Abnormal Function of the Parvocellular Visual System in Anisometric Amblyopia

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ABSTRACT

Purpose: To study the function of the parvocellular (P) and the magnocellular (M) visual systems with steady-state visual evoked potentials (VEPs) in anisometric amblyopes.

Methods: A matrix of isolated checks was superimposed on a steady background with different check sizes and temporal frequencies to form specific stimuli to preferentially activate the P or the M visual system. The amplitude of the VEP fundamental frequency was analyzed at the electrode Oz of 5 anisometric amblyopes and 22 normal subjects. The normal subjects were tested at two visual acuity (VA) levels, 20/20 and 20/40, modified by lenses, to match with the VA levels of the fellow eyes and the amblyopic eyes of the amblyopes, respectively.

Results: No significant amplitude difference was found between the dominant eyes and nondominant eyes of the normal subjects for either P or M stimuli at both 20/20 and 20/40 VA levels (P>.05). No significant amplitude difference was found between the fellow eyes of the amblyopes and the dominant eyes of normals for either P or M stimuli at 20/20 VA level (P>.05). A significant amplitude difference was found between the amblyopic eyes and the nondominant eyes of the normals for P stimuli (P<.05) but not for M stimuli (P>.05) at 20/40 VA level.

Conclusions: The amplitude of the VEP fundamental frequency was selectively reduced for P stimuli in anisometric amblyopic eyes. This clinical electrophysiologic finding confirms that only the function of the P visual system is abnormal in anisometric amblyopic eyes.


INTRODUCTION

Amblyopia is a common visual developmental anomaly in children, occurring as optically uncorrectable subnormal visual acuity (VA) in an otherwise normal eye. Anisometric amblyopia is one type of amblyopia with significantly different refractive error between the two eyes. The exact mechanism of anisometric amblyopia is still not known, which limits progress in its prevention and treatment.1
TABLE 1
DATA FOR THE FIVE ANISOMETROPIC AMBLYOPES

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Affected Eye</th>
<th>Surgery History</th>
<th>Gender</th>
<th>Age</th>
<th>VA of Affected Eye Uncorrected</th>
<th>VA of Affected Eye Corrected</th>
<th>VA of Fellow Eye Uncorrected</th>
<th>VA of Fellow Eye Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>V10</td>
<td>OS</td>
<td>None</td>
<td>Female</td>
<td>35</td>
<td>20/50</td>
<td>20/40</td>
<td>20/20</td>
<td>Same</td>
</tr>
<tr>
<td>V16</td>
<td>OS</td>
<td>None</td>
<td>Female</td>
<td>30</td>
<td>20/40</td>
<td>20/40</td>
<td>20/20</td>
<td>Same</td>
</tr>
<tr>
<td>V17</td>
<td>OS</td>
<td>None</td>
<td>Male</td>
<td>16</td>
<td>20/200</td>
<td>20/40</td>
<td>20/200</td>
<td>20/20</td>
</tr>
<tr>
<td>V68</td>
<td>OD</td>
<td>None</td>
<td>Female</td>
<td>65</td>
<td>20/70</td>
<td>20/40</td>
<td>20/50</td>
<td>20/20</td>
</tr>
<tr>
<td>V70</td>
<td>OS</td>
<td>None</td>
<td>Female</td>
<td>24</td>
<td>20/70</td>
<td>20/40</td>
<td>20/40</td>
<td>20/20</td>
</tr>
</tbody>
</table>

Abbreviations: VA=visual acuity.

Visual information is transferred from the retina to the cortical visual centers of the brain by two visual subsystems, the parvocellular (P) and the magnocellular (M) systems. These two systems are composed of two parallel visual pathways that differ in anatomy, physiology, and function. The P pathway is responsible for fine central form vision (VA) and color vision. It is more sensitive to high spatial frequency and low temporal frequency stimuli. The M pathway is responsible for peripheral coarse form vision (visual field) and fast movement perception. It has much greater contrast gain at the low end of the contrast range and responds better to low spatial and high temporal frequencies. These two pathways carry visual signals in parallel to the occipital cortex and other central nervous system areas.

Electrophysiologic studies, especially visual evoked potentials (VEPs), have been used to study the mechanisms of human amblyopia. Using specific stimuli to selectively probe brain activity in each of the two parallel pathways by proper selection of spatial frequency, temporal frequency and contrast is, however, a relatively new endeavor. This study examined the function of the two visual pathways in human anisometropic amblyopia by fundamental frequency analysis of steady-state VEP with stimuli designed to activate the P or M pathway.

MATERIALS AND METHODS

The study followed the tenets of the Declaration of Helsinki and received institutional review board approval. Written informed consent was obtained from the subjects or their parents. Five anisometric amblyopes and 22 normal control subjects comprised the study population. All patients had complete ophthalmologic examinations, which confirmed the diagnosis and ruled out unrelated visual problems (Table 1). The refractive errors of the amblyopic eyes and their fellow eyes were properly corrected by lens to achieve the best VA. The VA of the amblyopic eyes was 20/40±4. Twenty-two normal subjects (14 males and 8 females) ranged in age from 9-57 years. Twelve subjects were right-eye dominant, and 8 were left-eye dominant. By means of optical blur with consecutive lenses, the normal control subjects were tested at VA of 20/20 and 20/40 under monocular conditions.

Steady-state VEPs were recorded in response to stimuli produced by a Neuro-Scientific VENUS system (Neuroscientific Corp, Farmingdale, NY). A matrix of isolated checks superimposed on a steady background of 62 cd/m² formed the basic visual stimuli on a monitor. Checks with sides of 16’’ arc (lower fundamental spatial frequency) were modulated sinusoidally in appearance/disappearance mode at 12 Hz (higher temporal frequency) and at 8% (lower) contrast for the M pathway stimulus. Checks with sides of 8’’ arc (higher fundamental spatial frequency) were modulated sinusoidally at 6 Hz (lower temporal frequency) and at 16% (higher) contrast around a steady pedestal of 32% contrast with the background for the P pathway stimulus. The display subtended a visual angle of 9’’.

Visual evoked potential data were acquired and analyzed by a NeuroScan Synamp system (Neuroscan Labs, Sterling, Va). Amplifier bandwidth was 1-100 Hz with an A/D rate of 1 kHz. Analysis times were 84 msec for the M stimuli with a total of 600 sweeps and 168 msec for the P stimuli with a total of 300 sweeps. The amplitude of the fundamental frequency was measured at electrode Oz by harmonic analysis (discrete Fourier analysis). The ground electrode was placed on the forehead and the reference was linked to ears.

The amplitude of the VEP fundamental fre-
frequency of the normal subjects was analyzed by the following paired \( t \) tests: dominant eyes versus nondominant eyes for \( P \) or \( M \) stimuli at 20/20 VA, dominant eyes versus nondominant eyes for \( P \) or \( M \) stimuli at 20/40 VA, and 20/20 VA versus 20/40 VA in dominant eyes and nondominant eyes for \( P \) or \( M \) stimuli. Then, the amplitude was compared between the affected eyes of the amblyopes and the nondominant eyes of normals at 20/40 VA level by Student's \( t \) test. Finally, the amplitude was compared between the fellow eyes of the amblyopes and the dominant eyes of the normals at 20/20 VA level by Student's \( t \) test.

**RESULTS**

Effects of Visual Acuity on the VEP Fundamental Frequency in Normal Controls

The amplitude of the VEP fundamental frequency at electrode Oz was analyzed on 22 normal subjects under monocular test conditions. Typical normal waveforms of the steady-state VEPs are shown in the Figure. These waveforms represent averaged data of 22 normal subjects tested at 20/20 VA. Table 2 shows the mean ± SEM amplitudes of these normal subjects for \( P \) and \( M \) stimuli at 20/20 and 20/40 VA levels. No significant amplitude difference was found between the dominant eyes and nondominant eyes for either \( P \) or \( M \) stimuli at either 20/20 or 20/40 VA levels (\( P > .05 \)). For the same eyes, the amplitude was significantly reduced with reduced VA to 20/40 for both \( P \) and \( M \) stimuli (\( P < .05 \)).

**Affected Eyes of the Amblyopes Versus Nondominant Eyes of Normals**

The affected eyes of the amblyopes had a VA of 20/40 ± 4 letters. Comparing the amplitude of these amblyopic eyes with that of the nondominant eyes of the normals at 20/40 VA level showed no significant difference for \( M \) stimuli (\( P > .05 \)) but a significant difference for \( P \) stimuli (\( P < .05 \)) (Table 3).

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**TABLE 2**

<table>
<thead>
<tr>
<th>Stimuli &amp; VA</th>
<th>Dominant Eye</th>
<th>Nondominant Eye</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( M )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/20</td>
<td>2.49±0.35</td>
<td>2.37±0.26</td>
<td>NS</td>
</tr>
<tr>
<td>20/40</td>
<td>1.98±0.26</td>
<td>1.84±0.27</td>
<td>NS</td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/20</td>
<td>3.30±0.26</td>
<td>3.43±0.31</td>
<td>NS</td>
</tr>
<tr>
<td>20/40</td>
<td>2.51±0.23</td>
<td>2.67±0.27</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: NS=not significant.
Fellow Eyes of the Amblyopes Versus Dominant Eyes of Normals

The fellow eyes of the anisometropic amblyopes had a VA of 20/20. The amplitudes of the amblyopic fellow eyes did not significantly differ from that of the dominant eyes of the normals at 20/20 VA level for both P and M stimuli (P > .05) (Table 4).

**DISCUSSION**

Human parallel visual pathways, the M (transient) pathway and the P (sustained) pathway, differ in anatomy, physiology, and function. They have both different lateral geniculate projections and cortical representations. The M pathway originates from M retinal ganglion cells, which have large soma with medium-sized dendritic fields and large axons. These ganglion cells are present at relatively higher density in the fovea, declining as retinal eccentricity increases. The P visual pathway is relatively insensitive to low contrast (low contrast gain), responds linearly to increasing contrast without saturation, and responds better to lower temporal frequencies. It is responsible for fine form vision (VA) and color vision. Due to these differences, the relative contributions of the two pathways to the VEP depend on spatial frequency, temporal rate, and contrast of the stimuli. A higher temporal frequency and lower contrast favors the M pathway and reduces the contribution of the P pathway. Conversely, stimuli using lower temporal frequency with higher contrast favor the P pathway.

The organization of the central nervous system pathways is not complete at birth but continues into early life as a developmental progression from immature to adult axonal patterns. It includes the postnatal segregation of neural projections from the two eyes in the lateral geniculate nuclei, as well as the formation of ocular dominance columns in the visual cortex. During this developmental progression, activity-dependent competition of the postsynaptic neurons in the central visual pathways is critical for forming the final patterning of axonal connections.
Abnormal patterns have been found in animal amblyopic models created by early ocular deviation or unilateral visual blur by long-term administration of atropine. In an animal model of anisometric amblyopia, when one eye of the macaque monkey was blurred, the distribution of deoxyglucose uptake in the visual cortex was strongly biased toward the areas related to the fellow eye when high spatial frequency stimuli were used. The cells of the parvocellular layers of the dorsal lateral geniculate nucleus receiving input from the amblyopic eye were smaller and more lightly stained, histologically, than those of the fellow eye. However, no similar alteration was found with low spatial frequency stimuli or in cells of the magnocellular layers. These alterations presumably occurred because the amblyopic eye was handicapped in the competition with the fellow eye for synaptic connections, known as competitive inhibition, in the central visual pathways during early cortical development. Thus, pathways of the normal fellow eye gained more cortical representation at the expense of those of the amblyopic eye. An abnormal early sensory experience disrupting the normal maturation of the cerebral cortex and leading to selective impairment of the P pathway is hypothesized for amblyopia.

There is limited information about the central nervous system organization in human amblyopes. A postmortem study of the brain of a person with anisometric amblyopia found a decrease of cell sizes in the parvocellular layers of lateral geniculate nucleus innervated by the amblyopic eye. No such difference in cell sizes existed between corresponding layers of the magnocellular laminae. These findings were similar to those in animal models. Clinical studies also indicate that VA and the ability to perceive high spatial frequency stimuli appear to be selectively damaged in human amblyopia. However, whether human amblyopia has a similar cortical basis, as has been seen in the animal models, is an important question to be solved.

Visual evoked potentials are responses in visual cortex to visual stimuli and are influenced by the quality of the visual stimulus. The quality of the visual stimulus is affected by VA. Our study shows the amplitude of the fundamental frequency of steady-state VEP is reduced with degraded visual acuity to P and M stimuli. This suggests that VA affects the VEP amplitude for both types of stimuli, and it must be carefully considered when studying visual dysfunction of M and P pathways with steady-state VEP. Steady-state VEP obtained from patients with visual disorders should be compared with normal controls tested at the same VA level.

Compared with the normal subjects' data tested at the same VA, the amplitude of steady-state VEP in the affected eyes of anisometric amblyopes is reduced for P stimuli, but not for M stimuli. No such abnormality was found in the fellow eyes of these anisometric amblyopes under the same conditions. This suggests that the visual pathway impairment of the anisometric amblyopes involves the P pathway related to the amblyopic eye only. This finding is consistent with the proposed binocular inhibition hypothesis of amblyopia. In anisometric amblyopia, marked disparity in the quality of binocular inputs prevents binocular fusion and results in abnormal binocular competitive interaction. The good eye gains cortical representation at the expense of the weak eye. This leads to active interference with the affected eye's input to higher visual centers and produces amblyopia.

Anisometric amblyopia has refractive differences between the two eyes without ocular deviation. The two eyes have corresponding foveal points throughout the retinal-cortical projections. The binocular fusion inability and competitive inhibition of this disorder are mainly caused by differing image quality and size between the eyes. In this situation, the fovea of the more ametropic eye receives poor stimulation due to defocusing under either monocular and binocular views, and its related neural development is hampered. As central vision is predominantly involved, a selective impairment of the P pathway of the amblyopic eye appears to be a reasonable hypothesis.

Disinocularity caused by imbalance of the visual pathways between the eyes seems to be an important ambyogenic cause. As specific stimuli with proper combinations of spatial frequency, temporal frequency, contrast, color, motion, pattern size, and location on the retina could provide stimulation predominantly to the P or the M pathway, these stimuli might be used to enhance or depress the activation of selected visual pathway and thus might be helpful in minimizing the binocular inhibition and in restoring the normal relationship of the visual pathways in amblyopia. Steady-state VEP with P and M stimuli is an objective method to test the visual function clinically. Used properly,
it could offer valuable information in detecting and preventing amblyopia in its early stage.

CONCLUSION

Clinical electrophysiologic study of steady-state VEP with specific stimuli suggests the function of the P visual system related to the affected eye is selectively impaired in anisometric amblyopia. This supports the binocular inhibition hypothesis of amblyopia and provides useful information for preventing and treating amblyopia in its early stages.

REFERENCES