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# Risk Factors in Amblyopia

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**Summary**

**Any intervention to prevent serious amblyopia is based on the knowledge about normal versus subnormal visual development. Our ability to predict with high degree of certainty which children will develop amblyopia will be dependant on the characteristics of various risk factors for initiating the development of squint or amblyopia. We have used longitudinal studies of population based cohorts of young children to define some of these risk factors such as refractive errors. Three hundred and ten children with an astigmatism ≥1.0 D at one year of age were refracted yearly between the age one and four years. Astigmatism and anisometropia were found to be highly variable during infancy and early childhood. Longitudinal follow-up seems to be needed to separate the normal from the abnormal refraction development, which initiates the development of the amblyopia. Children with constant or increasing astigmatism or anisometropia between one and four years were 'at risk'.**

**In parallel we have studied important factors for successful treatment of amblyopia. Based on these findings we conclude that a population screening at four years of age seems to be advantageous in Sweden in order detect and successfully treat most cases of amblyopia.**

Any intervention to prevent serious amblyopia has to be based on our knowledge about normal versus abnormal visual development. I will specifically focus on the refractive errors as key factors for initiation of amblyopia.

The definition used here for amblyopia is a condition due to visual deprivation and/or abnormal binocular interaction for which no organic cause can be detected by, for example, ophthalmoscopy and which is potentially reversible by therapy. Since our ability to prevent the development of amblyopia are limited, an important task in good eye health care is to detect manifest amblyopia at a treatable stage. Programmes for screening for amblyopia have therefore been instituted in several countries. However, critical evaluations of the efficiency of the screening programs are few.[1] An abundant literature describes that the three main causes of amblyopia are strabismus, refractive errors and visual deprivation. The major portion of all amblyopic cases are unilateral ones with good vision in the other eye. Most also agree that besides visual deprivation, abnormal binocular interaction is important for the development of amblyopia. In a case with unilateral visual deprivation both abnormal binocular interaction and visual deprivation are held to be strong amblyogenic factors.[2] The different subgroups with amblyopia are generally detected at different ages due to the underlying cause (Fig. 1). Well informed parents may detect ocular opacities in the eyes

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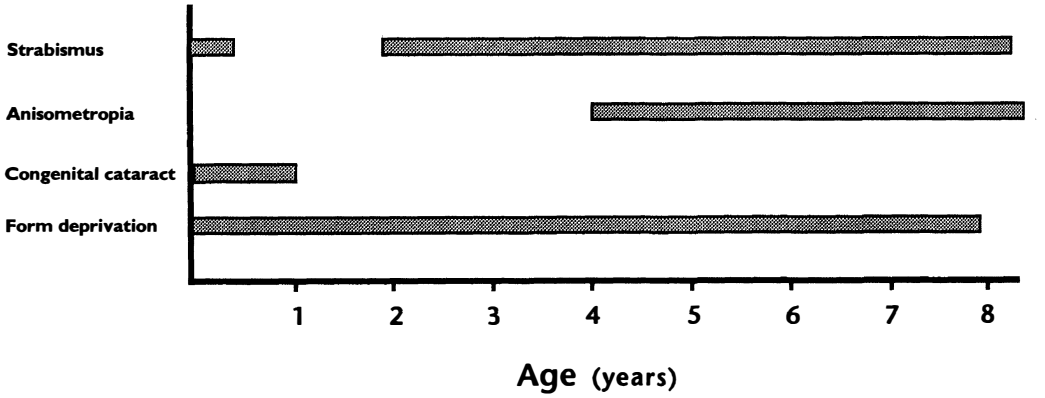


**Fig. 1.** *The four most common risk factors associated with amblyopia. The bars indicate the period during which amblyopia associated with these risk factors generally are detected.*

of their infants and the onset of strabismus during childhood. However, other amblyopia types without obvious symptoms have to be detected by ophthalmological examination, e.g. refractive errors (anisometropia, oblique astigmatism and ametropia) and small angle strabismus. A problem in amblyopia prevention and treatment is the late age of presentation of cases with straight-eyed amblyopia and small angle strabismus. In a study from Leicestershire Shaw and co-workers[3] found that the age at which the majority of children with anisometropic amblyopia presented was five years or above whereas the strabismic cases presented earlier.

The questions addressed here are: How can we separate normal from abnormal visual development? Can we, with our present knowledge, predict which children will develop amblyopia? Can we prevent amblyopia before it starts by knowing these factors? How can we detect amblyopia at an age when it is still treatable in most cases?

## Refractive errors

Several studies have presented simple and effective methods based on photorefraction for screening of refractive errors in infants and young children.[4–6] Thus methods for performing large scale refraction screening of children do exist, but do we have the knowledge to interpret the results? The object of the screening is to identify, from apparently healthy individuals, those who are at risk of developing a particular defect in the belief that early treatment will be easier and more effective. Present knowledge does not allow us to point out which of the refractive errors of infants are potential causes of amblyopia. Several studies have shown that newborn children exhibit a considerable amount of refractive error at birth and that the magnitude of the refractive error decreases as the infant grows older.[7–10] In many cases the refractive error has totally disappeared by school going age.

In Göteborg we have been interested in the natural history of the development of refractive errors and have addressed the question how to separate normal from abnormal refractive development. In a longitudinal, prospective study of infant astigmatism and its relationship to amblyopia[11] we have followed the changes in refraction between the ages of one and four years in 310 infants with astigmatism of 1 D or more at the age of one year during this three year period. The children were refracted by retinoscopy once a year during the test period. Cyclopentolate was given before retinoscopy.

We found that the distribution of the spherical equivalent in these children showed a decrease of the spread during the test period (Fig. 2). This indicates that the emmetropisation process has started. A change in the distribution of the cylindrical refractive error also occurred between one and four years of age. Approximately one third of the cases became non-astigmatic (Fig. 3).

At the age of four one third of the patients had a purely spherical refraction. A similar decrease in the incidence of astigmatism has

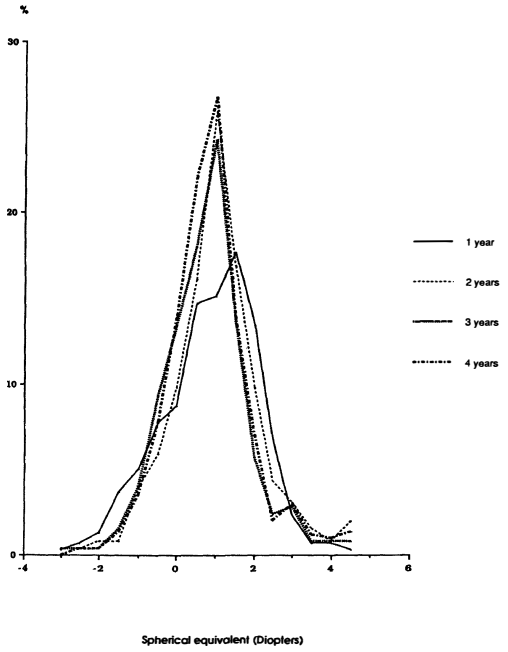


**Fig. 2.** *The distribution of the spherical equivalent (the refractive error of the least ametropic axis plus half the difference between the two axes) measured yearly from one to four years.*

previously been shown by Ingram and Barr[9] and Atkinson and co-workers.[12]

The dynamic changes of the astigmatic refraction are well illustrated by the fact that the majority of all infants (age one year) with an astigmatism equivalent to or greater than two diopters showed a decrease of their astigmatism. There were, however, some patients with an anomalous behaviour; they showed a stationary or even increasing astigmatism, as they grew older. Three types of changes with time could be observed. The largest group (93%) showed a decrease, another group was stationary and the third group had an increasing refraction of the most hyperopic axis.

Dynamic changes were also found with regard to anisometropia in our sample of children.[8] Eleven per cent of our astigmatic infants had an anisometropia of 1 D or more at the age of one year. At the age of four years there were still about 10% of children that had anisometropia. However, most of these cases were new cases that had developed their anisometropia during the second, third or fourth year. Ingram and Barr[9] also found a marked variability of anisometropia and an almost unchanged incidence of anisometropia between one and 3 and a half years. Fig. 4 summarises the dynamics of anisometropia in our study[8] with new cases entering the group with equivalent numbers becoming non-anisometropic. It is also interesting to note that marked decreases in anisometropia was found in some cases; for example in one child with an anisometropia of 4 D, where this refractive error almost vanished during the three year period.

*Relationship refractive error/amblyopia*

In order to evaluate refractive errors as risk factors for amblyopia we analysed the relationship between refractive errors and amblyopia in the group of infants with astigmatism.[7]

The group was followed longitudinally for three years and amblyopia was found in 7% of the children. The refraction data of these children were compared to the rest of the sample. In our follow-up analysis we used the following criteria for amblyopia:

An acuity difference of 0.1 log unit or more between the eyes measured with best correction on at least at two separate consecutive test sessions in eyes with no signs of disease; the acuity of the amblyopic eye improved at

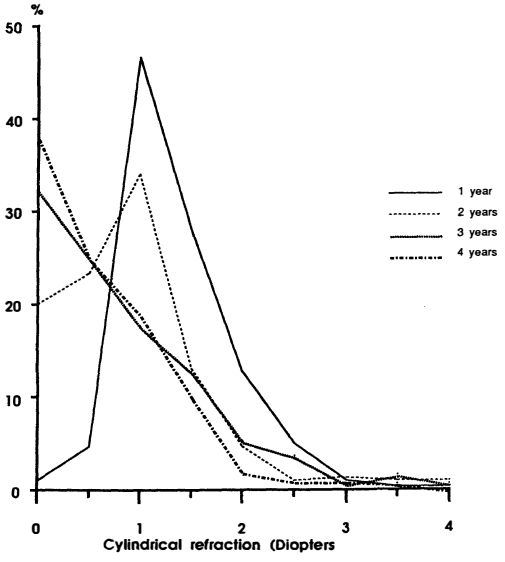


**Fig. 3.** *Distribution of the cylindrical refraction error measured yearly during the three year test period. A plus cylinder convention was used.*

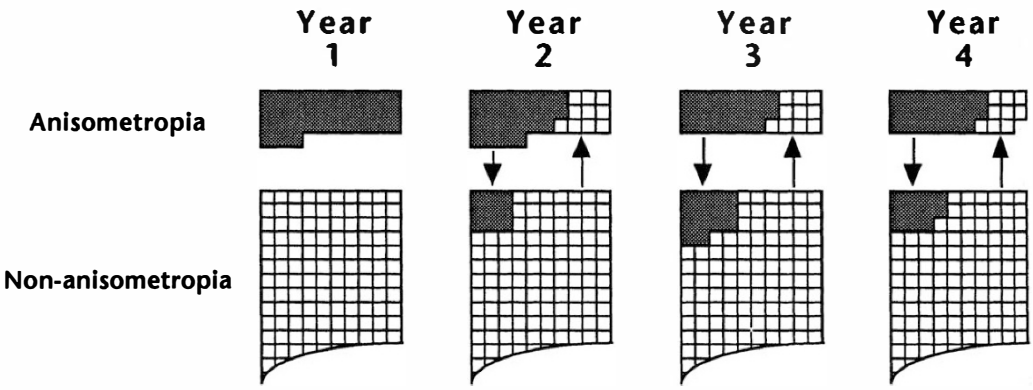


**Fig. 4.** *The variability of anisometropia. Non-anisometropia indicates the whole population based sample with no anisometropia. Each square represents one patient. The squares in the anisometropia group indicate patients becoming anisometropic since last year while grey squares in the non-anisometropic group are patients becoming non-anisometropic since last year.*

least one line following the occlusion treatment. We separated the amblyopic cases in subgroups with respect to the severity of their amblyopia. The group with increasing astigmatism and stationary astigmatism had a clear over-representation of amblyopia. In the subgroup with increasing astigmatism almost one third of the cases developed amblyopia.

How informative then is a single refractive value? Ingram *et al.*[13] and Atkinson *et al.*[14] have, in their pioneering studies, found that infants with a bilateral high hypermetropia have an increased risk for squint or amblyopia.

Could we predict the risk for amblyopia in our sample? Our finding was that the presence of two diopters of hyperopia in at least one meridian at one year did not define any 'at risk' population while it was related to some increased (2×) risk in the four-year group.

Choosing +3.5 D at one year as our criterion increased the risk to four times that of the other population. Thus high hypermetropia at one year of age has in our sample only a moderately predictive value for amblyopia. The importance of various refractive errors or combinations of them as risk factors for amblyopia is presented in Table I. Increasing astigmatism, oblique astigmatism, and strabismus were the factors with the highest relative risk.

*Detection by vision screening*

How can we define the 'at risk' population which is our basis of knowledge for planning of selective or population screening?

*Selective screening:* Potential groups for selective screening are those with heredity, mental retardation and other high risk fac-

**Table** *Risk factors for amblyopia in a sample of 310 children (Abrahamsson et al)*[8]

| *Refractive error* | *RR** |
|---|---|
| Against-the-rule astigmatism | 0.1 |
| Astigmatism decreasing between 1 and 4 years of age | 0.2 |
| Astigmatism ≥2.0 D at 1 year of age | 0.6 |
| Astigmatism <2.0 D at 1 year of age | 1.1 |
| Astigmatism unchanged between 1 and 4 years of age | 2.0 |
| Anisometropia at 4 years of age | 2.1 |
| With-the-rule astigmatism | 3.1 |
| Anisometropia at 1 year of age | 3.7 |
| Hyperopia ≥3.5 D at 1 year of age | 3.8 |
| Astigmatism increasing between 1 and 4 years of age | 6.7 |
| Oblique astigmatism | 14.5 |
| Strabismus | 14.7 |
| Against-the-rule, decreasing astigmatism | 0.1 |
| With-the-rule, decreasing astigmatism | 2.1 |
| Hyperopia ≥3.5 D and decreasing astigmatism | 2.8 |
| Against-the-rule, increasing astigmatism | 3.1 |
| With-the-rule, increasing astigmatism | 4.1 |
| Hyperopia ≥3.5 D and increasing astigmatism | 5.8 |
| Oblique, decreasing astigmatism | 10.5 |
| Oblique, increasing astigmatism | 14.7 |

Relative risk: How many times more likely are exposed persons to become diseased, relatively to non-exposed persons in a sample?

tors. Among the early visual disorders the presence of a family history of eye disease may enable us to detect those at high risk. In this group with visual defects in infancy it is most important to detect bilateral visual impairment and we have to screen selectively at an early age all those with a family history of congenital cataracts. Besides these obvious reasons for visual assessment, we also have selectively to screen all mentally retarded children since they run a high risk of having a visual disorder. In preliminary studies in Sweden it has been shown that the relative risk of having bilateral visual impairment of 6/60 or less is more than one hundred times that of the normal population. It has also been shown that the majority of these children need glasses due to refractive errors in order to be able to see well. The key to detection of early visual disorders otherwise, is probably good parent education in combination with attention and increased awareness of visual abnormalities and early referral of these cases by medical professionals.[15] The important message is: always to listen to the mother if she tells that there is something abnormal about the eyes of her infant. Take infants with congenital cataract as one example. Some may be detected due to the heredity risk factor but since the majority of the cases are idiopathic we have to rely on the information given by the parents in order to detect them early. According to our experience, in Göteborg, the mother is able to give us the earliest information about eye abnormality in two-thirds of the cases (Sjöstrand and Abrahamsson, unpublished) and the health care system and doctors in only one third of the cases. In this group of children the importance of early detection is proven. If we can operate and give contact lenses to the child before the end of the development of the fixation reflex (about three months of age) the child will have a much better visual prognosis.[16]

What about the risk factors for amblyopia with an onset after infancy? Can heredity help us to identify the children at risk and is it worthwhile selectively to screen children with a family history of strabismus.

Ingram and Walker[17] found that siblings of children presenting with squint/amblyopia have four times more chance of having a visual defect if they have a refractive error. My colleagues Aurell and Norrsell (personal communication) in Göteborg have made the interesting observation that only the children with heredity in combination with an unchanged high hypermetropia are at risk of acquiring strabismus. These data in combination with the fact that strabismus shows evidence of multifactorial inheritance[18] indicate that selective screening of siblings of affected children at an age of about two years is of value. However, we need more information about the predictive value of various risk factors and of the possibility of preventing the initiation of amblyopia or strabismus of later onset in these cases.

*Population screening.* The lack of highly predictive risk factors for most cases of ambloypia makes it impossible to prevent or detect a major portion of cases presenting with straight-eyed amblyopia and small-angle strabismus by selective screening. One way to accomplish the aim of detecting manifest visual disorders including amblyopia is by population screening. Few studies have evaluated the available methods for population screening. Köhler and Stigmar[1] have underlined the importance of high attendance rate (possible to attain when included in a general health control) and an efficient acuity testing. At four years of age the linear E test detected the majority (97%) of eye disorders.[1] However, evaluations of the long term implications of population vision screening for general eye health in the population are sparse.[19]

*Outcome of amblyopia therapy*

How important is the age at presentation for the outcome of vision in cases with amblyopia?

In the study from Leicestershire by Shaw *et al.*[3] they demonstrated that strabismic cases generally were found before five years of age whereas the straight-eyed amblyopes were identified only in 15% of the cases before the age of five (the median age at presentation 6.3 years of age). How successful is outcome of therapy if amblyopia is detected at a later age? It has been shown by Flynn and Cassidy[20] and Oliver and co-workers[21] that start of therapy after seven to eight years of age has a worse

prognosis. We have turned the question around and asked if the age of presentation of amblyopia of four years of age or before is compatible with successful treatment in most cases.

In a prospective study of 52 amblyopic cases aged $2\frac{1}{2}$ to eight years in Göteborg we studied the outcome of treatment in relationship to age and type of amblyopia. A new procedure for visual acuity testing[22] made it possible for us to test optotype acuity from $2\frac{1}{2}$ years and onwards. After three and $3\frac{1}{2}$ years of age we tested with linear HOTV and the tumbling E test was used after the age of four to five years.

Our findings in this prospective study were that the amblyopia was treatable in >95% of the cases, if straight-eyed amblyopes were detected at four years and strabismic cases early after onset.

The total number of cases with successful treatment to within one line of difference or less between the eyes was high in all age groups if the compliance was good.

The few cases we observed in our study with worse visual outcome were in the group with bad compliance. These findings are in agreement with the observations by Oliver *et al.*[20] They found in a retrospective study that the age of the patient was the most significant factor influencing compliance and thus the visual outcome. The most important factors for a successful outcome in our experience are summarised as follows: lower age at presentation, good compliance, early referral of strabismic cases, and effective V.A. testing from $2\frac{1}{2}$ years and onwards.

## Conclusions

Amblyopia is a condition that can be caused by a number of factors, some of which are interrelated such as refractive errors, strabismus and amblyopia. At present we are lacking easily obtainable risk factors for efficient, selective screening in most cases. Identification of children at risk at a treatable age needs different strategies for detection of straight-eyed amblyopes, microstrabismus and large angle strabismus. Our Swedish experience[1] is that population screening based on efficient linear acuity testing seems to be advantageous. Other ambylopic cases, with abnormalities detected by parents, for ex strabismus, should be referred for treatment as early as possible after onset. Future longitudinal studies of the emmetropisation process during eye growth seems to be of importance for our understanding of refractive errors as key factors for initiation of amblyopia.

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