Flash visual evoked potentials in patients with periventricular leucomalacia in children less than 1 year of age

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Background and Aim: Children with periventricular leucomalacia (PVL) are known to have visual impairment of various forms starting from reduced vision, field defects, cognitive problems, and problems with hand eye coordination. There is very scant data/literature on the visual evoked potentials (VEPs) at an early age in children with PVL. We did a study to evaluate the flash visual evoked potentials (fVEPs) in children with PVL less than 1 year of age. Materials and Methods: A total of nine children diagnosed as having PVL on magnetic resonance imaging were included in the study. The mean age was 9.7±3.5 months. All children underwent handheld fVEPs under sedation at two different flash frequencies 1.4 and 8 Hz. Results: The mean latency of N1 and P1 on stimulation with 1.4 Hz was 47.9±15.2 ms and 77.7±26.0 ms, respectively. However, on stimulation with 8 Hz the mean latency of N1 and P1 was 189.8±25.6 ms and 238.4±33.6 ms, respectively. The mean amplitude with 1.4 Hz and 8 stimulation frequency was 5.6±4.5 and 5.9±3.5 μV, respectively. Conclusion: We have found for the first time that there is a change in the latency and the delay occurs at 8 Hz frequency but not at 1.4 Hz. We also conclude that amplitudes by fVEPs may be normal even in presence of periventricular changes. The amplitudes of fVEPs are not reliable in children with PVL.

Key words: Cortical visual impairment, flash visual evoked potentials, periventricular leucomalacia, stimulation frequency in visual evoked potentials, visual evoked potentials

Premature birth, asphyxia, infections during pregnancy, and birth trauma are predisposing factors for infant’s brain damage. The most prevalent form of brain injury in preterm infants is due to white matter lesions categorized as periventricular leucomalacia (PVL). PVL is a major cause of motor and cognitive impairment in preterm infants and may also be associated with epilepsy and visual impairments in later life. Recent improvements in the survival rate of extremely premature infants have resulted in an increased incidence of neurological squeal. Okumura et al. reported that PVL was observed in 80% of preterm infants with cerebral palsy. Apart from visual loss, the children with PVL may suffer from strabismus, amblyopia, nystagmus, visual field defects, delayed visual maturation, and increased cup disc ratio. In our own previous study on children with PVL, we found that around 81.6% children had associated strabismus. Fourteen (36.8%) children had nystagmus. It has been controversial whether electrophysiology offers better precision than behavioral techniques in measuring visual acuity in children with brain damage. The visual response has been evaluated previously with forced preferential (FP) looking test and with visual evoked potentials (VEPs) (flash or sweep). In the flash VEP (fVEP), the evaluation has been on the N300 in the preterm infants for the predictive value of their visual function.

We did a study to evaluate the fVEP responses in preterm children with PVL less than age of 1 year and the changes in fVEP responses at various stimulation frequencies.

Materials and Methods

A total of nine preterm children with magnetic resonance imaging (MRI) diagnosed PVL changes were included in the study. The retinal status was normal and the babies had undergone retinopathy of prematurity screening but none needed a laser photocoagulation. The babies were developmentally delayed and so were sent for VEP to our clinic. The final diagnosis of PVL was made on the basis of clinical signs of cerebral palsy and MRI findings including loss of white matter volume, irregularities of the ventricular wall, and abnormal signal intensities in the periventricular white mater. Standard handheld VEP (Roland Consult, Germany) fVEP was performed under sedation. Two or more trials were made to ensure reproducibility of the waveform. The single active electrode was placed at Oz, and the impedance was below 5 ohm. Flash light stimuli, using a hand-held Ganzfield, were presented at a frequency of 1.4 Hz and this was followed by 8 Hz frequency. Fifty responses were averaged for each trial with a band-pass of 1-100 Hz. Responses with excessive artifacts were automatically rejected.

Results

A total of nine infants (18 eyes) were taken for the study. The mean age was 9.7±3.5 months (3-12 months). The mean birth weight was 1638.3±231.7 gm (range 1460-1950 gm). Only two frequencies were used and evaluated. The averaged data for both the 1.4 and 8 Hz frequency were evaluated. The mean latency of N1 and P1 on stimulation with 1.4 Hz was 47.9±15.2 ms and 77.7±26.0 ms, respectively. The mean latency of N2, P2, N3, P3 was 108.6±32.8 ms, 143.3±36.9 ms,
179.4± 41.8 ms, and 211± 44.6 ms, respectively. The mean amplitude with the stimulation at 1.4 Hz N1-P1 was 5.1± 4.5 mV.

On stimulation with 8 Hz frequency with the same hand-held Ganzfeld, the mean latency of N1 and P1 189.8± 25.6 and 238.4± 33.6 ms. The mean amplitude with 8 Hz stimulation frequency was 5.59± 3 mV. The amplitude for both the frequencies was seen to be with in normal limits.

There seems to be a severe delay in the latency of the N1 and P1 when stimulated at a higher frequency. The machine typically has these two inbuilt frequencies at which the light source is delivered for the VEP recording.

**Discussion**

It is well-known that the ocular structures are healthy and the pupillary responses are brisk in children with PVL. The ocular findings do not explain the child’s visual impairment. fVEP has been used to document the visual acuity/potentials in these children. The sweep VEP has been done to predict the visual acuity and comparisons have been made with FP looking tests.

González-Frankenberger et al. found that there that the negative central component (NCC) in normal infants as well as the preterm infants with PVL at 50-52 weeks of gestation during sleep produced “habituation effect” on repetitive stimulation. The NCC was the P2-N3-P3 component in their VEP waveforms. They suggested that when the stimulus is repetitive, the amplitude reduces due to the habituation effect and this occurs even in normal infants. Our findings indicate that once the frequency of stimulation is increased, there is a delay in the latency of the waveforms.

Kidokoro et al. and Kato et al. did fVEP studies on preterm infants during first week of life. They have studied the N300 component and suggested that a latency delay of 330 ms would point significantly toward PVL changes. Kidokoro et al. studied the predictive values of a combination of electroencephalography (EEG) and fVEPs for the early diagnosis of PVL. They compared fVEPs with EEG and found that fVEPs were better for the diagnosis of PVL. Kato et al. presented similar findings and also showed a positive wave at 200 ms termed as P200 which was the first positive wave. Since the studies were done on neonates they mainly studied the N300 and presented the frequency at 0.2 Hz with duration of 10 s. No such study in children less than 1 year of age at increased frequency of stimulation has been done.

Though our study shows that as the frequency increases from 1.4 to 8 Hz the delay in latency is significant, we did not study this at various frequencies where the increase is in steps because these two frequencies were built in. Our study actually raises more questions than it answers. We believe that there may be a critical frequency at which the changes may start appearing. It may be possible and can be taken up in further studies. We did not have a control group since it is difficult to get the normal children for VEP. It is possible that this change in frequency may be critical in normal children less than 1 year of age and may be a normal growth pattern which may be delayed in children with PVL; these are however, just the questions which have come out of this particular study. The increase in the frequency may make it a more sensitive tool once a particular critical frequency is determined which would require further studies to do fVEP at different frequencies of stimulation.

**Conclusion**

We have found that the frequency of stimulation is an important in determining the latency in children with PVL in children less than 1 year of age. The increase in frequency of stimulation increases the latency though the amplitude is not changed much even at higher frequencies. The amplitudes of fVEP in children with PVL is not to be relied upon.

**References**

1. Volpe JJ. Brain injury in the premature infant: Overview of clinical aspects, neuropathology, and pathogenesis. Semin Pediatr Neurol 1998;5:135-51.
2. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. Pediatr Res 2001;50:553-62.
3. González-Frankenberger B, Harmony T, Ricardo-Garcell J, Porras-Katz E, Fernández-Bouzas A, Santiago E, et al. Habituation of visual evoked potentials in healthy infants and in infants with periventricular leukomalacia. Clin Neurophysiol 2008;119:2879-86.
4. Kidokoro H, Okumura A, Kato T, Hayakawa F, Natsume J, Kubota T, et al. Electroencephalogram and flash visual evoked potentials for detecting periventricular leukomalacia. Neuropediatrics 2008;39:226-32.
5. Jacobson LK, Dutton GN. Periventricular leukomalacia: An important cause of visual and ocular motility dysfunction in children. Surv Ophthalmol 2000;45:1-13.
6. Okumura A, Hayakawa F, Kato T, Kuno K, Watanabe K. MRI findings in patients with spastic cerebral palsy. I. Correlation with gestational age at birth. Dev Med Child Neurol 1997;39:363-8.
7. Jethani J. Ocular defects in children with cerebral palsy. Indian J Ophthalmol 2007;55:397.
8. Tinelli F, Pei F, Guzzetta A, Bancale A, Mazzotti S, Baldassi S, et al. The assessment of visual acuity in children with periventricular damage: A comparison of behavioural and electrophysiological techniques. Vision Res 2008;48:1233-41.
9. Kato T, Watanabe K. Visual evoked potential in the newborn: Does it have predictive value? Semin Fetal Neonatal Med 2006;11:459-63.
10. Mirabella G, Kjaer PK, Norcia AM, Good WV, Madan A. Visual development in very low birth weight infants. Pediatr Res 2006;60:435-9.
11. Kato T, Okumura A, Hayakawa F, Kuno K, Watanabe K. The evolutionary change of flash visual evoked potentials in preterm infants with periventricular leukomalacia. Clin Neurophysiol 2005;116:690-5.
12. Good WV. Development of a quantitative method to measure vision in children with chronic cortical visual impairment. Trans Am Ophthalmol Soc 2001;99:253-69.
13. Good WV, Hou C. Sweep visual evoked potential grating acuity thresholds paradoxically improve in low-luminance conditions in children with cortical visual impairment. Invest Ophthalmol Vis Sci 2006;47:3220-4.
14. Lim M, Soul JS, Hansen RM, Mayer DL, Moskowitz A, Fulton AB. Development of visual acuity in children with cerebral visual impairment. Arch Ophthalmol 2005;123:1215-20.

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