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Changes in the background EEG in response to activation procedures in strabismic amblyopes depending on type of fixation in the amblyopic eye

I. M. Boichuk, Badri Wael

Filatov Institute of Eye Diseases and Tissue Therapy, NAMS of Ukraine

Odesa (Ukraine)

Background: *Analysis of electroencephalogram (EEG) visual-evoked potentials (VEPs) is important for assessing the general integrity of the visual pathway. Pathology in any portion of the visual pathway causes changes in VEP. Percentages of alpha, beta, delta and theta rhythms in the EEG record, frequencies and amplitudes of these waves, and the level of alpha-rhythm suppression are essential for characterizing the state of the visual system.*

Purpose: *To indentify the features of the state of the visual system and changes in the background EEG in response to activation procedures in strabismic amblyopes depending on type of fixation in the amblyopic eye.*

Material and Methods: *Fifty-two strabismic amblyopic patients aged 5-8 years and 15 healthy children of the same age underwent an examination. Of the amblyopic children, 32 had unilateral amblyopia with esotropia (6-15 degrees). Of these 32 children, 20 had eccentric fixation and 12 children, central fixation. The 10–20 system of electrode placement was employed to perform EEG in all children. Rhythms of the background EEG, interhemispheric asymmetry and alpha, theta and delta wave percentages were assessed. Brain potentials were recorded using standard activation procedures to activate deep brain structures.*

Results: *Alpha rhythm was not discernable in the background EEG in the occipital areas in 3.0 ± 2.6 % of cases, and the alpha index was below the normal range in 48.6 ± 8.2 % of patients with a visual acuity worse than 0.3. Delta index was above the normal range (25%-45%) in 48.6 ± 8.2 %, and theta index was above the normal range (with a mean value of 48.4 ± 8.2 %) in 48.6 ± 8.2 % of children. Reduced percentage of alpha activity was found in almost half of strabismic amblyopic children, indicating immaturity of the synchronizing system and impaired oculomotor tuning in the eyes of these children. Abnormal bilateral EEG response to eye-opening stimulation and abnormal bilateral EEG rhythmic driving response (RDR) were seen in most children with eccentric fixation, but not in most children with central fixation. Photic stimulation in strabismic amblyopic children resulted in bilaterally asymmetrical and synchronous theta and delta waves in symmetric frontal (theta and delta percent time of 46.0 ± 8.4%) and occipital (theta and delta percent time of 50.0 ± 8.4%) responses.*

Conclusion: *Increased theta and delta wave percentages in frontal and occipital derivations were found in strabysmic amblyopes (irrespective of type of fixation in the amblyopic eye) compared to healthy controls. Abnormal EEG response to eye opening and abnormal EEG RDR were found in strabysmic amblyopes. This indicates the presence of functional changes in the midline brain structures including the corpus callosum, which impedes the development of binocular vision in strabismic amblyopes.*

Keywords:

strabismic amblyopia, fixation, electroencephalogram

Introduction

Analysis of electroencephalogram (EEG) visual-evoked potentials (VEPs) is important for assessing the general integrity of the visual pathway. EEG with VEP recording is used for studies in neonates, uncooperative children, and animals. Percentages of alpha, beta, delta and theta rhythms in the EEG record, frequencies and amplitudes of these waves, and the level of alpha-rhythm suppression are essential for characterizing the state of the visual system [1-3]. VEP represents the response of large populations of visual cortex neurons to synchronous stream of pulses induced by an afferent stimulus. Since the VEP reflects the activity of the sensory visual pathways from the retina to the visual cortex, pathology in any portion of the visual pathway causes changes in VEP; this requires utilizing a number of treatment procedures, which differ in the type of effect they exert on the patient's affected eye. This treatment is durable, financially burdensome for patients and often has poor outcomes, with a treatment success rate varying from 14.5% to 81.2% [3]. Therefore, further research is warranted on the etiology and pathogenesis of amblyopia to develop novel treatment methods with improved success rates, based on novel advances in the physiology and pathology of the visual system.

Rhythmic activity on the RRG develops in the first three months of age. Alpha rhythm develops and the amount of theta and delta activity gradually decreases from 7 to 12 months of age. Slow alpha rhythm (7-8.5 Hz) dominates the EEG with its frequency gradually increasing, and a small amount of theta and delta activity is present by 1 year. Between 1 and 7-8 years of age, slow rhythms are still gradually replaced by faster rhythms, and beta rhythm evolves. After 8 years of age, the EEG becomes dominated by the alpha rhythm [4-6]. However, the appearance of theta and delta wave amplitudes which do not exceed the amplitude of background alpha activity and are not of a regular type or related to a particular location should not be regarded as pathology [7]. The evolution of normal EEG completes and the frequency of the alpha rhythm progressively increases to a normal range of 8-12 Hz by the age of 16-18 years. Thereafter, the EEG remains stable throughout the rest of life if the brain undergoes no damage.

Alpha rhythm reflects the degree of cortical maturation [8-10]. Alpha rhythm depression with eye closure or opening is associated with oculomotor tuning [4, 11]. The beta rhythm is associated with cortical somatic, sensory and motor mechanisms and has demonstrated responses related to motor activity or tactile stimulation. In addition, beta activity that fails to respond to eye-opening and eye-closure is a common finding [1, 4, 6, 10, 12].

The presence of pathological theta and delta waves may be caused by impairment in the medial brain structures (medulla oblongata, the pont, midbrain, thalamus and hypothalamus), and lesions in some mediobasal limbic subcompartments (hippocampus, amygdala, orbital cortex and anterior cingulate gyrus) and the corpus callosum, which unites both hemispheres [2, 4, 5, 11]. Interhemispheric synchronization and coherence of rhythms in the EEG determines the state of the corpus callosum [13] and brainstem reticular formation [4]. In addition, non-specific thalamic nuclei participate in the synchronization of the EEG activity, whereas the brainstem reticular formation is involved in the mechanism of desynchronization [14, 15]. Functional relationships between these systems involve the suppression of the function of synchronization mechanism of non-specific thalamic nuclei by the reticular formation impulses.

EEG records are commonly used for the diagnosis of the severity and type of central nervous system (CNS) lesions [5, 7, 14, 16]. EEG signs of impairment in the subcortical structures associated with the oculomotor apparatus have not been previously examined in patients with amblyopia. The motor and sensory components of vision are, however, of similar importance for visual perception.

The purpose of this study was to indentify the features of the state of the visual system after the response of the background EEG to activation procedures in strabismic amblyopes depending on type of fixation in the amblyopic eye.

Material and Methods

Sixty-seven children underwent an examination. These included 52 children aged 5-8 years with strabismic amblyopia and 15 healthy children of the same age. Of the amblyopic children, 32 had unilateral amblyopia with esotropia (6-15 degrees), and 20 had mild amblyopia with alternating strabismus. In addition, 32 children had eccentric fixation and 20 children had central fixation. The best-corrected visual acuity (BCVA) was less than 0.3 in 32 children and ranged from 0.5 to 0.75 in 20 children. In addition, binocular function was assessed using the Worth 4-dot test and synoptophore. Most children exhibited the monocular vision, and only 20 ± 7.1 % children exhibited normal fusional amplitude as assessed by the synoptophore. Background EEG was recorded from all children. EEG was performed using an 8-channel EEG machine (Medicor EEY8S) and a 16-channel computer QUATTOR system employing 10–20 system of electrode placement for 37 children and 30 children, respectively.

Rhythms of the background EEG, interhemispheric asymmetry and alpha, theta and delta wave indices were assessed. Brain potentials were recorded using standard activation procedures to activate deep brain structures [2, 5]. Activating function of the brainstem reticular formation was assessed by EEG response to bilateral eye opening through the alpha-rhythm depression reaction. In addition, activating function of the rostral reticular formation was assessed by the hyperventilation EEG through increased theta and delta-wave indices in the frontal and anterior parietal derivations [2]. An EEG response to hyperventilation was assessed as per the protocol [2]. An EEG response to alternating eye opening was used as an indicator of the integrity of the prechiasmal pathway. A response to 10-Hz photic stimulation (the rhythmic driving response, RDR) was used as a measure of maturity of cortical neurons [3, 15]. The performance of the thalamocortical relay was assessed through the RDR to unilateral and bilateral photic stimulation with the eyes closed to exclude the effect of reticular formation. In addition, eyes closed EEG synchronization was assessed at symmetric EEG derivations (Fp2 - F4 – Fp1 - F3; F4 - C4 – F3 - C3; C4- P4 – C3-P3; P4-O2 – P3-O1) to detect the absence of connection through the corpus callosum [4, 11, 13].

Statistica 8.0 (StatSoft, Tulsa, OK, USA) software was used for statistical analysis. Mean (M) and standard deviations (SD) were calculated for quantitative variables. The Kolmogorov-Smirnov test was applied to test for a normal distribution and Student t test was used to determine if statistically significant differences existed. Multiple post hoc comparisons were performed using the Newman–Keuls correction or chi2 test for contingency table analysis.

The study followed the ethical standards stated in the Declaration of Helsinki, the European Convention on Human Rights and Biomedicine and relevant laws of Ukraine.

Results

Among the control children, 65.0 ± 12.3 % exhibited a well-organized EEG (as per the classification by Zhirmunskaia [5]). In addition, regional differences were preserved and predominant in 80.0 ± 11.5 % of the controls. The interhemispheric asymmetry of 10% or less was found in 60.0 ± 12.6 % of the control children. The EEG alpha rhythm was poorly modulated, more common in the occipital derivations, and was of 7-8 Hz and 20-40 μV amplitude in 68.8 ± 10.4 % of the control children. Slow activity in the form of theta and delta waves (25-30 μV) was greatest in the occipital derivations in 15.0 ± 9.2 % of healthy children. Unilateral or bilateral eye opening-closing was found to block alpha rhythm in 68.0 ± 10.4% of children. The RDR was moderate for both hemispheres, and the interhemispheric amplitude difference was not significant. Photic stimulation resulted in symmetric waveforms in transverse derivations of the EEG, with the amount of slow oscillations corresponding to the background activity. Hyperventilation resulted in synchronization of alpha rhythm in 60 ± 12.6 % of healthy children, and in occurrence of slow theta and delta waves in frontal derivations not exceeding 20% of recording time in 40% of healthy children. As per the recommendations by Gnezditskii [2, 11] and Zenkov [4], these values were considered to be normal for healthy children aged 5 to 8 years.

Our examination of amblyopic strabismic children demonstrated abnormal background EEG patterns, with the severity of abnormality varying with the visual acuity in the amblyopic eye. The interhemispheric asymmetry exceeding age-matched reference values (> 10%) was found in 40.0 ± 12.6 % of children with a visual acuity worse than 0.3 ($p < 0.01$). The interhemispheric asymmetry was larger in these children than in those with refractive or strabismic amblyopia and a visual acuity better than 0.3 ($p < 0.05$) in the amblyopic eye.

Increased alpha fronto-occipital coherence was seen in 80.0 ± 11.5 % of strabismic amblyopic children. The difference compared to controls was statistically significant ($p < 0.05$).

Alpha rhythm was not discernable in the background EEG in the occipital areas in 3.0 ± 2.6 % of cases, and the alpha index was below the normal range in 48.6 ± 8.2 % of patients with a visual acuity worse than 0.3. Delta index was above the normal range (25%-45%) in 46.6 ± 12.8 %, and theta index was above the normal range (with a mean value of 48.4 ± 8.2 %) in 20.2 ± 8.9 % of children. Abnormality in the background EEG was less severe in unilateral strabismic amblyopes with a visual acuity better than 0.3. Increased alpha fronto-occipital coherence was seen in 70.0 ± 10.2 %, the alpha index was below the normal range in 17.7 ± 5.2 %, and the delta index was above the normal range (25% -45%) in 30.0 ± 10.2 % of children. Fig. 1 shows data on the response of background EEG to activation procedures in unilateral strabismic amblyopes depending on whether fixation was central or eccentric.

No EEG response in both hemispheres to bilateral eye opening was found in most patients with eccentric fixation ($\chi^2 = 5.1$, $p = 0.02$); in the hemisphere contralateral to the amblyopic eye to bilateral eyes opening, in 90.7% of cases

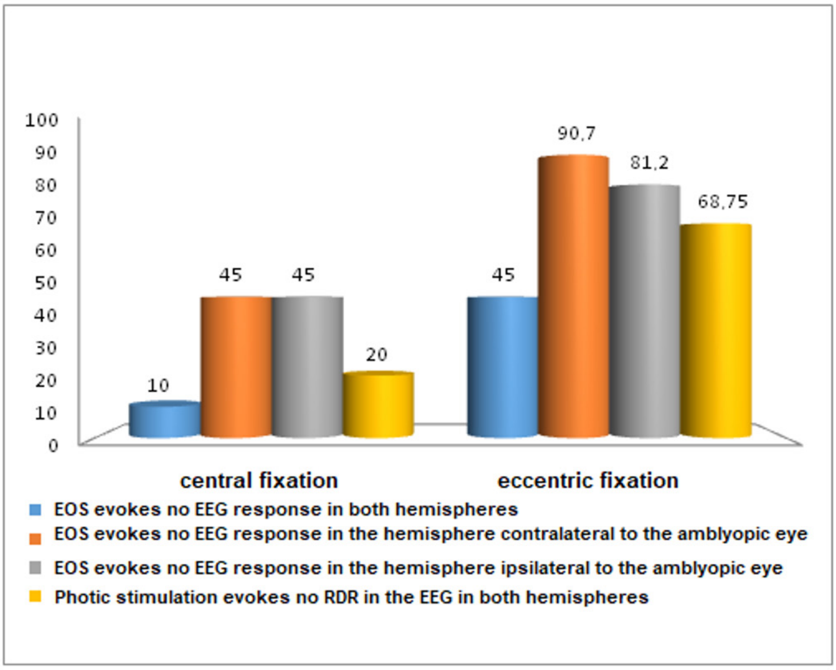

Fig. 1. Rates of abnormal EEG response to activation procedures in strabismic amblyopes depending on type of fixation in the amblyopic eye. Notes: EEG, electroencephalogram; EOS, eyes-opening stimulation; RDR, rhythmic driving response

($\chi2$ = 10.01, p = 0.001); and in the hemisphere ipsilateral to the amblyopic eye, in 81.2% of cases ($\chi2$ = 5.8, p = 0.001). No normal rhythmic driving response (RDR) (a change in the frequency of the rhythm according to the stimulation rhythm and a change in EEG amplitude in occipital derivations) to bilateral stimulation was seen thrice more frequently in children with eccentric fixation compared to those with central fixation (68.75% versus 20%, p= 0.001; Fig. 1). Photic stimulation in strabismic amblyopic children resulted in bilaterally asymmetrical and synchronous theta and delta waves in symmetric frontal (theta and delta percent time of 46.0 ± 8.4%) and occipital (theta and delta percent time of 50.0 ± 8.6%) derivations.

Discussion

Because desynchronization (activation) of the visual cortex is enabled by the brainstem reticular formation, the loss of desynchronization is caused by reticular formation dysfunction, which may indicate also the presence of impairment in control of the oculomotor apparatus in patients with amblyopia. It is this EEG abnormality (reflected in the loss of alpha rhythm suppression response to bilateral eye opening and RDR) that we observed in most (67-90%) strabismic amblyopic children. Zenkov [4, 15] reported that this type of changes indicates a reduced activating capacity of the reticular formations in rostral (superior) and pontine (middle) brainstem as well as immaturity of the midbrain structures [4, 8, 15].

The response to rhythmic photic stimulation depends of the state of the thalamocortical relay and mesencephalic reticular formation [4, 11]. Because in the current study, rhythmic photic stimulation was performed with eyes closed, we determined mostly response of retinal cones and associated afferent portion of the pupillary response, and response of the proprioceptors whose pathways are associated with mesencephalic reticular formation and superior colliculus. No RDR was seen in 80.0 ± 11.5 % of strabismic amblyopes with eccentric fixation and 70.0 ± 12.2 % of strabismic amblyopes with central fixation. This abnormal EEG response to rhythmic photic stimulation with closed eyes indicates weakened unilateral and bilateral thalamocortical links and loss of oculomotor regulation at the level of upper brainstem reticular formation. Generally, in the current study, reduced percentages of alpha activity were found in almost half of strabismic amblyopic children (48.6 ± 8.2) %), indicating immaturity of the synchronizing system and impaired oculomotor coordination between the eyes in these children. Alpha rhythm blockage or suppression is characteristic for healthy children, and the absence of this feature in strabismic amblyopic children indicates problems with the transmission of specific impulses to the projection areas of the visual cortex

Increased theta and delta powers in the frontal and occipital regions were found in children with strabismic amblyopia compared to healthy children of the same age. This indicates the presence of functional changes in the midline brain structures including the corpus callosum [13, 14]. The presence of bilaterally asymmetrical and synchronous theta and delta waves in frontal and occipital responses indicates a partial or complete loss of interhemispheric links via the corpus callosum between superior oculomotor control centers (frontal eye fields and the primary motor occipital cortex, within a half-sphere and between the two hemispheres). We found no such changes in healthy controls or amblyopes with central fixation.

The above CNS functional abnormalities may become a major stumbling block in the restoration of binocular vision in strabismic amblyopes, which is frequently seen in clinical practice.

Conclusion

Increased theta and delta wave percentages in frontal and occipital derivations and abnormal rhythmic responses to bilateral eye opening and RDR (indicating the presence of functional changes in the midline brain structures including the corpus callosum) were found in strabysmic amblyopes (irrespective of type of fixation in the amblyopic eye), compared to healthy controls. These changes were more pronounced in amblyopes with eccentric fixation compared to those with central fixation.

Photic stimulation in strabismic amblyopic children resulted in bilaterally asymmetrical and synchronous theta and delta waves in symmetric frontal (theta and delta percent time of 46.0 ± 8.4%) and occipital (theta and delta percent time of 50.0 ± 8.6%) responses. Changes of this kind were not noted in healthy children.

The abnormalities revealed in oculomotor control-related interhemispheric links may explain problems in the development of binocular vision in strabismic amblyopes. These findings allow to recommend background EEG studies and analysis of changes in the EEG in response to activation procedures (particularly, bilateral eye opening and RDR) in strabismic amblyopes as measures helpful for predicting the success of further treatment of and correction for these abnormalities by ophthalmologists in cooperation with neuropathologists.

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Disclosures

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