al., 2002).

3.4.2 Stimulation procedures

In neurological practice a sound (Click) generated by pulses through headphones is used as an auditory stimulus. The hearing threshold is determined and the click is applied at an intensity 30,40,50 or 60 decibel (dB) above that hearing threshold. The stimulated ear (in monoaural stimulation) is called ipsilateral ear, the other is the contralateral one (Starr et al., 1976).

To avoid stimulation of the contralateral ear by bone and air conduction on applying the click to the ipsilateral ear, the former should be masked by noise at an intensity of 30 to 40 dB less than of the click stimulus (Leslie et al., 2002).

3.4.3 Electrode montage

The recording montage is at least, and usually, a 2-channel montage channel 1 is ipsilateral ear to vertex and channel 2 is contralateral ear to vertex. The recording electrodes are located, one for each ear lobule and a third electrode is located on the scalp at the vertex at Cz position of 10-20 international system (Stockard et al., 1979a and Leslie et al., 2002).

3.4.4 Interpretation (Poon's, 2003b)

3.4.4.1 Abnormal I-III interpeak latency (IPL): This abnormality suggests the presence of a conduction defect in the brain-stem auditory system between the eighth nerve close to the cochlea and the lower pons.

3.4.4.2 Abnormal III-V IPL: This abnormality suggests the presence of a conduction defect in the brain-stem auditory system between the lower pons and the midbrain.

3.4.4.3 I absent & III-V is normal: Wave I (the eighth nerve activation potential) could not be recorded. This is usually due to a peripheral hearing disorder. Because of this, the state of conduction in the brain-stem auditory pathway between peripheral eighth nerve and lower pons could not be determined. Lower pons to midbrain conduction was normal.

3.4.4.4 IV or V absent or of abnormally low amplitude: This abnormality suggests the presence of a conduction defect in the brain-stem auditory system rostral to the lower pons.

3.4.4.5 Absent II, III, IV and V with normal I: This abnormality indicates a significant lack of function in brain-stem auditory tracts.

3.5 Factors affecting BAEPs

Factors which affect BAEPs are either technical and / or subject related factors

3.5.1 Technical factors

3.5.1.1 Intensity of the stimulus (click)

The intensity of the click stimulus affects the amplitude and absolute latencies of BAEPs peaks. Stockard et al., 1979 reported that absolute latencies increase and amplitudes diminish with decreasing intensity by about 0.03 msec/dB.
Chiappa, (1983) found that waves II, IV and VI diminish more quickly than waves I, III,V with decreasing intensity and also reported that the constancy of the interpeak latency is more reliable in neurologic applications than the use of absolute latency.

3.5.1.2 Rate of the stimulus

Increasing click rate results in increased absolute latency of all BAEPs waves and decrease in the amplitude of most of them. Interpeak latencies increase slightly at higher rates (Stockard et al., 1978 & 1979). Stockard et al., 1980b added that, using rates higher than 30 per second will often worsen pre-existing abnormalities in the BAEP. Some studies used higher rates to reveal the abnormalities. However, Chiappa et al., 1979 mentioned that increasing click rate from 10/second to only 30/second has no value.

3.5.1.3 Stimulus mode

Binaural stimulation produces higher amplitude waves III, IV, V at all stimulus intensities than monoaural stimulation and, because of the monoaural contribution to wave I but binaural contribution to wave IV and V, binaural stimulation logically produces a higher V/I amplitude ratio than monoaural stimulation at a given stimulus intensity. Binaural stimulation should be avoided in routine clinical applications because monoaural abnormalities are common in neurologic disease and may otherwise be masked by the response from the normal ear (Stockard et al.,1978). Separate monoaural stimulation of each ear also allows for comparison of interaural asymmetries in interpeak latency (IPL) and thus may indicate abnormality even when BAEPs from each ear are within normal limits when considered separately (Berlin and Hood, 1984).

3.5.1.4 Filter setting

Filter settings affect relative amplitudes more than interpeak latencies and, in diagnostic applications, should remain fixed at the values used when collecting each laboratory's normative data. The ideal bandpass for clinical purposes is probably 100 to 3,000 Hz or higher. A low frequency filter of much less than 100 Hz allows EMG, EEG and other signals into the average, and a cutoff much higher than 100 Hz distorts the low-frequency BAEP components. A high frequency cutoff of at least 3,000 Hz is necessary to resolve the highest-frequency components of BAEP; settings of less than 1,000 Hz increase the apparent latencies of the BAEPs and decrease their resolution. Increases in high-pass filter above 100 Hz markedly reduce V/I amplitude ratio because of the longer duration of wave V than I. High pass-filtering at 30 Hz or lower is needed in audiologic BAEP applications (Stockard et al., 1978).

3.5.1.5 Site of reference

Using the electrode applied to the contralateral ear as a reference produces a decrease in the II-III interpeak latency and increase the IV-V interpeak latency. Peak latencies of waves II and V are increased when the electrode applied to the contralateral ear is used as a reference in comparison to the use of electrode applied to the ipsilateral ear (Stokard et al., 1978).

De Montes et al., 2002 concluded that BAEP obtained with reference to Cz and Fz are ideal for interpretation, since there is greater constancy, global amplitude and morphological clarity of the first five deflections and less morphological complexity of the other waves.

3.5.2 Subject factors

3.5.2.1 Age

Below the age of 2 years, interpeak latencies are prolonged relative to adult values (Starr et al.,1976). By the age of 2 years, the ranges for adults are reached, the absolute latencies of wave I, III, V increase by 0.1-0.2 msec with age. However, the I-V interpeak latency remains the same (Rosenhall et al., 1985). One obvious explanation for the age-related latency shift is progressive myelination of the auditory tract in infants (Tarantino et al., 1988).
The effects of age on the brain-stem auditory evoked potentials were studied on 156 healthy subjects with ages ranging from 18 to 76 years. There was a small progressive prolongation in the peak latency with increasing age, particularly peak V. Although a correlation between the age and the I-III interval was not observed, there was also a small increase with age in the interpeak latencies of III-V and I-V (Chu, 1985).
Since age effects on central conduction time in the acoustic pathway are still debated, brainstem auditory evoked potentials were recorded in normoacoustic subjects, with no history of neurologic or otologic pathology. Linear regression has been used for statistical analysis. Data obtained show an age-related prolongation of latency values which is particularly marked for wave I, while other waves (particularly wave III) do not show a significant change. Thus, IPL values do not increase with increasing age: in particular IPLs I-II and I-III decrease, showing a negative "r" value, and IPLs I-V and II-V (which is to be considered the true "central conduction time" through the acoustic pathway) do not show a significant change. These data seem to demonstrate that the aging process is essentially a peripheral phenomenon which does not involve the central part of the acoustic pathway (Costa et al., 1990).
Brainstem auditory evoked response (BAER) was recorded in children from birth to 6 years and adults to study the development of wave amplitude. The amplitudes of all BAER waves increased with age, the greatest changes occurring during early infancy. Adult values were reached at 6 months of age for wave I and 2 years for wave V. The two waves continued to increase above the adult values until the highest amplitude value was reached at 3 years for wave I and 5 years for wave V. Subsequently, the amplitudes decreased towards the values in adults. The V/I amplitude ratio, which was slightly lower than the adult value shortly after birth, decreased during the first year of life and reached the minimum value between 1 and 4 years. Thereafter, it increased towards the adult value. Throughout the maturational stages the ratio was smaller than in adults. The amplitude of wave V was relatively stable and its variation was much smaller than those of wave I and V/I amplitude ratio (Jiang et al., 1993).

3.5.2.2 Sex

Females have shorter interpeak latencies than males. This may be explained by shorter corresponding segments of the auditory pathway due to smaller brain size. However, no difference could be detected before the age of 8 years (Stochard et al., 1979).
Sex differences in the amplitudes and latencies of the auditory brain stem potential (BAEP) were investigated using 3 levels of intensity and 3 stimulus presentation rates. The females displayed consistently larger BAEPs for waves IV, V, VI and VII than the males. The only latency differences which reached significance over all the intensities and rates occurred for

wave V. The females showed significantly shorter wave V latencies than the males. Since hearing losses and individually determined click thresholds were comparable between the two groups tested, the exact sources of the uneven distribution of amplitude and latency effects are in question. Differences in the relative distances of the anatomical generators are considered in accounting for the sex differences. Because the precise origin of the sex differences cannot be stated with certainty, attempts to develop normative data for the BAEP should consider the possible influences of sex differences (Michalewski et al., 1980).

3.5.2.3 Hearing disorders

Peripheral hearing disorders give a similar effect on BAEP as decreasing stimulus intensity i.e. the absolute latencies of all waves are increased but no change of the interpeak latencies (Chiappa, 1983).
In patients with sensorineural hearing loss, Coats and Martin, 1977 found an abrupt increase in the latency of wave I at 50 to 60 dB, 4 to 8 kHz hearing loss; this abrupt increase in wave I peak latency was not paralleled by a similar increase in wave V latency, thus the I-V interpeak latencies in these subjects were shorter than in those with normal audiograms.

3.5.2.4 Body temperature

A decrease in body temperature leads to increase in both the absolute and interpeak latencies (Picton et al.,1982).

3.5.2.5 Hypoglycemia

Kern et al., 1994 studied the effects of insulin-induced hypoglycemia on the auditory brainstem response (ABR) in humans. ABRs were examined in healthy men during euglycemia and after 20 minutes and 50 minutes of steady-state hypoglycemia of 2.6 mM induced with insulin. Hypoglycemia increased interpeak latencies III-V and I-V, whereas changes in the latency of wave I were not significant.

3.5.2.6 Medications

3.5.2.6.1 Barbiturate

BAEPs are not affected significantly by barbiturate doses sufficient to render the EEG "flat" (i.e. isoelectric) or by general anesthesia (although it was reported that BAEP has been lost with combined lidocaine and thiopental infusion) (Garcia-Larrea et al., 1988).

3.5.2.6.2 Nicotine (smoking)

Reports of tobacco-induced electrocortical activation have frequently indicated that this effect is mediated via nicotine's action on sub-cortical structures. Twelve regular smokers were tested on two separate sessions involving sham or real smoking. On each session, BAEPs were recorded during a baseline period and immediately after smoking. BAEPs, recorded from Cz, were elicited by presentation of 1,000 monaural, rare fraction click stimuli. Latency and amplitudes of peak components I, III and V were assessed and analyzed. No significant effects were observed for latency measures or for amplitudes of peaks I and III. A significant effect was observed for peak V with tobacco resulting in larger amplitudes relative to sham smoking. Peak V reflects activity from upper pontine-lower midbrain sites (Knott, 1987).

3.5.2.6.3 Aminophylline

To determine the neurophysiological effects of aminophylline on apnea of prematurity, the BAEPs of 30 apnoeic infants and 34 age matched controls were evaluated and compared. After

six days of treatment with aminophylline, the brain stem conduction time (interpeak latency of I-V) in apnoeic infants decreased compared with controls of a similar postconceptional age. The mean latencies of the peaks and interpeaks of all waves except wave I were significantly lower in the apnoeic infants after than before receiving aminophylline. No significant differences were found in the latencies of BAEPs between the apnoeic infants who responded and those who did not respond to aminophylline treatment. These results suggest that aminophylline may enhance conduction along central auditory pathways and stimulate the regulatory effect on the respiratory centre of the brain stem (Chen et al.,1994).

3.6 Clinical applications of BAEPs

BAEPs are very resistant to alteration by anything other than structural pathology in the brainstem auditory tracts. Disorders of the peripheral vestibular system do not affect BAEP. Thus, patients who had labyrinthine diseases (i.e. Ménière's disease, labyrinthitis, vestibular neuronitis) had no BAEP interwave latency abnormalities using the limits employed for clinical neurological purposes (Garcia-Larrea et al., 1988).

Brainstem auditory evoked potentials have obtained widespread clinical application in assessing neurologic and audiologic problems. These have maximal clinical utility in evaluating comatose patients, in patients with suspected demyelinating disorders, posterior fossa tumors, or in audiologic evaluation, especially in infants. They are also used for intraoperative monitoring of eighth-nerve and brainstem function during different types of posterior fossa surgery (Markand, 1994).

ABR audiometry is considered an effective screening tool in the evaluation of suspected retrocochlear pathology. However, an abnormal ABR suggestive of retrocochlear pathology indicates the need for MRI or CT scanning. In general, ABR exhibits a sensitivity of over 90% and a specificity of approximately 70-90% (Schmidt et al., 2001).

3.6.1 BAEPs in multiple sclerosis (MS)

An abnormal response may be seen with higher frequency in symptomatic patients; however, a positive test may be recorded in the absence of clinical brainstem symptomatology. BAEPs should be considered if the clinical symptom implicates a lesion outside the brain stem. In this case an abnormal BAEPs would further support the diagnosis of MS. If, however, the clinical sign (e.g., diplopia) points to the brain stem, BAEPs abnormality is merely confirmatory. In various studies about 20% of the population tested for a second lesion have an abnormal BAEPs and about half of these go on to develop MS in the next 1-3 years (Kjaer, 1987).

Purves et al., 1981 reported pattern-shift VEPs to be abnormal in 45%, SSEP abnormal in 35%, and BAEP in 14% of patients without brainstem signs. Combining all 3 modalities, 97% of patients with definite MS, 86% of patients with probable MS, and 63% of patients with possible MS had abnormal findings on at least one of these tests. Similar findings were reported by Ferrer et al., 1993. Kjaer, 1987 reported 38% abnormal BAEPs in patients with silent lesions, while 50% of these patients had an abnormal VEPs and only 13% an abnormal SEP.

Brain-stem auditory evoked responses (BAERs) were examined in 178 patients with multiple sclerosis (MS) and compared to the frequency of abnormalities in visually evoked responses (VERs) and in CSF electrophoresis. In clinically definite MS, BAERs were abnormal in 61% and a significant relationship was noted between disability due to MS and the frequency and severity of BAER abnormalities. In suspected MS, BAERs showed evidence of a second lesion in 14% whereas VERs indicated a second lesion in 24%.

Abnormal BAERs in patients with suspected MS with brain-stem signs were significantly associated with the presence of ataxia. In progressive possible MS, abnormal BAERs were found in 49% but indicated a second lesion in 35% of patients and were significantly related to the duration of illness. In progressive possible MS, abnormal VERs but not abnormal BAERs, were significantly associated with the presence of cerebrospinal fluid (CSF) oligoclonal IgG banding. Normal BAERs in association with clinical brain-stem abnormalities were found in 24% of patients with clinically definite MS, 50% with suspected MS and 33% with progressive possible MS (Hutchinson et al., 1984).
Furthermore, Lehmann and Soukos, 1982 examined patients with certain, probable and possible MS using checkerboard VEP and click-BAEP and concluded that VEPs were clearly more useful than BAEPs in the early diagnostics of MS, however in occasional cases, BAEPs might contribute to the early diagnosis.
Chiappa, 1990 found that the BAEP is positive in 21% of clinically unsuspected cases. Most authors have concluded that BAEP yields the smallest percentage of patients, but it still adds to the detection rate because it is abnormal in a different subset of patients.

3.6.2 CNS tumors

3.6.2.1 Cerebellopontine angle lesions

BAEP may be abnormal when audiometry fails to disclose a lesion. The characteristic findings are increased I-V and increased I-III interpeak latencies ipsilateral to the lesion. Bilateral prolongation of latencies and interpeak latencies may be seen. Gordon and Cohen, 1995 evaluated the efficacy of auditory brainstem response (ABR) as a screening test for small acoustic neuromas by performing a prospective trial to determine the diagnostic sensitivity of brainstem auditory evoked response (BAER) in these tumors. Randomly selected patients with surgically proven acoustic neuromas underwent preoperative BAER tests within 2 months of surgery. A test result was considered abnormal when the interaural I-V interpeak latency difference was greater than 0.2 ms, the absolute wave V latency was abnormally prolonged, or waveform morphology was abnormal or absent. 87.6% Of the tested patients, had an abnormal BAER and 12.4% had completely normal waveforms and wave latencies. Patients with tumors greater than 2 cm in total diameter had abnormal BAER results. Patients with tumors 1.6-2 cm / 1-1.5 cm / 9 mm or smaller, 86% / 85% / 69% had abnormal BAERs respectively. These data show that BAER sensitivity decreases with decreasing tumor size. Therefore, MRI scanning is the preferred study because the accuracy for detection of tumor smaller than 1 cm through BAER is 70%. Nevertheless, BAER is useful in patients who have implanted medical devices (e.g., pacemakers) that prevent MRI scanning.

3.6.2.2 Meningomyelocele

The brainstem auditory evoked potentials (BAEPs) of twenty-seven meningomyelocele (MMC) patients were analyzed and compared with the results of a normal population. The longest wave V or I-V interpeak latencies were seen in patients with shunted hydrocephalus and cranial nerve defects. The shortest wave V and I-V interpeak latencies were found in patients without hydrocephalus. However, these latencies of MMC patients were significantly longer than the latencies of a normal population. It is assumed that I-V interpeak latency prolongation in MMC patients, which is related to the severity of the clinical signs of the Arnold Chiari malformation, is mostly due to an elongation of the brainstem (Lutschg et al., 1985).

It is difficult to estimate the accurate onset of symptoms clinically resulting from Chiari II malformation. Brainstem auditory evoked potentials (BAEPs) may be a useful method in the selection of potential candidates for surgery. BAEPs were studied in asymptomatic infants under 6 months of age with meningomyelocele (MMC). Both the wave latencies and interpeak latencies (IPLs) gradually became shorter during the first 6 months of life in asymptomatic infants with MMC. In particular, shortening of the III-V IPLs and the I-V IPLs was observed from 1 to 4-6 months of age in these infants. These may be characteristic parameters of central auditory function (III-V IPLs) and global auditory function (I-V IPLs). Maturation of brainstem function as viewed by BAEPs in asymptomatic infants with MMC was delayed when compared to data in normal neonates and infants. These data on asymptomatic infants with MMC could potentially be a good reference for selecting the modalities of treatment in infants with symptomatic Chiari II malformation (Fujii et al., 1996).
Taylor et al., 1996 studied BAER in infants with meningomyelocele to determine whether EPs reflect early neurological status and whether BAER have prognostic value in neurological outcome. The infants, aged 1 day to 3 months, were tested while still in hospital after the meningomyelocele repair. Normal BAEPs were found in 41% of patients while abnormal BAEPs were found in all infants studied who had symptomatic Arnold-Chiari malformation. So, BAEPs showed a positive predictive value of 88% and accuracy of 84% in predicting central neurological sequelae.

3.6.3 Brainstem stroke

Brainstem stroke syndromes are primarily determined by clinical criteria. There are few diagnostic procedures which are of benefit for the evaluation of brainstem ischemic events. Brainstem auditory evoked responses are important electrophysiologic technique for assessing brainstem function. The response is variable; some lesions cause abnormal latencies while some do not (Tsuda et al., 1995).
To evaluate the use of BAERs in patients with brainstem ischemic events, 35 individuals with recent brainstem strokes, selected by strict clinical criteria, were evaluated with BAERs. The initial BAER was abnormal in 22 of 35 patients (63%). When the clinical course and site of the lesion are correlated with the BAER results. An unstable course, characterized by progression or remission and relapse, was present in 19/35 (54%) of patients, and 15/19 (79%) of these individuals had an initially abnormal BAER. The other 16 brainstem stroke patients with a stable clinical course had an initially abnormal BAER in 7 instances (44%). This difference is statistically significant at the $P = 0.04$ level. The principal sites of ischemia were mesencephalic in 11/35, pontine in 13/35 and medullary in 11/35. The association of an abnormal BAER with an unstable clinical course seemed independent of the site of the lesion, However, of the 9 deaths that occurred, all were in patients with mesencephalic or pontine lesions, and 8 of these individuals had an initially abnormal BAER. Abnormal BAERs in patients with brainstem ischemic lesions correlate with an unstable clinical course. Furthermore, individuals with ponto-mesencephalic infarction and abnormal BAERs have an especially poor prognosis. The BAER may be of prognostic value in the early evaluation of patients with brainstem ischemic strokes (Stern et al., 1982).
Brain stem auditory evoked potentials were studied in patients with the lateral medullary (Wallenberg's) syndrome. The observed changes included: prolongation of the interpeak latencies from wave I-V and III-V; prolongation of the interaural latency difference for wave V; splitting or absence of wave III and the presence of a broad partly fused wave III-V complex. This study showed that BAEP can be used to confirm the diagnosis of this syndrome and ascertain the site of the lesion (Elwany,1985).

A study of brainstem auditory evoked potentials was carried out in subjects suffering from vertebrobasilar TIA in order to obtain a comparative evaluation of cortical-subcortical functions. The obtained data demonstrate a delay of peak III of the BAEPs in patients with previous vertebrobasilar TIA. These data show that the study of the BAEPs is useful in evaluating the damage produced by anoxia (Benna et al., 1985).

3.6.4 Respiratory insufficiency following encephalitis

Schwarz et al., 1996 showed prolonged interpeak latencies (I-III, I-V, III-V, IV-V) and delayed absolute latencies of waves II, III, V, and I, at least on one side, in the BAEP. The auditory pathways are near the respiratory control centers in the brain stem; therefore, the electrophysiologic abnormalities of wave III and the IV-V complex may be a reflection of the disturbed central control of ventilation.

3.6.5 Prediction of posttraumatic coma in children

BAEP studies were performed within 72 hours of admission in children with severe head injury in order to predict the outcome of posttraumatic coma. Outcomes were categorized as brain death or survival. On first assessment, 40% of comatose children had normal BAEP. About 78% survived and 22% deteriorated and died. 32% 0f children had abnormal findings; 69% of them improved and survived, whilst 31% deteriorated and died. All children who did not have recordable BAEP died. These data suggest that BAER is a useful test in predicting neurological outcome in this setting (Butinar and Gostisa, 1996).

3.6.6 Comatose patient

BAEP can be done while the patient is sedated. It can be used as a prognostic indicator. Survival is unlikely in the absence of BAEP. The brain-dead patient has invariably abnormal BAEPs either the absence of all waveforms or the presence of wave I and the absence of all subsequent waveforms (Goldie et al., 1981).

3.6.7 Intraoperative monitoring

ABR, often used intraoperatively with electrocochleography, provides early identification of changes in the neurophysiologic status of the peripheral and central nervous system. This information is useful in the prevention of neurotologic dysfunction and the preservation of postoperative hearing loss. For many patients with tumors of cranial nerve (CN) VIII or the cerebellopontine angle, hearing may be diminished or completely lost postoperatively, even when the auditory nerve has been preserved anatomically.

Typical uses of intraoperative auditory brainstem response

- **Monitoring cochlear function directed at hearing preservation**

Cerebellopontine angle tumor resection (acoustic neuroma surgery); Vascular decompression of trigeminal neuralgia; Vestibular nerve section for the relief of vertigo; Exploration of the facial nerve for facial nerve decompression; Endolymphatic sac decompression for Ménière's disease.

- **Monitoring brainstem integrity**

Brainstem tumor resection; Brainstem aneurysm clipping or arteriovenous malformation resection (Kileny et al., 1988).

3.6.8 Screening of hearing in newborns

Several clinical trials have shown automated auditory brainstem response (AABR) testing as an effective screening tool in the evaluation of hearing in newborns, with a sensitivity of 100% and specificity of 96-98%. When used as a threshold measure to screen for normal hearing, each ear may be evaluated independently, with a stimulus presented at an intensity level between 35-40 dB. Click-evoked ABR is highly correlated with hearing sensitivity in the frequency range from 1000-4000 Hz. AABRs test for the presence or absence of wave V. No operator interpretation is required (Oudesluys-Murphy et al., 1996).

4. Conclusion

The VEP is preferable in optic nerve and anterior chiasmatic lesions, while MRI is clearly superior in retrochiasmatic disease. Note that the VEP is nonspecific as to the underlying etiology and pathology (Andrew et al., 2002).

The most common uses of BAEP are in MS and in acoustic neuroma. It is a useful screening test, with limitations; MRI scanning may be preferable when a small lesion is under consideration. Increased I-III interpeak latency indicates a lesion from CN VIII to the superior olivary nucleus, while increased III-V interpeak latency suggests a lesion from the superior olivary nucleus to the inferior colliculus ipsilateral to the ear stimulated. Intraoperative monitoring during cerebellopontine angle tumor surgery may be helpful in aiding the surgeon to preserve as much function as possible (Gordon and Cohen, 1995).

Involvement of CNS sensory pathways in hereditary motor and sensory neuropathies has been reported by Carroll et al and Jones et al. However, at that time molecular genetic diagnosis was not yet available and their finding could not be linked to a particular gene defect. Jones et al speculated that the abnormalities might be due to a dying back phenomenon of the affected peripheral nerves. On the other hand, Scaioli et al failed to show central nervous system involvement in patients with Charcot-Marie-Tooth (CMT). Recently, evidence for involvement of the central acoustic pathway was obtained by measuring BAEPs in patients with CMT1X with Cx32 mutations. However, no other CNS pathways were examined in this study (for example, VEPs or transcortical magnetic stimulation measurements) and it remained unclear whether the disorder would also affect structures other than the acoustic pathway.

Bähr et al and Tony et al found that, not only acoustic but also visual and central motor pathways are affected, suggesting a much larger central nervous system involvement than has been presumed from clinical examinations, in which such widespread central nervous system abnormalities have not been reported to date. These findings underscore the necessity of a careful analysis of CNS pathways in patients with CMT and Cx32 mutations. Thus, screening for Cx32 mutations seems to be important in patients with a peripheral neuropathy and abnormalities in motor and sensory central nervous system pathways.

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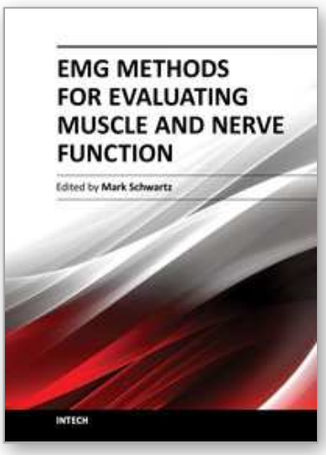

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