Original Article

Factors predicting recurrence in successfully treated cases of anisometropic amblyopia

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Context: Recurrence after successful treatment of amblyopia is known and understanding the risk factors could help effective management. **Aim:** To measure incidence of recurrence in successfully treated cases of anisometropic amblyopia and evaluate factors predicting it. **Settings and Design:** Cohort Study at a tertiary level institution. **Materials and Methods:** Successfully treated anisometropic amblyopes aged 4–12 years were followed up for 1 year after stopping therapy. Best corrected visual acuity (BCVA), refractive error, stereoacuity and contrast sensitivity were evaluated at baseline and follow-up. **Statistical Analysis:** Intergroup analysis with appropriate tests: Chi-square test, Fisher's exact test, Wilcoxon rank sum test and paired *t*-test. **Results:** One hundred and two patients with mean age at diagnosis 7.06 ± 1.81 years were followed-up for a mean duration of 1.0 ± 0.2 years. The mean pre-treatment BCVA (LogMAR score) at diagnosis was 0.73 ± 0.36 units which improved to 0.20 ± 0.00 with treatment and after 1 year of stopping treatment was 0.22 ± 0.07. Thirteen (12.74%) patients showed amblyopia recurrence during follow-up. Risk of recurrence was higher with older age of onset of treatment (6.64 ± 1.77 years without recurrence v/s 8.53 ± 1.39 years with recurrence, $P = 0.0014$). Greater extent of improvement of VA ($P = 0.048$) and final VA at stopping occlusion ($P = 0.03$) were associated with higher recurrence. Binocularity status or stereoacuity changes were not associated with risk of recurrence. **Conclusions:** Significant numbers of children suffer recurrence of amblyopia after stopping therapy. Older age, better BCVA after stopping therapy and greater magnitude of improvement in BCVA are important risk factors for recurrence. Careful follow-up is essential for early detection and management of recurrence.

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Anisometropic amblyopia can be effectively treated with refractive correction and occlusion therapy or penalization.[1,2] Despite an excellent therapeutic success rate, it is difficult to predict whether the improvement would sustain after stopping amblyopia treatment. Current literature shows a wide range of recurrence rates varying between 6 and 67%.[3-10] However, the factors affecting the recurrence of amblyopia are unclear and it is difficult to predict high risk cases for recurrence which would benefit from a closer follow-up. The aim of this study is to estimate the recurrence rate of amblyopia in successfully treated cases of anisometropic amblyopia and determine the factors predictive of recurrence.

Materials and Methods

A retrospective-prospective cohort study was conducted at a tertiary eye care institution after prior approval from the institutional ethics committee and a written informed consent from the guardians of every participant.

The study recruited patients with anisometropic amblyopia in the age group of 4-12 years who had successfully completed the prescribed occlusion treatment. The patients were followed up for a minimum of 1-year thereafter. All the patients had been exclusively managed at our institution. For including patients in the study, anisometropic amblyopia was defined as a two line difference between the best corrected visual acuity (BCVA) of both eyes in the presence of a significantly higher refractive error in the worse eye (usually an anisometropia greater than 1.5 D for hyperopia, 4 D for myopia and 1 D for astigmatism) and the absence of any organic pathology explaining the vision loss. Further, the worse eye should have shown an improvement with equalisation in visual acuity of both eyes after use of appropriate refractive correction and occlusion therapy. The patients were excluded if there was any organic cause of loss of vision or presence of strabismus or other form of amblyopia and also if they were unable or unwilling for follow-up or had received any treatment elsewhere. Since successfully treated diagnosed cases of anisometropic amblyopia were included a wide range of anisometropia was examined without strict minimal or maximal limits.

A standard protocol for amblyopia treatment was followed in all cases which entailed use of appropriate refractive correction and occlusion therapy. Occlusion therapy was provided in the form of a full-time total occlusion of the better eye for *x* days alternated with occlusion of the amblyopic eye for one day (where *x* was equal to the age of child or 6 days whichever was lesser). The follow-up schedule included two monthly visits after beginning occlusion therapy followed by bimonthly visits till the first 6 months and every 3 months thereafter if there is satisfactory improvement of vision, else bimonthly visits are continued. Attainment of visual acuity of 0.1 LogMAR or equalisation of visual acuity of both eyes or absence of improvement of visual acuity on 3 consecutive bimonthly visits marked the end point of full time total

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occlusion. Occlusion therapy was then tapered in all the children over a period of 6 months before complete cessation of therapy. Successful treatment of anisometropic amblyopia was defined as an improvement of two or more lines from the baseline or visual acuity of 0.1 LogMAR or equalization of visual acuity of both eyes.

After enrolment, previous records of age at the start of treatment, gender and baseline visual acuity (best corrected) at the time of starting amblyopia treatment were noted. Every patient underwent a baseline ocular examination at the beginning of the study which also included documentation of BCVA after a cycloplegic refraction, evaluation of binocularity using Bagolini's striated glasses and Worth four dot test, stereoacuity testing on Randot test and contrast sensitivity testing with Pelli-Robson chart. The patients were followed up at 3-monthly intervals, for a minimum of 1 year after completely stopping occlusion therapy. During the follow-up each patient was evaluated for the aforementioned visual function parameters; however, a cylcoplegic refraction was repeated every 6 months. Recurrence of amblyopia was defined as a two or more line reduction of VA on LogMAR chart from vision recorded at the time of completion and stopping amblyopia therapy. If a recurrence was noted, full time, total occlusion therapy was restarted.

Analysis was performed on SPSS 15.0 (IBM SPSS Inc., Chicago, IL, USA) using appropriate statistical tests. For comparison between two groups (those with recurrence and non-recurrence), chi square test, Fisher's exact test, Wilcoxon rank sum test and paired 't' test were used wherever appropriate.

Results

One hundred and two patients of anisometropic amblyopia were followed up for a minimum of 1 year after completion of successful occlusion therapy. The mean age of the children at the time of diagnosis of amblyopia, was 7.06 ± 1.81 years (age range 4-12 years). Out of these 102 patients, 53 (52%) were males and 49 (48%) were females.

The mean baseline visual acuity of the amblyopic eye prior to starting occlusion was 0.73 ± 0.36 logMAR units which improved to 0.20 ± 0 logMAR units after treatment. The extent of visual acuity improvement was 0.49 ± 0.28 logMAR units. At 1 year after stopping treatment, the final visual acuity was 0.22 ± 0.07. The mean interocular visual acuity difference between the amblyopic and fellow eye was 0.51 ± 0.16 units before starting the occlusion therapy. Binocular vision was present in 96 (94%) out of 102 patients at the time of completion of treatment. The remaining six patients (6%) had suppression of the amblyopic eye. The patients were orthotropic and none of them had diplopia.

Eighty-six of the 102 patients (84%) had a stereoacuity of 70 secs of arc or better of which 68 patients (67%) achieved a stereo-acuity equal to or better than 40 sec of arc. on the near Randot test at the time of completion of therapy. Of the remaining 16 patients, 10 had a stereoacuity in the range of 70 sec of arc to 1000 sec of arc while 6 had no stereoacuity.

Out of 102 patients, 13 patients (12.74%) showed recurrence of amblyopia within this follow up period of 1 year. Of the eyes which recurred, only one eye had achieved a visual acuity of 0.1 LogMAR units at the end of successful amblyopia therapy. Of the 45 eyes which had achieved a visual acuity improvement of two or more lines but not equalization of vision, 2 showed recurrences. Factors were compared between two groups of children; those with recurrence and those with non-recurrence of amblyopia [Table 1]. Age at diagnosis was found to be significantly lower (P = 0.0014) in non-recurrence group as compared to those with recurrence. On further analysis it was found that if the age at the time of diagnosis was more than 7 years, the risk of recurrence of amblyopia would increase by 7.7 times (odds ratio 7.7).

The extent of improvement in visual acuity as well as final visual acuity at time or stopping the occlusion were other factors that significantly influenced the rate of recurrence. The greater the extent of improvement in visual acuity with therapy, more was the risk of recurrence and if vision at the time of completion of therapy was better than 0.1 LogMAR, the odds of recurrence of amblyopia would increase by 5.3 times.

Interocular visual acuity difference at baseline was examined as a factor predictive for recurrence. The baseline visual acuity difference was divided into two subgroups, one having less than 4 lines interocular visual acuity difference and the other having four or more lines difference. (P = 0.30, Chi-square test) There was no difference in the chance for recurrence of amblyopia in either subgroup. In a similar manner, the interocular visual acuity difference at the time of stopping successful amblyopia therapy did not have a bearing on recurrence (P = 0.68, Chi-square test).

No other factor including the presence or absence of binocularity or the amount of stereopsis showed any significant association with the risk of recurrence. While the absolute amount of refractive error did not show a significant association with risk of recurrence, a subgroup analysis including degree and type of refractive error was not possible in view of the small numbers involved.

All the patients with recurrence showed decrease in all their visual functions along with the decrease in visual acuity. Of the 89 patients who did not show recurrence of amblyopia on follow-up, 8 patients showed improvement in stereoacuity from a median of 140 sec of arc to 70 sec of arc during the 1 year of follow-up while others remained stable.

Discussion

Various studies have addressed the issue of recurrence of amblyopia after completion of therapy but have been inconclusive due to discordant results. The wide variability in literature is attributed to a variable sample size, length of follow-up, type of amblyopia included and type of treatment instituted.[3-10] In this study, 102 patients with anisometropic amblyopia were treated using a standardised protocol and received a sufficient and well defined follow up, thus minimising confounding factors.

The recurrence rate of amblyopia in the present study was observed to be 12.7% during this period and mean age at cessation of therapy was 9.5 years as against previous studies with similar follow up periods which have reported recurrence rates ranging from 7 to 27% with the mean age at cessation of therapy from 3.8 to 9.3 years.[7-10] However, these studies differ in the inclusion criteria and had included strabismic as well as

Table 1: Depicts the comparison of various visual parameters between those who underwent recurrence of amblyopia versus those which did not

Parameter	Non-recurrence (*n*=89)	Recurrence (*n*=13)	Significance (*P* value)
Gender			
Male	51.7%	53.8%	0.884
Female	48.3%	46.2%	
Age at diagnosis			
(Mean±SD) (years)	6.64±1.776	8.53±1.391	0.0014
Baseline VA at the diagnosis			
Median (range) (LogMAR)	0.23 (1.52, 0.3)	0.59 (1.22, 0.48)	0.189
Interocular VA difference			
Mean±SD (LogMAR)	0.51±0.159	0.47±0.149	0.201
VA at cessation of amblyopia therapy			
Median (range) (LogMAR)	0.19 (0.50, 0.0)	0.084 (0.40, 0.0)	0.03
Total duration of occlusion therapy			
Median (range) (months)	20.70 (8-36)	20.76 (13-36)	0.86
Extent of visual acuity improvement			
Median (range) (LogMAR)	0.4 (0.15, 0.95)	0.67 (0.15, 0.94)	0.048
Bagolini striated glass frequency (%)			
Cross response	84 (94.4)	12 (92.4)	0.568
Unilateral suppression	5 (5.6)	1 (7.6)	
Worth 4 dot frequency (%)			
Binocularity	84 (94.38)	12 (92.31)	0.568
Unilateral suppression	5 (5.62)	1 (7.69)	
Stereo-acuity			
Median (range) (Secs of arc)	50 (40-1000)	50 (40-1000)	0.607
Contrast sensitivity			
Mean±SD (Pelli-Robinson)	1.74±0.76	1.71±0.17	0.31
Spherical equivalent			
Median (range) (D)	0.66 (−13.5,+11)	1.34 (−11,+11)	0.472
Cylinder			
Median (range) (D)	0 (-4,+3)	0 (−1.5,+2.25)	0.975
Interocular refractive error difference			
Median (range) (D)	2 (−10,+7)	3 (-8,+8)	0.499
Spherical equivalent frequency (%)			
Hyperopic	54 (60.67)	8 (61.54)	0.99
Myopic	35 (39.33)	5 (38.46)	
Type of refractive error frequency (%)			
Simple myopia/hyperopia	35 (39.33)	8 (61.54)	0.203
Compound hyperopia	34 (38.20)	2 (15.38)	
Compound myopia	20 (22.47)	3 (23.08)	

mixed type of amblyopia which are known to behave differently and have a worse prognosis. In the absence of strabismus at the end of therapy and relatively good stereoacuity, there was still a significant recurrence of amblyopia despite appropriate refractive correction. This is an intriguing result and it is not clear as to the cause of the recurrence in these cases. Considering that the children were compliant with their glasses, it may have to do either with the children being of an older mean age than the other studies or with too early a cessation of therapy or an inherent altered dominance of one eye. However, it is a yet poorly understood mechanism working at the cortical level.

In our study age of the patient at time of diagnosis was found to be the most significant risk factor for recurrence. The odd's ratio for age at the time of diagnosis was 7.7 (95% C.I. of 1.61-36.94), suggesting that if the age at the time of diagnosis if more than 7 years, the risk of recurrence of amblyopia would increase by 7.7 times. The study by Malik *et al*., showed that the risk of recurrence was greater in the treated cases of amblyopia (anisometropic and/or strabismic), when the age of the patient at the time of diagnosis was greater than 15 years.[11] Bhola *et al*., found that the age at cessation of therapy was an important factor and had an inverse relationship with the rate of recurrence.[5] This may be understood by the fact that there is a plasticity at the cortical level which is higher at a younger age

and the ability of the cortex to reroute the neural synapses at a later age is more limited resulting in not only a lower chance of successful treatment but also possibly a higher chance of vision regression after therapy.

Vision at the time of completion of therapy was also an important factor for recurrence of amblyopia. Referring to the table, it is seen that the eyes with recurrence had a better visual acuity. In fact, the better the final visual acuity, the more was the risk of recurrence. It was found that if the visual acuity at the time of completion of therapy is better than 0.1 LogMAR, the risk of recurrence of amblyopia increases by 5.3 times. Similarly it was observed that risk of recurrence rose with the extent of improvement in visual acuity. The improvement in visual acuity is a sign of plasticity (immaturity) of nervous system which is more liable to any kind of adaptation. Thus these patients would also be at a higher risk of suppression of the amblyopic eye once the treatment is stopped. A comparable finding was reported by Holmes *et al*., who had raised the question about stability of visual acuity before deciding for cessation of amblyopia treatment.[9] It is deemed important that amblyopia therapy is weaned and then stopped only after repeated measurements of visual acuity remains stable over a long period of time.

Contrary to a report by Levartovsky *et al*., our study failed to find any significant association between the baseline visual acuity at the start of occlusion therapy and the risk of recurrence.[11,12] However, since all the patients in the present study had extremely poor vision at the beginning of their amblyopia therapy (as is commonly seen in our practice) it is difficult to comment upon the effect of baseline VA at the beginning of the treatment on the rate of recurrence.

Interocular visual acuity difference at the time of successfully completing amblyopia therapy was not found to be a predictor of recurrence. However, in view of majority of the patients having a difference of less than four lines, the numbers in the second subgroup having four or more lines interocular visual acuity difference was very small, therefore precluding a definitive conclusion. In contrast, the data conclusively proves that interocular visual acuity difference at baseline (prior to starting occlusion therapy) is not a predictor of recurrence of amblyopia after successfully completing therapy.

Amount of anisometropia has been implicated as a risk factor for recurrence for amblyopia by some authors.[3,13] In contrast, we did not find any significant difference in the amount of anisometropia between the cases with and without recurrence. Also due to the small numbers involved, the type or extent of refractive error could not be conclusively examined as a risk factor.

Development of stereopsis after amblyopia and presence of binocularity should be associated with a lesser risk of recurrence but in our study stereoacuity did not appear to be protective for recurrence. We did not find any difference between the cases with and without recurrence in terms of stereoacuity or binocularity. In view of this, it is possible that even in the absence of any strabismus and presence of stereoacuity, the amblyopic eye may still show residual central suppression that may be missed on routine clinical examination.[9]

To conclude significant numbers of children suffer recurrence of amblyopia after stopping therapy and older age, better visual acuity after stopping the therapy and greater magnitude of improvement in visual acuity are important risk factors. Careful follow-up of these children is essential for early detection and management of recurrence.

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