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The Sensitive Period for Anisometropic Amblyopia

S. J. HARDMAN LEA, J. LOADES, M. P. RUBINSTEIN.
Nottingham

Summary

Fifty-five children with pure anisometropic amblyopia presented consecutively between 1983 and 1986. Analysis of their records was undertaken with respect to the age at presentation, the initial visual acuity after spectacle correction, and the final acuity attained after treatment. The results show that the final vision achieved does not depend on the age at presentation. The implications of these findings are discussed and their relations to the sensitive period for the development of amblyopia from other causes outlined.

The mammalian visual system is functionally immature at birth and, under the influence of appropriate binocular stimulation, achieves adult performance later in youth.[1] Interference with this process of stimulation produces the long lasting visual deficit of amblyopia. In humans this may be due to any one or a combination of occlusion, strabismus, astigmatism or anisometropia.[2] Animal laboratory studies, pioneered by Hubel and Wiesel,[3] have given rise to the concept of the sensitive or critical period of visual development: during this period sight may be permanently affected by abnormal visual experience, after this period has elapsed it is not.

In man the exact extent of the sensitive period cannot be examined by means of intervention studies as it is in animals. Instead, observation of the effects of naturally occurring conditions and their treatment enable mapping of the time duration within which amblyogenic conditions pose a threat to normal visual development. By comparison of the post treatment visual capability of children with visual stimulus deprivation and the age of onset of the deprivation von Noorden[4] has estimated that the sensitive period for ocular occlusion ranges up to 5 3/4 years, with less effect if occlusion starts over the age of 30 months. Awaya and co-workers[5] have examined the effects of either short term or long term occlusion starting at different ages. They concluded that the sensitive period for short term occlusive events extends only up to 18 months after birth. They also discovered that the extent to which vision may be improved after treatment for occlusive amblyopia depends on the age at which treatment begins. In terms of the effects of therapy, the visual system was found to remain modifiable up to the age of eight years, although at this age only 50% of cases treated showed any improvement in vision.

It is not known in man whether other causes of amblyopia may have the same or different times over which they can affect visual development. The aim of this study was to explore the period during which the development of the visual system is susceptible to change in the balance of refractive error. This has theoretical considerations in terms of both neuronal plasticity and the relation to the sensitive period for amblyopia from occlusion. Furthermore there are important clinical implications as regards the testing and management of visual problems in children.

Correspondence to: S. J. Hardman Lea MA FRCS FCOphth, Ophthalmology Department, University Hospital, Nottingham NG7 2UH.

We have therefore investigated the effects of treatment of children presenting with anisometropic amblyopia and correlated the visual improvement obtained with the age at which treatment commenced.

Materials and methods

A retrospective analysis of the records of the ophthalmology and orthoptic departments of the University Hospital, Nottingham was undertaken for the years 1983–1986 and the notes of all children with a diagnosis of pure anisometropic amblyopia on presentation were examined. All children attending had a full ophthalmic examination, refraction under cyclopentolate mydriasis/cycloplegia and complete orthoptic assessment including linear Sheridan Gardner or Snellen acuity (as appropriate), ocular motility,stereopsis and four dioptre prism test to identify bifoveal fixation.

After the initial diagnosis of purely anisometropic amblyopia had been made, treatment was initiated. This entailed full spectacle correction only, with follow up at monthly intervals in the initial period. Failure to improve visual acuity resulted in patching of the non-amblyopic eye. Although there was some variation in the schedule of patching used (exemplifying the limitations of a retrospective analysis) the normal protocol was of two to three hours total occlusion per day.

Inclusion criteria

A lower age limit of 36 months was imposed to allow linear visual acuity testing[6] so that amblyopic visual improvement might be compared over the course of several years. All cases had amblyopia as judged by Phelps standard[7] of at least two Snellen lines difference between the eyes after full spectacle correction. All children had anisometropia with a difference of at least 1.00 DS between the eyes. At this level Ingram[8] has shown a significant association with amblyopia ($p < 0.001$).

Exclusion criteria

Anisometropia of more than 5.50 DS interocular difference was excluded from the study because it is known that the aniseikonia that accompanies high anisometropia inhibits binocular interaction.[9] Astigmatism of more than 1 DC was not considered: not only can astigmatism cause amblyopia of itself, but the combination of cylindrical and spherical elements by calculation to derive a 'net sperical' value is not suitable for monitoring the progress of any one individual.[10]

Ocular motility defects were excluded from the study as strabismus causes amblyopia. Only microtropia with identity, as defined by Helveston and von Noorden,[11] was allowed.

The case notes were analysed with respect to the age at presentation, the amount of amblyopia as represented by the initial visual acuity with spectacle correction, the final visual acuity achieved with spectacles as appropriate, stereopsis before and after treatment, and the amount of anisometropia. Any shift in the amount of anisometropia at follow up visits was noted.

Results

Fifty-five children fulfilled the criteria for pure anisometropia. These comprised 26 males and 29 females, with ages ranging from 36 to 91 months—average 62 months (standard deviation 14.5 months). Of this group 53 were aniso—hypermetropic and two were aniso—myopic. Figure 1a shows the degree of anisometropia of all subjects at presentation and Figure 1b the extent of amblyopia as indicated by the best corrected visual acuity obtained at the first visit. The range of follow up times of these patients was from 36 to 59 months, with an average of 47 months.

Figure 2 plots the initial visual acuity against the final acuity obtained. This serves to show that all except three children had improved vision after treatment with the average improvement being three lines of the Snellen chart. Two of these three were the anisomyopes. (Note that in this figure both axes appear non-linear. The Snellen chart is itself nonparametric in that there are not equal increments of visual angle subtended at the eye between each line. In all figures of this study the vision has been plotted to take account of this.) Figure 3 tries to show more clearly the amount of improvement attained by treatment of all children. Because of the non-linearity of the Snellen system, this frequency chart plots the improvement in terms of minutes of arc of acuity, such that an improvement from 6/36 (6 minutes) to 6/6 (1

minute) would be scored as exhibiting an improvement of five minutes of arc.

Figure 4 plots the age at presentation of this group of children against the final best corrected acuity achieved after treatment. The regression line indicates that there is a very poor correlation between age at presentation and final visual acuity attained and this is confirmed using the Kendall rank correlation method, which shows $p > 0.05$. Furthermore, there is no significant difference in the number of children achieving 6/12 vision or better after treatment when comparing the groups starting treatment above or below the age of five years (using Fishers exact probability test $p > 0.05$).

Figure 5 extends this information by plotting the improvement of acuity after treatment, in terms of minutes of arc, against the age at presentation. Once again, there is no evident relationship between the two factors, and statistical analysis using the Kendall rank correlation shows $p > 0.05$ for the association of age and improvement in vision.

Figure 6 demonstrates the relationship between the final, best corrected visual acuity after treatment and the amount of anisometropia at presentation. There is no significant association between these factors, with $p > 0.05$ by Kendall rank correlation.

The initial visual acuity before therapy does, however, depend on the amount of anisometropia. Figure 7 plots these values and reveals a significant correlation between the two, with $0.05 > p > 0.01$. As Figure 8 demonstrates there is no such relationship between initial visual acuity and the age at presentation ($p > 0.05$).

Microtropia with identity was not an exclusion criterion for this study. Figure 9 displays the numbers of microtropes and non-microtropes in our series and compares the numbers of each group who finally achieved. 6/9 vision or better. There is no significant difference in this respect ($p > 0.05$ on chi sq. test). Stereopsis proved difficult to quantitate in this study, as a combination of Frisby and Titmus stereotests had been used—the shortcomings of such tests for comparative analysis has been discussed elsewhere.[12] By assigning cases into either gross stereopsis present or absent groups we have attempted to determine whether final VA achieved is related to the presence of stereopsis in any form. Figure 10 shows the results. While there is no significant association in these results (> 0.05 by chi sq. test) the number of non-stereoscopic children is not large enough for any reliable conclusion.

Lastly, Figure 11 displays the maximum change in the amount of anisometropia during the period of follow up for all cases. Very few children underwent a shift of more than 0.5 D.

Discussion

Several areas for comment arise from our results. Firstly, how do these findings relate to previous clinical work concerning anisometropic amblyopes? Sen has looked at a rather more varied population of anisometropes, some of whom had also been exposed to pleoptic treatment.[13] He shows that some improvement is possible up to the surprising age of 20 years. He also suggests an overall impression that younger children tend to show improvement more often than older children, although this observation did not reach statistical significance. De Vries' analysis[14] agrees with our finding that the initial depth of amblyopia depends on the degree of anisometropia. Others concur with this observation.[8,15] Final acuity, in comparison, remains independent of the initial amount of anisometriopia in our patients.

The cases we report were carefully defined to be a homogeneous group: the only non-uniform characteristic was that some patients exhibited bi-foveal fixation while others did not. This latter group are classified as microtropes with identity,[11] indicating that the more amblyopic eye has parafoveolar fixation which does not alter with ocular dissociation during the cover-uncover test. This seems to be a specific sensory adaptation adopted by some anisometropes and is uncommon in isometropic individuals. Our results do not show any difference in the final acuities achieved comparing the microtropic and non-microtropic groups. We therefore felt that both types of fixation could be considered for analysis in the one study, at least with respect to vision after treatment.

The results presented here confirm Sen's suggestion that good results after treatment of

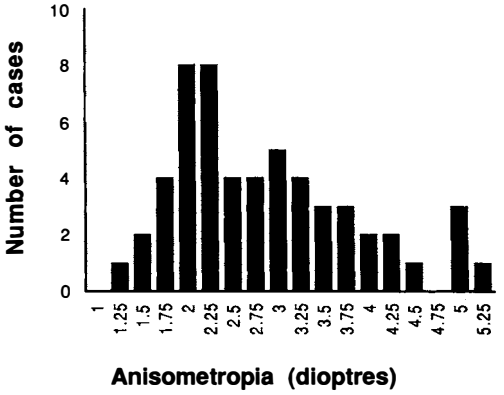

Fig. 1a. *Range of anisometropia at presentation.*

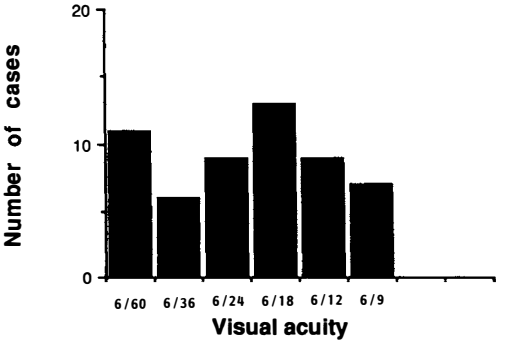

Fig. 1b. *Range of visual acuity at presentation after spectacle correction.*

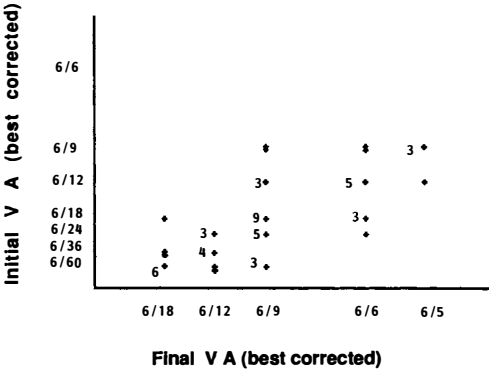

Fig. 2. *Relationship between initial best corrected visual acuity and visual acuity finally achieved after treatment. Any points plotted below the 45° leading diagonal thus represent improvement in acuity after treatment.*

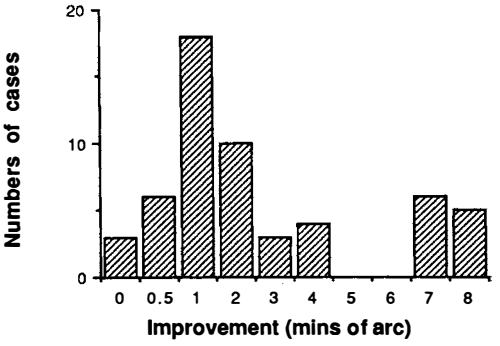

Fig. 3. *Frequency of improvement in minutes of arc of acuity after treatment.*

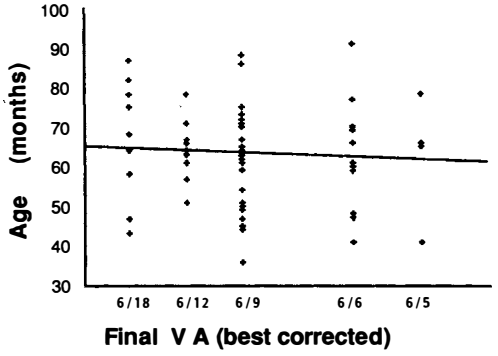

Fig. 4. *Age of children at presentation compared with final visual acuity attained after treatment.*

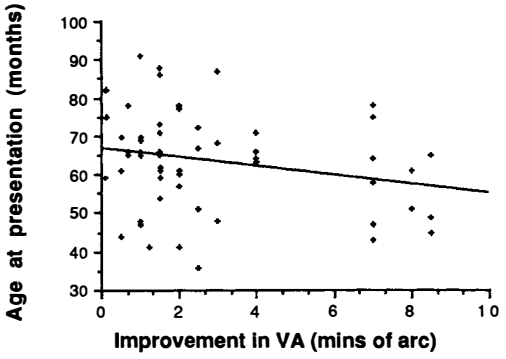

Fig. 5. *Age of children at presentation compared with improvement in minutes of arc of acuity after treatment.*

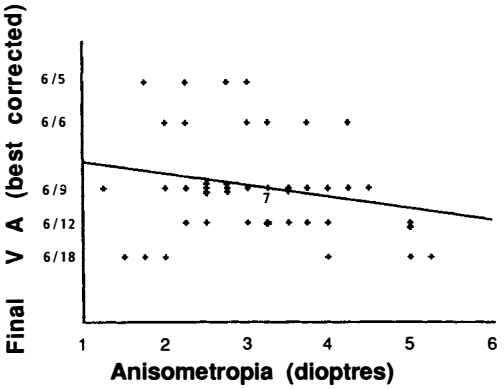

Fig. 6. *Relationship between final visual acuity obtained and the extent of anisometropia at presentation.*

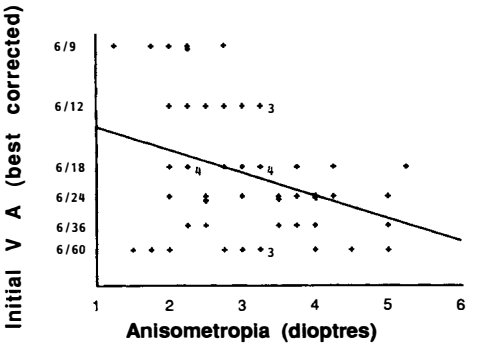

Fig. 7. *Initial best corrected visual acuity plotted against extent of anisometropia at presentation.*

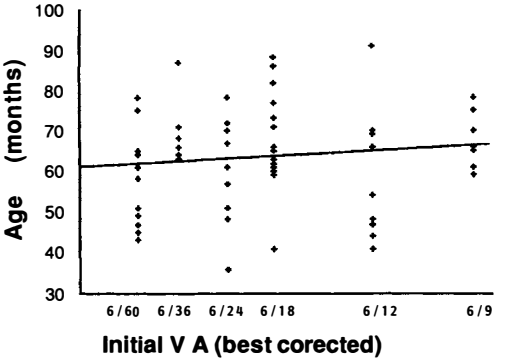

Fig. 8. *Initial best corrected visual acuity plotted against age at presentation.*

Figure 9: *Final visual acuity attained by microtropic subjects compared with cases with bifoveal fixation*

Final VA	*Microtropes*	*Non-microtropes*	*Total*
6/9+	*15*	*22*	*37*
8/9–	*10*	*8*	*18*
	25	*30*	*55*

Figure 10: *Final visual acuity achieved by those with or without any degree of stereopsis at presentation. (Six of the original 55 cases had no evident record of stereopsis at first visit.)*

Final VA	*Stereopsis*	*No stereopsis*	*Total*
6/9+	*28*	*6*	*34*
6/9–	*8*	*7*	*15*
	36	*13*	*49*

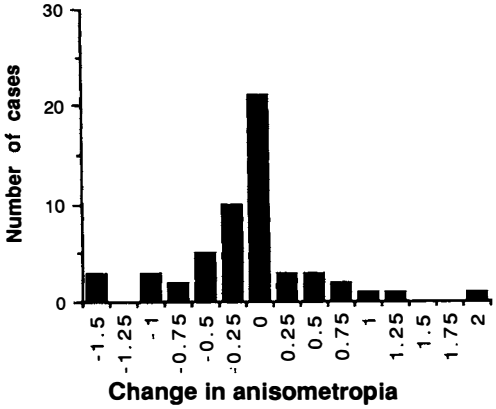

Fig. 11. *Maximum change in extent of anisometropia over total follow-up period.*

anisometropic amblyopia are obtained throughout childhood, up to the age of 91 months at least. However, no diminution of effectiveness of therapy with age was observed in our cases. Those presenting over the age of five achieved equally good final

vision as those presenting at an earlier age. We have not attempted to assess the amount of treatment required to achieve the end result for each case. It is thus possible that our older patients may have required more extensive efforts to attain their optimal vision. Nevertheless, as there seems no reduction of post treatment vision with advancing age at presentation, it may be that those sporadic cases of improvement in visual acuity in the amblyopic eye of an adult after losing the non-amblyopic eye through trauma or tumour[16] were originally anisometropic.

We had hoped to perform a more detailed analysis of the stereoscopic capability before and after treatment as we felt that some degree of initial stereopsis might be a favourable prognostic factor in these children. Unfortunately the tests performed did not allow reliable statistical analysis, except in the relatively crude manner described.

How may these findings be related to other work on visual development and amblyopia? Our understanding of the process of amblyopia rests on the fundamental principle of 'the sensitive period'. It is problematic to find a universal definition of this term but we may define it as *that passage of time during which the development of the immature visual system may be altered by change in the quality, quantity or balance of the visual input via the two eyes.* Such alteration can produce a permanent functional impairment in vision after development is complete (i.e. amblyopia). Conversely, improvement of the performance of an already impaired immature visual system can be achieved providing that there is an appropriate change of visual stimulus within this period.

The concept of the sensitive period underpins much of the laboratory, animal and clinical work in visual development. However, as von Noorden and Crawford have stressed, there are many different sensitive periods for the visual system of any one animal.[17] If it is to remain a valuable aid to our understanding, use of the term sensitive or critical period must always be defined with respect to three parameters. Firstly the animal under investigation must be specified; secondly the way in which the visual stimulus to the developing visual system has been altered in the study must be described and lastly the property of vision which is then investigated should be detailed.

In this fashion, Hubel and Wiesel have shown that for the cat, the sensitive period for the effect of ocular occlusion on the ocular dominance of the visual cortex lasts up to the age of three months.[18] Similarly, Harwerth and co-workers have demonstrated that for the rhesus monkey, the sensitive period for the effect of occlusion on psychophysical spatial acuity tests extends up to 25 months, while the period for the effect on binocular vision lasts rather longer.[19] In man, several studies have investigated the sensitive period for the effect of occlusion on visual acuity after treatment of the cause of that occlusion.[4–5,20] In general, these agree with those findings obtained in the rhesus monkey, given the necessary multiplication factor of $\times 4$ to allow for the slower rate of development in man and the initially greater maturity of the monkey visual system at birth,[21] and suggest that the sensitive period for occlusion is virtually complete by the age of eight years.

In addition, the period is not uniform in that the effect of occlusion is much more marked if arising under the age of about 24–30 months. There is much less information available about the outcome of other causes of amblyopia, although occlusion is probably less common than these. There is evidence which suggests that the effect of anisometropia on form vision is different from that of monocular occlusion.[2] The sensitive period with regard to anisometropia might therefore have a different time course from that of occlusion. Unfortunately, laboratory work is complicated by the fact that anisometropia is a difficult condition to produce in animals—the high powered lenses used in some studies[22] cause aniseikonia. Experiments have been performed using atropinisation of one eye in kittens[23,24] but there are no reports of plotting the sensitive period for this disruption of normal vision.

Our study of man is itself limited in that it does not demonstrate the sensitive period for the development of anisometropic amblyopia, but only that the period for the possible improvement of acuity in an already compro-

mised visual system extends uniformly up to the age of nearly eight years without tailing off.

Considering the problem of the sensitive period for development, we do not know when the unfavourable anisometropic stimulus arose in the children in our study. However, there is little information to suggest that anisometropia increases with age after birth, and in our patients there was no significant change in the amount of anisometropia when followed over three years from first attendance. We therefore suspect that our cases were anisometropic since birth, although this cannot be proved. With regard to the upper limit for the critical period for anisometropic amblyopia the only information available recounts that amblyopia has resulted from atropine penalisation of a previously non-amblyopic eye in children up to the age of four years.[25] Above this age no further details have been recorded. We do not know therefore whether the sensitive period for the *development* of anisometropic amblyopia is the same as the period for the *treatment* of the condition, the upper limit of which must lie above the age of 91 months according to this report.

In practical terms, what is the implication of our study? Anisometropia is part of the group of amblyogenic conditions which do not have any associated physical signs such as might alert the family of an affected child. Strabismus and occlusion are in this sense more likely to be detected at an early age. The findings reported here suggest that in terms of the final vision achieved, there is little advantage in early treatment (or, by implication, in detection) of pure anisometropic amblyopia. Furthermore, vigorous therapy for children presenting at a relatively late age may produce surprisingly gratifying results. It must, however, be stressed that we have investigated only those anisometropes without other potentially amblyopic conditions. Regretably, astigmatism or strabismus are frequently concurrent with anisometropia and we do not know how their presence might affect our finding of a prolonged sensitive period for the treatment of anisometropic amblyopia. Further work on this aspect continues.

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