Multi-channel visually evoked potentials in the assessment of visual pathway structure and function in children with marked brain abnormalities

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Abstract

Background/purpose

To demonstrate how multi-channel visual evoked potentials (VEP) can provide quantitative measures of visual function in in children with marked cortical anatomy abnormalities.

Methods

Four children with marked brain pathology (2 holoprosencephaly, 2 giant interhemispheric cysts with hydrocephalus) underwent pattern reversal and flash VEP recordings from 16 equally distributed electrodes. Voltage maps of the major VEP components were constructed, and their distributions compared to the MRI findings.

Results

No reproducible responses were evident in one case. Responses were present, but as expected based on the MRI finding not over the occipital electrodes in 3 cases. As a result the standard clinical VEP electrode placement would not have detected any reponses. The distribution of responses during monocular testing obtained in 2 cases suggested normal decussation of the visual pathways at the chiasm, while voltage mapping eluded to which part of the abnormally positioned brain tissue is functional visual cortex. VEPs provide a quantifiable measure of visual function that could be used to assist in determining visual acuity levels, and provided a baseline for monitoring in the context of raised intracranial pressure.

Conclusions

These cases demonstrate that in children with markedly abnormal brain anatomy multichannel VEP recordings are able to provide quantifiable measures of visual pathway function detected in atypical locations. These recordings were also able to identify functional anatomical structures that were not apparent on inspection of the MRI. In a clinical setting the use of additional recordings from non-standard electrode placement based on the MRI findings is suggested.

Introduction

In pediatric ophthalmology practice, a combination of subjective and objective testing is routinely used to assess visual function in children of different ages and abilities. Visually evoked potentials (VEP) use electrodes placed on the skin over the occipital regions to detect responses to time locked pattern or flash stimulation. Although at times difficult to achieve in children, the benefits of these techniques– particularly where behavioral vision testing is not possible due to age or ability – is well documented.

The International Society for Clinical Electrophysiology of Vision (ISCEV) standards for clinical visual evoked potentials states that the minimum standard for a VEP recording is a single active channel at Oz. It recommends that for detection of trans occipital asymmetries, up to five electrodes should be placed over the occipital lobe, referred to a mid frontal reference[1,2]. In the research setting larger arrays of electrodes are used to investigate the pediatric visual system in both normal development and disease processes[3,4].

The location of any evoked potential recorded from the scalp is dependent on the location of the cortex activated and the orientation of the dipole. In some cases the orientation of the dipole results in responses not being recorded where you would expect. An example of this can be observed in control subjects with normal brain anatomy. The main component of the pattern reversal VEP (the p100) is recorded over the occiput contralateral to the hemisphere being stimulated. This is due to the cortical generators being located down the calcarine sulcus, and therefore the dipoles project obliquely towards the opposite hemisphere[5]. Clinically this is known as paradoxical lateralization. As a result during full field stimulation the pattern reversal VEP is symmetrical across the midline due to equal activation of the left and right hemispheres. Therefore in patients with marked brain pathology it stands to reason that it would not be possible to predict the location of the cortex activated by the visual pathways, and what orientation the dipoles would project to. Consequently employing a larger array of electrodes would maximize the chances of identifying a response.

In this case series we aim to demonstrate how either using large arrays of electrodes, or in a clinical setting using non standard placement of a smaller array during VEP testing can assist in detecting visual function and identifying its location in children with marked brain abnormalities.

We present four cases; two with holoprosencephaly and two with giant interhemispheric cysts and severe hydrocephalus. Holoprosencephaly is the most common disorder of the developing forebrain in humans, with a frequency up to 1 in 250 conceptuses and approximately 1 in 10,000 live births. It is caused by chromosomal abnormalities in 50% of cases[6] and is characterized by failure of the forebrain to bifurcate into two hemispheres- a process normally complete by the fifth week of gestation[7]. Giant interhemispheric cysts are congenital and also rare. There is no uniformity in pathogenesis among previously reported cases[8]. Both conditions are associated with agenesis of the corpus callosum in some but not all cases[8,9].

Subjects and methods

The study was approved by the National Health Service Research Ethics Committee for London and followed the tenets of the Declaration of Helsinki.

Visual Electrophysiology methods

Sixteen silver–silver chloride electrodes were used to record the electroencephalogram (EEG) positioned at sites in accordance with the International 10–20 system[10] (Fz, F3, F4, Cz, C3, C4, T7, T8, Pz, P3, P4, Oz, O1, O2, P7, P8,) referenced to linked mastoid. The impedance of the electrodes was maintained below 5kΩ throughout the recording. Continuous EEG was collected using a Neuroscan-SCAN system (version 4.3; Compumedics USA, Ltd., El Paso, TX, USA) at a sampling rate of 1,000 Hz, with a low pass of 100 Hz and a high pass of 0.3 Hz and stored on a computer for offline analysis. The continuous EEG data were epoched offline with a time base of -100 to 500ms. To ensure reproducibility of the responses, a minimum of two trials with a minimum of 120 epochs were recorded and then grand averaged together. Voltage maps were constructed of the main positivity of the VEP waveform. The Neuroscan software applies a color gradient to the range of voltage amplitudes. As there are fewer electrodes than pixels in the map the values between electrodes are filled using an interpolation algorithm employing the voltage from the four nearest neighboring electrodes.

Flash stimuli were presented using a hand-held strobe (Grass model PS22), at a stimulation rate of 3 Hz, and intensity setting 4.0. Pattern stimuli consisted of a reversing checkerboard at a rate of three reversals a second with checks of 97% contrast subtending angles of 6.25 to 400 minutes of arc depending on the co-operation of the child. All children had recordings to 50 minutes of arc. Stimuli were presented in a 28 degree field. The stimuli were displayed on a plasma display screen (Model PDP 433MXE –Pioneer Electronics Corp. Tokyo, Japan.) with a luminance of 66 cd/m^2. The screen was positioned with the center of the screen at eye level and at a distance of 1 meter from the patient in mesopic conditions. The children were encouraged to maintain fixation by an assistant orientating the child to the stimulus by using small noisy toys where needed. To maintain alertness and attention, the stimuli were alternated with cartoons. Fixation accuracy was monitored via a close

circuit TV system, and data acquisition was paused if any fixation loss was seen. The pattern stimuli were generated using Neuroscan-STIM software (version 4; Compumedics USA, Ltd., El Paso, TX, USA). Monocular responses were recorded for each eye where possible and/or appropriate.

The voltage maps constructed were compared to T1 weighted axial and sagittal magnetic resonance images (MRI)

Patient 1

A four year old girl with severe semi-lobar holoprosencephaly who was not expected to survive past birth was referred for assessment of her visual function. MRI showed severe dysmorphia of the brain, agenesis of the corpus callosum, an absent third ventricle as well as fused thalami and basal ganglia. Her parents reported normal visual behavior milestones throughout her life despite clinicians suggesting very poor visual function and prognosis. Her visual acuity in either eye was 0.86 cycles per centimeter at 84cm using Teller acuity cards. Fundus and media examination was unremarkable, with normal pupil reactions, normal refraction for age and no nystagmus evident.

Patient 2

A 2 year old girl was referred to the department for visual electrophysiology testing with a diagnosis of alobar holoprosencephaly and VP shunted hydrocephalus. Standard electrode placement recordings at a local hospital did not reveal any VEPs. At clinical assessment no consistent visual behavior could be demonstrated, yet her parents had seen some occasional evidence, such as fixing and following them as they moved through a room or smiling to their faces as they silently appeared in front of her.

On examination no consistent fix and follow was elicited, no nystagmus was seen, and there was a highly variable manifest horizontal deviation of the left eye. Fundus and media examination showed bilateral iris and chorioretinal coloboma partially involving the optic discs with preservation of the neuroretinal rim superiorly.

Patient 3

A 34 week old girl was referred to the ophthalmology department after being diagnosed antenatally with a giant interhemispheric cyst, with almost complete agenesis of the corpus callosum and obstructive hydrocephalus. An interuterine third ventriculostomy was attempted but failed., She was born at term by cesarean section and a VP shunt was placed shortly after birth. A post natal MRI showed features felt to be on the septo-optic dysplasia spectrum, but the pituitary gland and stalk were within normal limits. On examination she was able to fix and follow well with a behavioral measure of 0.3 on Cardiff Cards at 1 Meter with either eye. Ocular motility was full and there was no nystagmus. Direct and consensual pupil reactions and anterior segment examination were normal. On fundoscopy her optic nerves were pink in color but borderline in size with a greyish ring around either disc. The fundus was slightly hypopigmented. On retinoscopy she had mild bilateral hypermetropia within normal limits for her age that did not require correction.

Patient 4

A 62 week old female presented after emergency referral to the Neurosurgery Department at Great Ormond Street Hospital for hydrocephalus, where a lack of visual behaviour and no demonstrable fix and follow was noted. Family and birth history was unremarkable. An MRI detected a large cystic mass caused by the dilated fourth ventricle secondary to Blake's pouch cyst in the middle of the optic radiation. MRI and VEP's were obtained before the child proceeded to have an emergency endoscopic third ventriculotomy.

Results

In three of the four cases (patients 1-3) visual evoked potentials were recorded with similar morphologies, but all with atypical and differing scalp locations as a result of the underlying brain abnormalities (figure 1,iii & 2). In all cases pattern reversal stimuli with test checks subtending 50 minutes of arc evoked responses consisting of a positivity-negative complex with the mean latencies at 139ms ± 4.3SD and 218ms ± 15.37SD respectively (figure 2). In patients 1 and 2 it was possible to record VEP responses to smaller test checks of 25 and 12.5 minutes of arc.

In patient 1 responses were recorded maximally over the posterior temporal regions at electrode sites P7 and P8; in case 2 over the frontal regions (electrodes F3 and F4) and over left parietal regions (electrode P7) in case 3. In case 4 no VEPs could be recorded to pattern or flash stimulation.

Voltage maps of the major positive peak of the pattern reversal VEP demonstrated the atypical distribution of the responses compared to normal subjects (figure 1, iii).

In patient 3 the responses were only recorded over the left hemisphere. Although this may reflect right hemisphere visual pathway dysfunction, the absence of a response over the right hemisphere may also be due to the inability to record the activity due to the dipole orientation.

In patients 1 and 2 monocular pattern testing was achieved (figure 3.), both patients had holoprosencephaly. Responses for either eye showed bilateral activation of the tips of the holosphere seen maximally at electrode sites P7 and P8 in patient one, and C3 and C4 in patient 2.

Discussion

In the literature, there are cases of children with similarly marked brain abnormalities who have undergone visual electrophysiology using the standard of occipital placed electrodes. In some of these cases responses are detected over the occipital electrodes[11], and in others they are not[12].

In the cases with recordable VEPs, two had minimal activity over the occipital regions while one had none. Without recordings with larger arrays of electrodes all of the cases could potentially be reported as having no evidence of post retinal activation.

Clinical visual electrophysiology systems commercially available tend to support 3-5

active channels in keeping with the requirements for the ISCEV VEP recording standard, with multi channel systems available more in the research setting. Therefore we suggest that in similar cases seen in clinical labs, if no responses are evident at the normal electrode sites, based on the MRI findings the clinician can estimate where the dipoles may be orientated and move the 3-5 active channels from the standard locations to another area of the head where responses may be detected.

In the holoprosencephaly patients the recorded VEPs were at the posterior parts of the holosphere in keeping with the cortical structures described in the literature from histopathology and functional MRI studies[13,14]. In both holoprosencephaly patients monocular responses were similar in distribution for each eye, suggestive of a functional chiasm that was not detectable by MRI.

Despite the striking neuroimaging abnormalities the presence of pattern reversal responses to 50 minutes of arc suggests the potential for pathways to support good vision levels. In patients 1 and 2 the potential for good vision was further supported by the presence of VEP responses to 25 and 12.5 minutes of arc. In patient 4 the absence of any responses to pattern or flash stimulation indicated marked general and macular pathway dysfunction. In two of the patients reported (2 and 4) it had not been possible to obtain an estimate of visual acuity using behavioral testing. In patient 2 the parents felt the child could see, but were not able to get confirmation of this with behavioral visual acuity assessment. The pattern reversal responses gave objective evidence to assure them of the presence of cortical visual function. In patient 4 there was an absence of any visually evoked responses. This child had the most normal looking occipital cortex of all of the cases, yet the least function, illustrating the need for functional testing in combination with neuroimaging.

All the 4 cases presented were being monitored by neurosurgical teams for raised inter cranial pressure (ICP). Changes in ICP have a well-documented affect on VEP amplitude and latency[15–17]. Therefore in these children where responses were present, the responses not only gives a quantitative measure of visual function but also provides a baseline for monitoring the effects of changes in ICP.

Conclusions

In these cases of marked structural brain abnormalities, employing multichannel recordings allowed us to obtain structural and functional information about their visual pathway. The presence of the well defined pattern reversal responses in 3 cases would have been missed if we had used a standard 3 channel montage over the occipital regions. Although review of the MRI in isolation would not have been able to determine the presence or absence of a chiasm in cases 1 and 2, the monocular VEPs revealed bilaterally distributed responses that can be explained by the presence of a functional chiasm.

We suggest that children with markedly abnormal brain anatomy undergoing visually evoked potentials should have multi channel recordings carried out to stand the best chance of recording responses and maximizing the structural and functional information gained. In a clinical setting where a multichannel system may not be available we suggest clinician's attempt recordings from non-standard VEP electrode placement sites directed by the MRI findings.

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Figure legends

Figure 1. T1-weighted sagittal (i) and axial (ii) magnetic resonance images (MRI) from all patients (P1-P4). Voltage maps (iii) of the pattern reversal main positivity at around 140ms from patients P1-P3.

Figure 2. (a-c) Pattern reversal VEP waves forms from all 16 channels in patients 1-3. The grey shaded area corresponds to the location of with maximal responses. (d) Representative VEP waveform from each patient.

Figure 3. Pattern reversal VEPs to 50 minutes of arc during right and left eye independent stimulation from electrode placement sites P7 P3 P4 and P8.