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REVIEW

Amblyopia: prevalence, natural history, functional effects and treatment

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Amblyopia, defined as poor vision due to abnormal visual experience early in life, affects approximately three per cent of the population and carries a projected lifetime risk of visual loss of at least 1.2 per cent. The presence of amblyopia or its risk factors, mainly strabismus or refractive error, have been primary conditions targeted in childhood vision screenings. Continued support for such screenings requires evidence-based understanding of the prevalence and natural history of amblyopia and its predisposing conditions, and proof that treatment is effective in the long term with minimal negative impact on the patient and family. This review summarises recent research relevant to the clinical understanding of amblyopia, including prevalence data, risk factors, the functional impact of amblyopia and optimum treatment regimes and their justification from a vision and life skills perspective. Collectively, these studies indicate that treatment for amblyopia is effective in reducing the overall prevalence and severity of visual loss from amblyopia. Correction of refractive error alone has been shown to significantly reduce amblyopia and less frequent occlusion can be just as effective as more extensive occlusion. Occlusion or penalisation in amblyopia treatment can create negative changes in behaviour in children and impact on family life, and these factors should be considered in prescribing treatment, particularly because of their influence on compliance. Ongoing treatment trials are being undertaken to determine both the maximum age at which treatment of amblyopia can still be effective and the importance of near activities during occlusion. This review highlights the expansion of current knowledge regarding amblyopia and its treatment to help clinicians provide the best level of care for their amblyopic patients that current knowledge allows.

Key words: amblyopia, anisometropia, compliance, disability, natural history, prevalence, strabismus, treatment

Amblyopia has been defined as a unilateral or bilateral decrease of visual acuity caused by deprivation of pattern vision or abnormal binocular interaction, for which no cause can be detected by physical examination of the eye and which in some cases can be reversed by therapeutic measures.[1] Amblyopia is a disorder of development of the visual system that can present with varying levels of severity and usually affects one eye only, although the non-amblyopic eye often has an array of small but measurable deficits.[2] There is no obvious ocular pathology underlying the reduced visual acuity but rather, there is some predisposing condition that influences the development of visual acuity after birth. The most common predisposing conditions for amblyopia are strabismus (causing disruption of binocular vision development), refractive error (particularly anisometropia or hyperopia) or, more rarely, media opacification causing reduction in image quality (such as congenital cataract). The earlier in post-natal visual experience the predisposing condition presents, the greater the potential impact on vision. In addition, the longer the duration of abnormal visual experience the more profound the level of amblyopia.

Usually, amblyopia is classified according to the presenting visual condition believed to have caused the impaired visual development. An example of this classification is that used by Attebo and colleagues,[3] where amblyopia is identified in their population cohort as:

1. Anisometropic, if there is a difference in the sphere or cylinder between the two eyes of one dioptre or more and no strabismus is present.
2. Strabismic, if heterotropia or microsquint is present without anisometropia or high refractive error.
3. Mixed, if anisometropic amblyopia and strabismic amblyopia co-exist.
4. Stimulus deprivation, if there is some obstruction to vision during the sensitive period of visual development (this includes high refractive errors).

Clinically, amblyopia is defined by one or more lines difference in visual acuity between the eyes,[4] however, other monocular visual functions are also affected, including grating acuity, vernier acuity and contrast sensitivity. Amblyopic eyes can also have defective accommodation and can display oculo-motor deficits, including unsteady fixation and inaccurate tracking; the tracking of the non-amblyopic eye can also be less accurate than in age-matched controls.[5] Binocular vision adaptations may be present including suppression, eccentric fixation or abnormal retinal correspondence.[6,7] Most strabismic amblyopes lack any measurable stereopsis even if visual acuity has recovered, while many anisometropic amblyopes have some residual stereopsis that may be as good as the resolution of the amblyopic eye permits.[7] These deficits in stereopsis are present under habitual binocular conditions and may represent the main functional difference between patients with amblyopia and those without.

The different patterns of monocular and binocular visual loss seen in strabismic versus anisometropic amblyopia suggest the existence of two distinct developmental anomalies.[6-8] A recent review explores the literature pertaining to the physiological locus of amblyopia and indicates that the specific neurophysiologic mechanism underlying amblyopia may be interocular image conflict that reduces interocular summation, while promoting interocular inhibition. This is interpreted as reducing the effectiveness of excitatory neural connections in the cortex, while sparing inhibitory connections.[2] Recent psychophysical studies have suggested that the visual dysfunction in amblyopia may begin at the retina.[9]

During the past 20 years, different critical periods have been demonstrated for different visual functions during the development of the visual system. Visual functions processed at higher anatomical levels within the system have a later critical period than functions processed at lower levels. This general principle suggests that treatments for amblyopia should follow a logical sequence, with treatment for each visual function starting before its critical period is over. However, critical periods for some visual functions, such as stereopsis, have not yet been completely defined and therefore, the optimal treatment has not been fully determined.[10]

The prognosis for obtaining and maintaining essentially normal vision in an amblyopic eye depends on many factors, including the age of the patient at detection, the cause and severity of amblyopia, the presence of complicating factors, the interval between the onset of amblyopia and the beginning of treatment and compliance with treatment. In addition, treatment success may be a function of the duration of abnormal visual experience under the influence of the predisposing amblyogenic condition, rather than simply the age at treatment.

The mainstay of treatment of amblyopia is management of the underlying amblyogenic condition, thereby increasing visual stimulation of the amblyopic eye and removal of barriers leading to abnormal visual input to the brain. This is followed by occlusion or penalisation of the dominant eye that aims to enhance cortical processing of visual input from the amblyopic eye by temporarily limiting cortical input from the dominant eye. Penalisation may take the form of image degradation by instillation of atropine drops, refractive blur or translucent patching of the better eye.

For many years, preschool vision screenings have aimed to provide a safety net by identifying children with risk factors for amblyopia while they are still within the critical period of treatment efficacy (traditionally believed to be up to eight years of age). Refractive error and non-cosmetically obvious strabismus have been targeted conditions of screenings, with the premise that risk factors of media opacity or large angle strabismus would have been identified by a parent or primary health provider during infant or early child health assessments. A 1997 review of literature into the conditions targeted in preschool vision screening, namely refractive error, amblyopia and non-cosmetically obvious strabismus, concluded that there is a lack of good quality research into the natural history of these conditions, the disability associated with them and the efficacy of available treatments.[11] Following its publication, the review's conclusions were much debated in the ophthalmological literature, with criticism that recommendations made by the review lacked objectivity and that a lack of adequate data on the effectiveness of amblyopic treatment may result in a premature disassembly of preschool vision screening programs.[12-14] A positive outcome of this publication is that the randomised controlled trials that it called for are now appearing in the literature.

The aim of this review is to present a balanced representation of recent research regarding the prevalence and natural history of amblyopia, the efficacy of treatment and its impact on the patient. In doing so, we aim to contribute to the clinical understanding of optimum treatment regimes for amblyopia and their justification relative to a whole of life consideration of a patient's needs.

PREVALENCE

The reported prevalence of amblyopia depends on the study population and the definition of amblyopia used. Adult popu-

Population investigated	Percentage reported with amblyopia
Recruited soldiers	
Irvine*	1.0
Helveston*	1.0
Theodore et al*	1.4
Evens and Kuypers*	1.8
Glover and Brewster*	2.4
Downing*	3.2
Preschool and school-age children	
Friedman et al*	0.5
Russell et al*	1.3
DaCunha and Jenkins*	1.7
Flom and Neumaier*	1.8
McNeil*	2.7
Frandsen*	3.1
Vereecken et al*	3.5
Thompson et al[4]	3.0
ALSPAC: early screening[18]	1.1
ALSPAC: late screening[18]	2.0
Eibschitz-Tsimhoni et al:[19] early screening	1.0
Eibschitz-Tsimhoni et al:[19] late screening	2.6
Older population	
Vinding et al*	2.9
Brown et al[15]	3.06
Attebo et al[3]	3.2
Ophthalmic patients	
Irvine*	4.0
De Roeth*	4.5
Cole*	5.3

* Studies cited by von Noorden[1]

Table 1. Reported prevalence of amblyopia in selected populations

lation studies have reported the prevalence of amblyopia to range from one to five per cent,[3,4] however, population selection bias may influence prevalence rates. For example, studies from clinical ophthalmic populations are not representative of the general population and typically present with higher prevalence rates of amblyopia. Recent Australian adult population-based cohort studies that aimed to avoid such bias reported the prevalence of unilateral amblyopia to be 3.06 per cent (n = 4,721)[15] and 3.2 per cent (n = 3,654),[3] when amblyopia was defined as visual acuity of 6/9 or worse.

Reported prevalence of amblyopia in selected populations is shown in Table 1.

The predisposing cause for amblyopia varies between studies, dependent on the characteristics of the study sample, particularly, how amblyopia is defined. In the unselected adult population study of Attebo and colleagues,[3] where amblyopia was defined as visual acuity of 6/9 or worse, the main cause was anisometropia (50 per cent), with strabismus being the predisposing condition in 19 per cent, mixed (both strabismus and anisometropia) in 27 per cent and visual deprivation in four per cent. While in a cohort of children with moderate amblyopia (amblyopic VA 6/12 to 6/30, n = 409; mean age 5.3 years) the causes were found to be strabismus in 38 per cent, anisometropia in 37 per cent and mixed in 24 per cent[16] and in children with severe amblyopia (amblyopic VA 6/30 to 6/120, n = 175; mean age 4.8 years) the causes were found to be anisometropia in 34 per cent, strabismus in 27 per cent and mixed in 38 per cent.[17]

Recent data regarding the prevalence of amblyopia at 7.5 years of age are provided by the Avon longitudinal study of parents and children (ALSPAC), a UK population birth cohort study.[18] Of 6,081 children, 16.7 per cent had attended preschool vision screening (age three to four years) and all the children had been offered vision screening in the school reception class (age four to five years). The prevalence of amblyopia was significantly lower in those children who had received preschool screening compared with those who had not (1.1 per cent versus 2.0 per cent, p = 0.05). This finding confirms that of a large Israeli study, which found a one per cent prevalence of amblyopia in eight-year-old children previously screened and treated for amblyopia compared with 2.6 per cent in a matched population that had not received treatment.[19]

In summary, the most recent population studies of amblyopia indicate a prevalence of approximately three per cent in untreated childhood and current adult populations. With detection and treatment of the amblyogenic condition by five years of age, the prevalence of clinically significant amblyopia reduces to around two per cent. With detection and treatment before three years of age, the prevalence of clinically significant amblyopia reduces to around one per cent. The results of the ALSPAC and Israeli childhood amblyopia studies suggest that early screening for and treatment of conditions that predispose amblyopia reduce the prevalence of amblyopia in school-aged children.

RISK FACTORS FOR AMBLYOPIA

Amblyopia is more than four times as common in infants who are premature, small for gestational dates or who have a first degree relative with amblyopia. In infants with neuro-developmental delay, the prevalence of amblyopia is six times higher than in healthy, full-term infants.[20,21] Patients at greatest risk for amblyopia are infants who experience early stimulus deprivation. Visual deprivation prior to three months of age need not be prolonged to cause amblyopia and is highly correlated with later development of sensory nystagmus in bilateral cases and strabismus in monocular and bilateral cases.

In strabismus, the diplopia caused by the misalignment can lead to binocular rivalry and suppression of input from the non-dominant eye at the level of the visual cortex. Infantile esotropia (that is, congenital esotropia) generally presents before six months of age, when the developing visual system is at most risk of amblyopia. If not corrected early, the resultant amblyopia can be profound and difficult to reverse. In patients who have had early surgery with an outcome of good visual acuity in both eyes, very poor stereopsis can still result due to the early disruption of binocular vision.[7]

Refractive error represents a risk for developing amblyopia, either due to creation of dissimilar images in anisometropic amblyopia or as a driving factor for accommodative esotropia. Children identified at screening as at risk for amblyopia due to hyperopia of 3.5 D or more in any meridian were 13 times more likely to become strabismic and six times more likely to show measurable acuity deficits by four years compared with controls.[22] Wearing a partial spectacle correction reduced these risk ratios to 4:1 and 2.5:1, respectively, and did not interfere with the process of emmetropisation (the reduction in magnitude of refractive error seen in children aged between nine months and four years).[22]

Most studies report best-to-worst rankings for visual acuity at the initial visit and outcome at the end of treatment as anisometropic (best), followed by strabismic and lastly mixed strabismic/anisometropic amblyopia (worst) and the same ranking for least-to-greatest post-treatment deterioration in long-term follow-up.[2] Complicating the interpretation of expected treatment outcomes is the interrelationship between strabismus and amblyopia, as each can be causal of the other. Similarly, strabismus and anisometropia commonly co-exist and it may be difficult to determine which is the primary predisposing condition.

NATURAL HISTORY

The studies of early treatment intervention regimes allow better understanding of the natural history of amblyopia. The finding that those populations that undergo early intervention and treatment have lower prevalence of amblyopia than those that do not implies that amblyopia does not improve of its own accord.[18,19]

Further evidence that treatment is necessary for optimum visual acuity outcomes is provided by the randomised controlled treatment trial by Clarke and associates[23] where acuity was compared in those who had received one year of treatment with those who had not. Identified at pre-school vision screening as having monocular reduction in visual acuity worse than 6/9, 177 children aged three to five years were randomly assigned to a no-treatment group and were treated with glasses alone or with glasses and patch occlusion. Of the total sample, 173 (98 per cent) had a significant refractive error, 127 (72 per cent) of whom had anisometropia. Children in either treatment group had better visual acuity at follow-up than children who received no treatment (mean improvement 0.11 logMAR, just over one line of acuity). The effects of treatment depended on initial acuity, with those children with initial acuities in the range of 6/18 to 6/36 improving on average 0.20 logMAR following treatment. After 12 months, the no-treatment group received the treatment, with subsequent improvement in visual acuity and stereopsis equal to that of patients who had initially received treatment.[24] This latter finding indicates that in a group of mainly refractive amblyopes, treatment improves final vision, however, delay of treatment until five years of age does not appear to influence the final visual outcome.

To investigate the natural history of amblyopia without treatment, Simons and Preslan[25] reported longitudinal data on the course of amblyopia in a group of 18 children who were identified as amblyopic in a screening study but who either did not receive, or did not comply with, recommended treatment and then were retested a year later. Improvement in visual acuity in the amblyopic eye was reported in one child, in seven children visual acuity had deteriorated in the amblyopic eye and the rest of the group showed no change. These authors also reanalysed data from three other studies[26-28] and found that the visual acuity outcomes for those patients who had been compliant with treatment were significantly better than those who were not. They concluded that untreated children with either amblyopia or its risk factors are likely, at best, to show no improvement in the amblyopic eye if untreated and, in many cases, develop amblyopia.

Recent randomised, controlled treatment trials, together with reviews of patients who have not been compliant with treatment, indicate that the natural history of amblyopia is not that of spontaneous recovery. Intervention is required to maximise potential visual acuity in the affected eye. The age at which that intervention will still be effective has not been confirmed and is the subject of on-going studies.[29]

DISABILITY ASSOCIATED WITH AMBLYOPIA

Amblyopia is often considered to be a childhood condition, as this is when it is most often diagnosed and treated. Thus clinicians need to know which life skills relevant to a child may be affected if amblyopia is left untreated and be aware of any functional difficulties that a child may experience during and following treatment.

At least 64 per cent of parents of amblyopic children express concerns regarding disability associated with amblyopia. Parents of children with early diagnosis (before age five years) were more likely to consider amblyopia a very serious problem (58 per cent versus 39 per cent), while parents of children with late diagnoses reported more frequently that their child had problems attributed to amblyopia (80 per cent versus 64 per cent). Reported problems were typically those of school performance rather than related to social or athletic activities.[30]

These findings contradict those of Snowdon and Stewart-Brown,[31] who conducted semi-structured interviews on a small number of parents of children with amblyopia (n = 11). The authors concluded that these parents did not regard amblyopia as a disabling condition, with little impact on career choice or motor function. They report that adults with amblyopia found certain aspects of driving problematic, with driving at night identified as particularly difficult. This study also reports that practitioners who treat amblyopia generally agree that amblyopia may limit career choices due to visual standards and that there is a need to promote maximal vision in each eye to decrease lifetime risk of visual impairment. Their overall conclusions were that treatment of amblyopia by patching may result in more disabling outcomes than the condition itself; however, the small sample population limits the relevance of this study, as does the lack of information regarding visual acuity, stereopsis or aetiology and lack of data from a control group.

Potential disability in amblyopia has been investigated by assessing the risk of visual impairment attributable to loss of vision in the non-amblyopic eye. The projected lifetime risk of visual loss for an individual with amblyopia is at least 1.2 per cent. Rahi and associates[32] found that of 370 individuals with amblyopic visual acuity worse than 6/12, who had newly acquired visual loss in their non-amblyopic eye, 104 (28 per cent) had socially significant visual impairment (VA between 6/12 and 6/18), 180 (49 per cent) had visual impairment (VA between 6/18 and 6/60) and 86 (23 per cent) had severe visual impairment or blindness (VA less than 6/60). Only 36 (35 per cent) of 102 people previously in paid employment were able to continue to work. The authors argue that the risk of visual loss in the non-amblyopic eye and its consequences are greater than those previously assumed.

The patient's perception of quality of life associated with unilateral versus bilateral good vision has been calculated by utility analysis, which is a variation of cost-effectiveness analysis incorporating the value (improvement in the length of quality of life, quality of life or life) conferred by an intervention against the cost associated with that intervention. Good vision in both eyes provides a substantial improvement in utility value compared with good vision in only one eye. Patient feedback indicates that the psychological stress of having only one good seeing eye on which to rely and the apprehension induced by knowing that many eye diseases eventually affect both eyes is likely to play a major role in decreasing an individual's quality of life.[33] When specifically modelled in amblyopia, the cost of treatment of amblyopia, combined with the increase in utility value created by restoration of better vision in the second eye, indicates that amblyopic treatment is highly cost-effective from the third-party insurer viewpoint and contributes to the earning power of affected individuals.[34]

In summary, the potential visual disability due to loss of visual function of the non-amblyopic eye can be calculated and is an argument for treatment of amblyopia to maximise visual potential in each eye. The benefit of improvement in visual capacity of the amblyopic eye can also be quantified by quality of life scores and can result in positive cost-analysis of treatment. While parental concern regarding an amblyopic child's performance has been reported, specific research into those life skills that may be impaired by amblyopia is limited to studies with only small sample sizes.

IMPACT OF AMBLYOPIA ON VISUOMOTOR SKILLS

Reduced stereopsis is the most common visual deficit associated with amblyopia that is present under habitual binocular viewing. While much is known about the visual basis of stereopsis, the functional significance of reduced stereopsis has rarely been reported.[35] Studies that have investigated this issue have compared performance under monocular and binocular conditions,[36,37] generally concluding that:

1. Individuals with binocular vision have advantages in situations requiring spatial certainty, when compared with monocular individuals.[36]
2. Binocular vision facilitates control of manipulation, reaching and balance.[37]
3. People with no stereopsis have difficulty performing tasks that rely on three-dimensional visual clues.[38]

However, there are individuals who have better manual dexterity than can be predicted by stereoacuity measures alone.[38]

Parents of strabismic children whose eyes have been aligned surgically have reported that the children's visuomotor skills have suddenly and vastly improved following surgery.[1] This observation was confirmed in a study that assessed infants' performance on the Bayley Scale of Infant Development before and after surgery for infantile esotropia. Following surgery, 35 per cent of children showed an increase in performance on tests of fine motor skills and 41 per cent of children recorded an improvement in visually directed reaching and grasping. The greatest post-operative improvement was found in the sub-test item that involves depth perception, where the child is required to identify a depression in a piece of wood without monocular clues (such as a difference in colour).[39]

Of relevance to the question of how the restoration of binocular vision affects visuomotor skills, is the study of Ross and co-workers,[40] who tested for developmental delay in patients who had undergone treatment for retinoblastoma; 75 per cent of the test group were monocular as a result of enucleation. While on average the children's mental and motor ability scores were in the normal range, approximately 40 per cent of the mainly monocular test group were referred for delays of visuomotor development, including tasks that require eye-hand co-ordination and depth perception, such as placing pegs into holes or putting puzzle pieces into foam boards.

There is little published evidence regarding the relationship between stereopsis and motor skills in children with amblyopia. An exception is that of Hrisos, Clarke and Wright,[41] who found that stereoacuity, independent of visual acuity, significantly influenced performance on tasks requiring fine visuomotor control (bead threading tasks) in non-strabismic amblyopic preschool children with reduced acuity in one eye (6/9 to 6/60). No significant differences were found between these children and age-matched controls on other items in the battery that measured visuomotor integration, visual spatial processing, visual attention and gross visuomotor skills.

In summary, while it is assumed that reduced depth perception results in poor fine motor skill performance, there is little published evidence to support these assertions. Fine motor skill performance underlies many tasks of importance to preschool and school-aged children, such as handwriting and scissor skills. Exploring the relationship between reduced stereopsis and poor ocular-motor control (common findings in children with amblyopia) and fine motor skills is necessary to determine how amblyopia may impact on early educational development.

IMPACT OF AMBLYOPIA ON PSYCHOSOCIAL DEVELOPMENT

The psychosocial implications of strabismus and amblyopia on an individual's quality of life have gained recent attention in the literature. Anecdotal references to the undesirable cosmetic appearance associated with an obvious strabismus have been superseded by studies looking at the effect of strabismus and amblyopia on an individual's self-esteem, interpersonal relationships and employability.

In their review paper, Tolchin and Lederman[8] discuss ways in which congenital or infantile esotropia may affect the parent-child relationship during the first years of life and in turn, how this can have profound psychological consequences for the developing child. They concluded that there is evidence in the literature that the child's appearance plays a profound role in the developing parent-child relationship and that the cosmetically obvious ocular misalignment with infantile esotropia is one barrier to the eye contact necessary for a proper relationship to take place.

Eustis and Smith[42] found that 41 per cent of parents whose children underwent strabismus surgery believe that their child's psychological development or personal self-esteem was adversely affected by strabismus and 17 per cent of parents believe that the cosmetic stigma of strabismus was the single most important problem for their child. This parental belief was confirmed by Satterfield, Keltner and Morrison,[43] who found that patients with strabismus reported difficulty with self-image, securing employment, interpersonal relationships, school, work and sports. The difficulties experienced continued and intensified in the teenage and adult years, where patients with strabismus demonstrated higher levels of stress compared to age and gender-matched controls. This contrasts with the findings of Gray, Ansons and Kincey,[44] who found that individuals seeking surgery for cosmetically unacceptable strabismus were not in general 'neurotic' or experiencing high levels of social anxiety. Patients who underwent surgery for longstanding horizontal strabismus perceived that their psychosocial functions had improved post-surgery, but felt that other people would still rate them less highly than they rated themselves.[45]

Satterfield, Keltner and Morrison's finding[43] regarding difficulty securing employment was confirmed by two more recent studies,[46,47] which demonstrated that cosmetically obvious strabismus creates a significant negative social prejudice in patients, which can considerably reduce an applicant's ability to obtain employment.

Patients with amblyopia but without strabismus reported that amblyopia interfered with school and work to some degree and felt it affected their lifestyle.[48] Sixty per cent were concerned by associated teasing or ridicule, with the majority of patients reporting some concern that amblyopia had an effect on self-image. While most patients reported that their monocular condition had not affected their job choices, half reported that being monocular affected their lifestyle. Amblyopic subjects were also found to experience more distress in the areas of somatisation, obsession-compulsion, interpersonal sensitivity, anxiety and depression than control subjects.

While these studies provide an understanding of the adults' perspective on the psychosocial impact of amblyopia, further research is needed to investigate the impact of treatment for amblyopia or any disability associated with amblyopia on the psychological well-being of the child.

TREATMENT OF AMBLYOPIA

The treatment of amblyopia generally involves correction of the underlying predisposing condition followed by a period of deprivation of the dominant eye to promote normal visual experiences for the amblyopic eye. The results of randomised controlled treatment trials for various aspects of amblyopic treatment are now available. The younger the child when treatment commences, the more rapid the response to treatment and the better the visual outcome. In strabismic amblyopia the rate of improvement in amblyopia treated with full-time occlusion fell steadily from over 90 per cent at age 28 to 33 months to near zero, when therapy was initiated at age 12 years.[49] However, individual patients may achieve improved vision after the age of 10 years, with reports of improvement with treatment or after loss of the non-amblyopic eye even into adulthood.[50]

Refractive correction

Correction of any underlying refractive error is critical in the treatment of amblyopia.[6] It is only more recently that the extent to which the correction of refractive error alone reduces amblyopia has been specifically explored.[51,52] Correction of refractive error alone for a period of 18 weeks in newly diagnosed amblyopic children (n = 65; mean age 5.1 years) resulted in significant improvement in amblyopic visual acuity (mean improvement of 0.24 logMAR). This improvement did not significantly differ as a function of amblyopia type or age of the patient.[52] This has led to the conclusion that refractive adaptation is a distinct component of amblyopic treatment and that the beneficial effects of refractive adaptation need to be fully identified. Allowing refractive adaptation prior to commencement of occlusion or penalisation therapy may have significant benefits. The consequences of these findings for clinical practice are that following a period of refractive correction, children can start occlusion with improved visual acuity, possibly enhancing compliance, and in some cases patching can be avoided.[53]

Correction of abnormal ocular alignment or opacity

It has been conservatively estimated that 17 per cent of patients with amblyopia will undergo alignment surgery, 1.5 per cent require cataract extraction and 1.5 per cent require ptosis surgery.[34] While no large population-based study addressing the distribution and incidence of each type of strabismic amblyopia is available, a cost-utility analysis has assumed from case series and anecdotal evidence that approximately 60 to 75 per cent of strabismic amblyopes are accommodative, with 60 per cent of accommodative esotropes not fully correctable with spectacles and requiring surgery for ocular alignment.[34] The subgroup of strabismic patients with amblyopia who will undergo alignment surgery was estimated to be between 48 and 62 per cent of all amblyopic patients who have strabismus.

Occlusion and penalisation

The mainstay of treatment for the past quarter of a century has been occlusion of the better eye by an opaque patch. However, therapeutic regimes have lacked standardisation, with the length of patching ranging from a few minutes a day to all waking hours and in some cases treatment may last many months. Recent studies that have investigated the relative merits of occlusion and atropine penalisation have commented on the considerable variation in treatment practices with regard to the number of hours of initial patching prescribed.[54] While the number of prescribed hours had no relationship to patient age, it was found to be related to the acuity in the amblyopic eye (that is, the depth of amblyopia). On average, optometrists prescribed fewer hours of patching than ophthalmologists.[54]

Recent randomised controlled treatment trials have aimed to evaluate different treatment modalities for different levels of amblyopia. Trials of occlusive treatment by the Pediatric Eye Disease Investigator Group (PEDIG) have concluded that both atropine penalisation and patch occlusion are effective treatments for moderate amblyopia in children aged three to seven years;[55] that when patching is prescribed, two hours of daily patching is as effective for moderate amblyopia as six hours and that for severe amblyopia, six hours of daily patching is just as effective as full-time patching.[17] Weekend atropine provides an improvement in visual acuity of a magnitude similar to that of the improvement provided by daily atropine in treating moderate amblyopia in children three to seven years old.[56]

When occlusion is objectively (electronically) monitored, the overall compliance with prescribed patching treatment has been found to be 48 per cent, with considerable variation within and between patients. When six hours of patching per day was prescribed, on average the patient actually received a 'dose' of 2.8 hours, with only 14 per cent patching to an amount within 30 minutes of that prescribed.[53] Dose-response functions have been developed, based on how much patching the patient actually received, and the initial and final visual acuity. From these dose response functions, the relationship between visual acuity and treatment dose has been found to be monotonic, with 82 per cent of the improvement in visual acuity being achieved by six weeks of patching but with some further improvement up to 12 weeks. Dose rates of two to six hours per day resulted in the same final outcomes, although those with a high dose rate achieved a successful outcome more rapidly.[53]

While randomised controlled treatment trials have shown occlusion and penalisation therapy to be successful in treating amblyopia in children younger than seven years, the question of the upper age limit of successfully treating amblyopia has still not been addressed fully. A pilot study of treatment in children aged 10 to 18 years has indicated that visual acuity can be improved in older children and adolescents. Randomised controlled trials are underway to determine if there is an upper age limit for which amblyopic treatment can still be successful.[29]

Passive versus active treatment

While a preliminary study found an average of one logMAR line extra improvement when the patient performed near activities during occlusion or penalisation,[57] the benefits of active versus passive therapy during occlusion are yet to be confirmed by randomised controlled treatment trials. Despite this, the protocol of PEDIG has been to prescribe at least one hour of near visual activities during patching, for example, hand-eye activities, computer or Internet, reading, homework or accommodative tasks. Preliminary studies have indicated that the use of video display treatment and biofeedback can improve amblyopic visual acuity in adults, however, nearly all of the improvement in visual acuity achieved appears to regress if patients are followed over an 18-month period.[2] Although patching alone may be sufficient for improvement of visual acuity, it has been suggested that binocular performance is significantly better when vision therapy is included in the treatment regimen.[58]

Medical treatment

Attempts have been made to use catecholamines in amblyopic treatment, as they appear to extend or reactivate the visual system's 'sensitive period' of neural plasticity. Both levodopa[59-61] and CDP-choline, which stimulate availability of a variety of neurotransmitters and modulators, including dopamine, have been used. While improvements in visual function in amblyopic eyes have been reported in children and adults, long term follow-up indicates that a significant regression of improvement in visual function occurs.[62]

Treatment outcome

Numerous studies[7,23,55,63-67] have examined the visual acuity outcomes that can be achieved with treatment for amblyopia, however, this may diminish after treatment is completed. A recent prospective study which monitored the level of visual acuity following the finalisation of treatment concluded that approximately one quarter of successfully treated amblyopic children experience a reduction in visual acuity within the first year after treatment.[68] This recurrence rate was similar among patients who had previously been treated by patching and those who had been treated by penalisation with atropine and occurred more frequently during the first 13 weeks following cessation of treatment. Other studies have shown that about two-thirds of both strabismic and anisometropic amblyopes maintain, or even improve, visual acuity more than four years after treatment is completed,[69,70] however, anisometropia of greater than 1.5 dioptres appears to be a risk factor for regression.[71] The implication for clinical practice is that follow-up is warranted for at least 12 months following the completion of occlusion or penalisation. Further randomised clinical trials are needed to investigate the long-term risk of recurrence of amblyopia.

Quality of binocular vision can also be used as an outcome indicator. In a retrospective study of occlusive treatment outcomes, stereopsis was found to improve linearly with improved amblyopic visual acuity irrespective of the cause of amblyopia.[72] In comparison, in a large-scale study of adults with amblyopia or with a history of risk factors for amblyopia, 90 per cent of those who were believed to have had disruption of binocular vision during early visual development (that is, those with a history of strabismus) failed tests of binocular function, even if visual acuity was within normal limits. By comparison, 64 per cent of adults with anisometropia and 35 per cent of amblyopes with anisometropia passed these binocular tests.[7]

Emotional impact of treatment

Many parents of children undergoing occlusive treatment for amblyopia, even for relatively short periods of time, report distress or an increase in conflict at home. Most parents associate occlusion with reduced confidence seen in their child due to poor vision under occlusion conditions.[73] While not all parents report that their child's activities are affected, the degree of compliance with treatment and observations of changes in patterns of behaviour have been found to differ depending on the level of amblyopia.[74] No evidence of significant developmental delay or increased behavioural problems was found in a case-control study of congenital monocular cataract patients, who had their normally seeing eye patched for a significant percentage of their early childhood years. However, the sample size was limited in this study and the use of siblings for the control group introduced the possibility of parental bias in their subjective assessment of the two children.[75]

It has been shown in a randomised control trial of treatment that children undergoing patching were more upset and showed more resistance to their treatment than those prescribed glasses alone. In addition, many parents experienced difficulty with occlusion and were significantly more likely to be upset by this treatment than parents with children in glasses alone, however, the levels of distress and difficulty reported by parents were low.[76] This is in accord with a repeated measures study that recorded carer's perception of stress and psychosocial well-being of the child prior to and following commencement of treatment. Carers of children undergoing occlusion did not experience significantly more stress or perceive their child as exhibiting less psychosocial well-being than the non-occluded group. In addition, within the occluded group, carer's stress levels and child's psychosocial well-being did not significantly change following onset of occlusion.[77] Similarly, the PEDIG group[78] found that both penalisation modalities, patch occlusion and atropine, were well tolerated by the child and family, although treatment impact scores were consistently worse in the occlusion group compared with the atropine group.

Recent studies confirm that penalisation treatment for amblyopia creates negative changes in behaviour in many children and has an impact on family life. These changes appear to be more profound in children with a greater level of amblyopia. Whether this is due to greater visual impairment under penalised conditions or due to a longer duration of penalisation has not been established. The behaviour of the child under penalisation conditions influences compliance with treatment, which raises the possibility that the efficacy of treatment could be reduced by poor compliance in those children with the greatest need.

Functional impact of treatment

While often cited as the reason for poor compliance with occlusion or penalisation, the ability to perform everyday tasks under monocular conditions with reduced visual acuity has not been documented in children with amblyopia. Studies that have investigated performance on tasks requiring fine motor skills under monocular versus binocular conditions suggest that performance would be impaired by the penalisation phase of amblyopic treatment due to loss of residual binocular vision. It is likely that if amblyopic acuity is less than 6/12 then functional tasks would be further impaired. There is a lack of studies specifically investigating functional disability in areas of importance to children of the age most likely to be treated for amblyopia. Future studies need to address disability imposed by the treatment, especially performance under impaired monocular conditions imposed by penalisation. Also, once children have completed amblyopic treatment, they may still have some visual function anomaly such as reduced stereopsis, abnormal accommodation or poor ocular-motor function. The impact of these binocular visual anomalies on tasks important to children warrants investigation.

Costs of treatment

The medical costs associated with treatment of amblyopia can be calculated based on estimates of consultation fees, non-surgical and surgical fees. Specific costs in nominal US dollars in 2001 varied between $1,452 and $2,628 (depending on surgical or non-surgical treatment of the underlying cause) and averaged $1,623 per patient.[34] This same study weighed the cost of treating amblyopia against quality of life utility value gained due to improved visual acuity in the amblyopic eye and concluded that amblyopic therapy is particularly cost-effective because the visual acuity benefit is acquired at a very young age.

Compliance with treatment

Compliance with occlusion treatment is essential for an optimum outcome and has been the subject of numerous studies.[79,82] The level of compliance to treatment is influenced by patient age,[80,81] social deprivation,[82] level of visual acuity,[81] parental understanding of the condition and treatment[83] as well as by the financial and emotional cost to patient and family.[76,78,85] Strategies used to enforce wearing of a patch include encouraging, ordering, pleading, threatening, bribery, hospital administration, arm restraint by use of plaster cast and eye lid suturing.[79,86] Beardsall, Clarke and Mill[87] found that most parents of children with amblyopia were highly motivated to undertake recommended treatment after becoming aware of the reduced visual acuity at the initial visual examination. As non-compliance sometimes delays effective treatment, Beardsall, Clarke and Mill[87] suggest a protocol for occlusion aimed at giving maximal support for parents in the early stages of treatment. This was supported by Searle and associates,[85] who found parental compliance improved if they believed treatment was producing positive results and decreased if there was perceived restriction of the child's activities by patching. Similarly, it has been suggested that increased parental awareness of the rationale and urgency of occlusion, with reinforcement of details of the regimen, would help to reduce non-compliance.[83] This has been tested in a randomised controlled trial of written information, which concluded that a large proportion of patients would benefit by increasing parental knowledge in key areas, such as the critical period, importance of occlusion and potential negative consequences of not treating amblyopia.[88] Low socio-economic status, measured by qualification for Medicaid assistance, has been reported to indicate reduced likelihood for success for amblyopia therapy. Patients whose families qualify for Medicaid assistance (n = 71) had poorer final visual acuity, a greater number of missed visits and a lower estimate of compliance than those whose families did not qualify for Medicaid (n = 209).[28]

SUMMARY

Recent randomised controlled trials of treatment for amblyopia and early screening and treatment studies have provided evidence regarding the natural history of amblyopia and efficacy of treatment. These studies indicate that treatment of amblyopia reduces the incidence of amblyopia and results in better final visual acuity in the amblyopic eye. In addition, the earlier amblyogenic factors are detected and treated, the lower the prevalence and severity of amblyopia. In the context of overall outcomes for the population, it can be concluded that the results justify the treatment. Occlusion or penalisation in treatment of amblyopia can create negative changes in behaviour in children and have an impact on family life, more so in children with greater levels of amblyopia. As the child's behaviour influences compliance, it is essential to address this issue with the parent supervising the treatment when instigating the occlusion or penalisation. Allowing refractive adaptation prior to commencement of occlusion or penalisation may have significant benefits for the child, such as starting occlusion or penalisation with improved visual acuity, possibly enhancing compliance and in some cases unnecessary patching can be avoided.

Reports of disability for the patient with amblyopia are not conclusive and do not specifically address skills that are of importance to the childhood population. While the balance between possible disabilities attributable to the condition versus the treatment has not been established, the potential disability of incapacitating visual loss later in life, due to loss of visual function of the non-amblyopic eye, can be calculated and is an argument for treatment to maximise visual potential in each eye

The PEDIG studies have provided clinicians with more distinct guidelines with respect to the how and when of therapy using occlusion and penalisation in amblyopia. Randomised treatment trials in child and adolescent age groups, beyond the age traditionally considerd able to be effectively treated, are ongoing. Similarly, the outcome of ongoing randomised treatment trials examining the influence of near activity during patching will provide direction to 'active' versus 'passive' patching. The importance of parental education and support to maximise compliance with treatment has now been established and should be part of the treatment plan.[88]

Importantly, this review highlights the need for evidence-based guidelines for treatment of amblyopia to be developed so that clinicians can provide optimal advice and treatment for amblyopia with minimal impact for the patient. It also highlights the amount of recent research activity in this area and the need for clinicians to keep up-to-date with recent literature to provide the best level of care for their amblyopic patients that current knowledge allows.

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