Pupillary responses in amblyopia

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Abstract
Relative afferent pupillary defects (RAPD) were detected in 32-3% of patients with amblyopia by a modification of the swinging flashlight test and the synoptophore. After consideration of various clinical investigations the significant factors identified in patients showing a RAPD were: anisometropia, early age of onset where strabismus was present, level of visual acuity following treatment, longer period of occlusion therapy. These points bear similarities to the results of pattern electroretinograms (PERG) in amblyopes, and the possibility of the causative defect being at ganglion cell level is discussed. The effect of occlusion treatment cannot be predicted from the presence or absence of a RAPD.

An afferent or relative afferent pupillary defect has been reported to be present in between 9% and 93% of amblyopes. The main criticism of these findings is that poor fixation in the amblyopic eye may result in the light stimulus striking different retinal areas. Routine orthoptic examination does not include a test capable of detecting small afferent or relative afferent pupillary defects. When attempting to assess the latter, the swinging flashlight test is used, but this has drawbacks for the examination of children. The child will often look at the light causing constriction of the pupil due to the near reflex, which obscures the response to light, or the reaction may be blocked in excitable children. In addition other disadvantages to the test include: confusion due to hippos (one pupil being observed on the upswing and the other on the downswing), presence of anisocoria, and the danger of using too bright a light, as an after image can keep the pupils small and so prevent the pupillary escape.

Pupillomotor changes have also been reported in suppression.

The implication of the presence of a relative afferent pupillary defect in diagnosis and management of amblyopia has not been fully determined. The purpose of this study was to discover factors common to amblyopes who display a defect with a view to ascertaining whether assessment of the pupillary response is of clinical value during the treatment of amblyopia.

Methods and patients
To observe any asymmetry in pupillary response the synoptophore was used with modification of the bright light source normally used for the production of after images. The light intensity was reduced by fitting neutral density filters (NDF) of 0-4 log units into the same rubber holder as each eye piece lens. The after image light was then alternatively switched from one eye to the other, giving a period of stimulation of 1 to 2 seconds, and the initial pupillary constriction was observed. The light was then left in front of each eye for a count of 3 and the pupillary escape noted.

If a pupillary defect was observed, a neutral density filter was placed in the arm of the synoptophore in front of the eye without the defect. In practice it was not found possible to quantify the defect to within 0-1 log unit as has previously been reported, but merely to confirm its presence. Where no defect was initially apparent, a 0-3 log unit NDF was placed in either arm in turn to produce a difference in response. In some cases this revealed a subtle defect, as the pupillary response was still present but to a lesser extent in one eye while completely absent in the other. During the examination refractive correction was worn, the interpupillary distance corrected, and the tubes set at the subjective angle of deviation by rotating each arm equally, thus ensuring similar stimulation in either eye. The patient fixed simultaneous macular perception slides throughout.

Where possible this test was performed blind, but casual observation – as in cases of obvious anisometropia or strabismus, wearing of occlusion, comment on suppression – meant that the ambyopic eye was known to the examiner in some cases.

After the assessment of the pupillary reaction on the synoptophore the density of any suppression present was measured at the objective angle by dimming the rheostat in front of the non-suppressing eye until the 'suppressed' image could be seen and the rheostat number noted. The subjective and objective angles were compared to elicit the type of retinal correspondence. Where no suppression was noted.

Visual acuity was assessed (with the patient wearing refractive correction) by a linear test (Snellen or Snellen with key card). Some patients had their acuity tested with single optotypes (Sheridan Gardiner), fixation by the Visuscope and contrast sensitivity by the American Optical System (which is based on Arden's gratings). The size of pupils was measured, as any anisocoria or more than 2 mm could make the testing of pupillary responses inaccurate.

Further details were taken from the hospital records. These included: age at date of test, type of amblyopia, age at onset of strabismus, visual acuity prior to occlusion therapy (and test used), age at first occlusion, types of occlusion therapy undergone, continuity of occlusion, best previous visual acuity (if higher than on day of testing), refractive correction, and fundus examination. When any lesion of the fundus or media was present the patient was excluded.

Since the study was of necessity conducted during normal clinical sessions, the selection of
patients was haphazard. They were examined during their routine orthoptic examinations. Initially only patients with amblyopia were examined, but later all patients examined with no prior knowledge of whether or not amblyopia was present. No attempt was made to examine patients under the age of 3 years. Nine children were followed up through occlusion therapy.

A group of 25 children from a local junior school were used as controls.

Results
Seventy-six patients were examined with ages ranging from 3 years 2 months to 13 years 10 months. Sixty-five had amblyopia, this being defined as any difference in linear visual acuity. The type of amblyopia is shown in Table 1.

Of the patients with equal visual acuity four had previously had strabismic amblyopia which had responded to treatment, five had intermittent or alternating deviations, and two had equal but reduced visual acuity due to ametropic amblyopia.

The pupillary responses in 72% of patients were examined blind.

Of the 65 amblyopic patients 21 had a relative afferent pupillary defect in their amblyopic eye and two in their non-amblyopic eye. Of 25 controls tested a subtle defect was found in one child.

Contraction anisocoria is estimated to occur to an extent which is clinically visible in 5% of the population.1 This may explain the finding of a defect in the control and non-amblyopic eyes. However, it could have been observer error. The two patients with the defect in their non amblyopic eye were excluded from further consideration.

The type of amblyopia of the remaining 63 patients was first considered (Fig 1). For statistical evaluation the idioptic group was excluded because of the low number. By means of the likelihood ratio criterion the type of amblyopia was shown to be significant at the p<0.02 level, and further grouping of patients into those with or without anisometropia (Table 2) and those with or without strabismus (Table 3) showed only the difference in the former group to be significant (p<0.01). The actual amount of anisometropia, however, did not prove to be significant.

An accurate age at onset in those with strabismus was given in 35 patients. The Mann-Whitney U test showed the age at onset to be at a significantly younger age in those with a relative afferent pupillary defect (p=0.0294). However, as eight out of the nine patients with a pupillary defect also had anisometropia and only seven out of 26 without a defect were anisometropic, it was considered that this may have caused a bias.

Unfortunately the numbers were too small to analyse in the pure strabismic amblyopes, but in a comparison of patients with anisometropia and strabismus (Fig 2) the age at onset of the strabismus was found by the Mann-Whitney U test to be significant at the p<0.05 level.

Various factors concerning occlusion were considered: (a) age at first occlusion; (b) the delay from onset of strabismus to start of occlusion; (c) type and continuity (d) period of occlusion; and (e) time lapse from the last occlusion to the date of testing. Of these, the period of occlusion (Fig 3) was the only significant

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X^2 = 8.3, df = 1, p < 0.001
\]

Table 1 presents the number of patients with each type of amblyopia in the presence or absence of a relative afferent pupillary defect (RAPD) in amblyopia involving anisometropia and amblyopia without anisometropia. Statistical evaluation given

<table>
<thead>
<tr>
<th>Type of amblyopia</th>
<th>RAPD present</th>
<th>RAPD absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anisometropic</td>
<td>17</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>Strabismic</td>
<td>4</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>21</td>
<td>40</td>
<td>61</td>
</tr>
</tbody>
</table>

\[
X^2 = 7.2, df = 1, p = 0.0069
\]

Table 2 presents the presence or absence of relative afferent pupillary defect (RAPD) in amblyopia involving anisometropia and amblyopia without anisometropia. Statistical evaluation given

<table>
<thead>
<tr>
<th>Type of amblyopia</th>
<th>RAPD present</th>
<th>RAPD absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure</td>
<td>5</td>
<td>16</td>
<td>21</td>
</tr>
<tr>
<td>Anisometropic</td>
<td>34</td>
<td>34</td>
<td>68</td>
</tr>
<tr>
<td>Strabismic</td>
<td>40</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>79</td>
<td>70</td>
<td>149</td>
</tr>
</tbody>
</table>

\[
X^2 = 0.7, df = 1, p = 0.40
\]

Figure 1. Relative frequencies of different types of amblyopia: idiopathic, anisometropic (aniso), combination of strabismic and anisometropic (strab+aniso) and strabismic (strab) in patients with (shaded) and without (unshaded) a relative afferent pupillary defect (RAPD). Actual patient numbers shown in brackets.
factor (p=0.0188). This suggests that in patients with a relative afferent pupillary defect it was either more difficult to gain an improvement or their acuity was more difficult to stabilize.

Statistical examination of the results of retinal correspondence, state of fixation, density of suppression, and contrast sensitivity showed no significant differences.

Different aspects of visual acuity were examined including: (a) linear acuity in patients who had undergone occlusion and those who had not; (b) presence of crowding; and (c) the incidence of visual acuity being at least less than its best level. The only significant factor (p=0.0054) found was the level of visual acuity in patients who had undergone occlusion (Fig 4). Visual acuity was lower in those with a relative afferent pupillary defect. (The level of visual acuity was not significant prior to occlusion.) Finally nine patients were followed up through treatment. Three had a relative afferent pupillary defect and had not had prior treatment. In two of these the defect disappeared, but in the third it persisted. Three of the nine had a defect but had already undergone some occlusion; in one the defect disappeared, and three showed no relative afferent pupillary defect and had not been occluded. In one of these a defect was never seen, but in the other two a defect appeared in the non-amblyopic eye which disappeared after occlusion was stopped.

Discussion

AFFERENT OR EFFERENT?
The present study, owing to the method of testing used, does not answer this question. However, the defect has been shown to occur only on stimulation of the central area of the retina and not the periphery, and not by stimulation with blue light. Further, there is no delay in the consensual reaction on stimulation of the non-amblyopic eye.

CAUSE
A defect prior to the lateral geniculate nucleus (LGN) is the most likely explanation, though other reasons may be considered. Inhibition either of the retina or the Edinger-Westphal nucleus may occur. Evidence for the presence of centrifugal fibres in the optic nerve has been published, but doubt is now expressed about their presence. The central nervous system (CNS) has been shown to be capable of inhibition at the level of the Edinger-Westphal nucleus.
This may play a part in pupillomotor changes in suppression, but in the testing of amblyopes the stimulated eye is observed, and no effort of a psychosensory nature to prevent the reaction is being made.

A similar sized RAPD has been reported in optic tract hemianopia,\textsuperscript{19} where midnasal pallor of the optic disc in the ipsilateral eye is present. Experimentally, cutting of the optic tract (in monkeys) produces a similar afferent pupillary defect and pattern of atrophy.\textsuperscript{20} It is extremely unlikely that postchiasmal changes in amblyopia would cause such a pupillary defect in the presence of a normal disc appearance.

If the retina is considered at the site for the cause, then again several suggestions may be made. Retinal haemorrhages at birth could cause an undetectable retinal defect.\textsuperscript{21} However, from a series of babies followed up to an age at which visual acuity could be measured, these haemorrhages did not appear to have any detrimental effect on the normal development of vision.\textsuperscript{22}

Malorientation of the retinal receptors has been suggested as a cause of organic ambioplya;\textsuperscript{23,24} this would result in less light being absorbed. However, the findings of malorientation of the receptors is disputed,\textsuperscript{25} and normal cone electroretinogram recordings, suggestive of normal preganglionic cell function, have been reported in amblyopia.\textsuperscript{26}

Pattern electroretinograms (PERG), which reflect the integrity of the ganglion cell layer, are abnormal in amblyopia;\textsuperscript{27,28} though this has not been confirmed by every study.\textsuperscript{29,30} If the cause of the abnormal pupillary response lies at ganglion cell level, then some similarities in the type of patient having a RAPD and showing an abnormal PERG may be expected. Where an analysis of the PERG response has been related to different categories of patients and treatment,\textsuperscript{31} it was found that the greatest defects occurred in anisometropes and those patients who did not respond well to treatment. Furthermore, reductio in the amplitude of the PERG in the occluded, non-amblyopic eye, occurred, which reversed with the cessation of treatment.\textsuperscript{32,33}

X and Y ganglion cell function has been shown to be abnormal in eye,\textsuperscript{34} though again there is dispute.\textsuperscript{35} Often the strabismus (or anisometropia) is produced in the animal at around 3 to 4 weeks of age,\textsuperscript{36,37} though sometimes this has varied.\textsuperscript{38} The lower spatial frequencies (in the cat) are unaffected while strabismus is produced after eight weeks,\textsuperscript{39} and in infants the low frequency end of the contrast sensitivity function (CSF) curve does seem to develop to an adult-like shape earlier than the high frequency end.\textsuperscript{40}

The Y and W cells are probably responsible for the detection of low to medium spatial frequencies.\textsuperscript{41} It has been suggested that the luminance detectors originally identified\textsuperscript{42} which showed a regularly increasing frequency of discharge with an increase in adaptation level are W cells.\textsuperscript{43} Thus it is plausible that early-onset strabismus is more likely to show changes which result in a RAPD. However, the case for anisometropes is less clear, as it cannot be assumed that the difference in refractive error is present at birth. There is no mention of anisometropia in newborn babies screened with photorefraction,\textsuperscript{44-46} and the incidence in 6- to 9-month olds appears far less than in school age children.\textsuperscript{47,48} In fact between the ages of 1 and 3½ years anisometropia may either develop or resolve.\textsuperscript{49} Anisohypermetropia has been produced by radial keratotomy in kittens,\textsuperscript{50} and axial length changes have compensated for this provided accommodative function is intact and there is normal visual experience.

Accommodative function may be abnormal in anisometropic amblyopia. Although defective accommodation has been reported in amblyopia,\textsuperscript{51} the consensual response when the non-amblyopic eye is stimulated is normal.\textsuperscript{52} Unsteady fixation, perceptual difficulties, or lack of foveal function may be the cause of this apparent defect.\textsuperscript{53-56}

If accommodative function is normal, then a lack of normal visual experience in one eye may be the cause of the lack of emmetropisation and the resultant anisometropia. If the cause of such anisometropia is abnormal in the retina (pre-nerve level or ganglionic level), this may be the explanation for the differences in CSF between anisometropic and strabismic amblyopes\textsuperscript{57-59} and be the cause of the RAPD and abnormal PERG responses.

**TREATMENT**

During occlusion there may be some reversibility of the RAPD, or it may be that a defect is being produced in the occluded eye, thus masking that in the amblyopic eye. As mentioned above, the PERG reduces in the occluded eye and disruption of the orientation of retinal receptors occurs.\textsuperscript{60} Further study is needed to quantify the pupillary reactions of each eye to determine the answer to this question. It has been reported\textsuperscript{61} that increased latencies of contraction become more normal with treatment. As the level of visual acuity prior to occlusion therapy is not significant to the presence of a RAPD, this test cannot be used as an indicator of the outcome of occlusion therapy in amblyopia.

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