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Review Article

Anisometropic Amblyopia: Diagnosis, Treatment and Epidemiological Aspects

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ABSTRACT

Anisometropic amblyopia is one of the most important eye disorders caused by a loss of foveal resolution in the less focused eye, by localized mechanisms of foveal inhibition, or by loss of stereo acuity and binocular function. It occurs in presence of refractive errors, spherical or cylindrical, > 1.00 D, in presence or absence of strabismus, hyperopia > +3.50 D, myopia < –3.00 D, media opacity, astigmatism > 1.5 D at 90° or 180°, 1.0 D at oblique axis. The techniques used for the diagnosis include photoreactive screening, cycloplegic and non-cycloplegic retinoscopy, auto refraction, visual evoked response, wave-front analysis, and optical coherance tomography. The treatment protocol for anisometropic amblyopia comprises rectification of refractive error followed by improvement of visual acuity; further treatment involves atropine penalization of the better eye, occlusion with patching of the better eye or contact lenses, and combined atropine and spectacle therapy. Refractive surgery including laser in situ keratomileusis, laser epithelial keratomileusis and photorefractive keratectomy, are alternative treatment in patients where conventional modalities have failed. Children with anisometropic refractive error are less likely to have amblyopia if they are detected at a young age. The present review stands for an update on facts and phenomena of anisometropic amblyopiawith emphasis on its pathophysiology, diagnosis and treatment, based upon the available documents in SCI and non-SCI journals as well as in web-based journals and documents.

Key words: Anisometropic amblyopia, pathophysiology, epidemiology, diagnosis, treatment

1. INTRODUCTION

Anisometropic amblyopia remains a worldwide public health problem and it is the cause of great concern both to clinicians and patients/parents, because the condition goes undiagnosed and hence untreated enduring into adult stage; but it is reversible if detected early and with appropriate treatment for the presence of asymmetric refractive error in the two eyes. Amblyopia is a condition of diminished visual acuity either

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unilaterally or bilaterally caused by deprivation of form vision or abnormal binocular interaction, or both, for which no organic causes can be detected by the physical examination of the eye and which in appropriate cases is reversible by therapeutic measures.[1,2] Amblyopia is primarily a cortical phenomenon, caused by unequal competitive inputs from the two eyes into primary visual cortex area 17, although additional structural and functional abnormalities have been observed in the lateral geniculate nucleus of amblyopic animals and humans.[3] There are several types of amblyopia of which anisometropic amblyopia is the one. Anisometropia has been considered to bea significant amblyopiogenic factor.[4, 5] Anisometropia is the situation characterized by a considerable difference in the refractive state of the two eyes.[1] It is of axial type when there is dissimilarity between length of the anterior-posterior axis of the ocular bulbus and of refractive type when there is difference between dioptric mean refractive index of the eyes or in the curvatures of the ocular surfaces. It can also be categorized as simple hypermetropic, one hypermetropic eye and the other emmetropic; compound hypermetropic, both eyes hypermetropic; simple myopic, one eye myopic and the other emmetropic; compound myopic, both eyes myopic; and antimetropic, one eye myopic and the other hypermetropic.[6] The current review outlines the facts and phenomena of anisometropic amblyopia with emphasis on the pathophysiology, existing approaches to diagnosis and treatment, based upon the information published in SCI and non-SCI journals as well as the web-based journals and documents.

2. PATHOPHYSIOLOGY

Anisometropia that produce amblyopia is caused by a loss of foveal resolution in the less focused eye, by localized mechanisms of foveal inhibition (development of a suppression scotoma), or by loss of stereo acuity and binocular function (caused by loss of resolution or by a suppression scotoma).[3] There are also reports of ambylopia causing anisometropia.[3] Anisometropia is known to be associated with amblyopia both in the presence and absence of strabismus.[7] However, when amblyopia develops in association with anisometropia, it remains uncertain if the severity of amblyopia is directly related to the amount and degree of anisometropia, which is evident from the fact that despite early intraocular lens surgery in pediatric cataracts, amblyopia still plagues the outcome and even bifocals or contacts lenses fail to eliminate amblyopia, so the association between the two has been the subject of debate, and conflicting results have been obtained.[7-11] However, Garcia et al.[12] reported significant correlation between depth of amblyopia and the degree of anisometropia, in both myopic and hypermetropic patients, being greater for hypermetropic individuals; the difference between the axial length of the two eyes contributed to a major part of anisometropia, more so in myopic cases. Both spherical as well as cylindrical myopic and hypermetropicanisometropia caused increased amblyopia and decreased binocular function.[13]

The amount and type of refractive error difference between eyes were related to amblyopia and best corrected interocular acuity difference (IOAD); the development of stereoacuity depended on similarity of the refractive error between eyes because the best corrected random dot stereoacuity were hindered with smaller interocular differences.[1] The amount of refractive error and degree of anisometropia at presentation of a child with anisometropic amblyopia strongly correlated with final visual acuity, rather than the age of the child, suggestive of the fact that children with anisometropic amblyopia be treated regardless of age, and those with poorer visual acuity and higher degrees of anisometropia be treated more

aggressively.[7] Patwardhan[2] showed that patients of anisometropic amblyopia responded to treatment irrespective of age and thus effort should be made to treat even older patients.

3. EPIDEMIOLOGY

There are many clinical and epidemiological reports on the prevalence of anisometropic amblyopia. Garcia et al.[12] found a prevalence of 47.6% anisometropic amblyopia in students, with predominance in females (81%) and 9.5% prevalence of strabismus, both with exotropia, with 8 cases of unilateral amblyopia and 2 cases of bilateral amblyopia.

Anisometropic amblyopia without strabismus are often presented beyond the critical age period i.e., 6-8 years as they remain unnoticed in the absence of a screening program. The age at presentation was not associated with the final visual acuity of the amblyopic eye; hyperopic anisometropia was more prevalent at >3 D anisometropia being strongly correlated to higher grades of amblyopia.[14]Anisometropic amblyopia is more prevalent in the hypermetropic type, because accommodation, which is binocular phenomenon, occurs sufficiently to focus with the less ametropic eye while the other eye remain unfocused. Various previous studies show amblyopia to be much more common in spherical anisohypermetropes (simple and compound), compound hypermetropic anisoastigmatism while very low prevalence was observed in spherical anisomyopes (simple and compound) and in myopic anisoastigmatics.[15-17] Donahue [18] in a preschool photoscreening program on 120,000 children, identified 792 with anisometropia greater than 1.0 diopter and found that younger children with anisometropic refractive error had a lower prevalence and depth of amblyopia than did older children while amblyopia had developed by age 4, when they went through traditional screening.

4. DIAGNOSIS

Amblyopia is defined as a minimum of two Snellen lines difference in visual acuity. New vision screening technologies that allow early detection of anisometropia provide ophthalmologists an opportunity to intervene early, perhaps retarding, or even preventing, the development of amblyopia.[18] The traditional techniques for the detection of anisometropic amblyopia include direct assessment of acuity using Snellen, Early Treatment Diabetic Retinopathy Study (ETDRS) or other opto type charts in children and adults while forced-choice preferential looking and sweep visually evoked potentials are used for preschool vision screening. Novel vision screening tools that permit early recognition of anisometropiais important for early intervention, for checking, andstopping, the development of amblyopia.[18] During the last two decade, the techniques that have been used increasingly are based on the diagnosis of the anomalous factors causing amblyopia such as photo reactive screening, non cycloplegic retinoscopy, detection of high refractive errors of myopia, astigmatism, hyperopia, anisometropia, media opacities, and ocular misalignment.[19, 20] Other techniques of preschool vision screening include cyclo plegic auto refraction, non cycloplegic auto refraction, video auto refraction, visual evoked response, and wave-front analysis.[21, 22]

Press and Press [23] applied visual evoked potential (VEP) to facilitate titrating the anisometropic prescription toward isometropia while attaining and preserving symmetry in latency and amplitude of the wave form recordings to primary visual cortex between the two eyes. VEP response for the assessment of anisometropic amblyopia include measurement at a fixation distance of one meter using a pattern-reversal waveform generated by a high contrast black and white checkerboard pattern that is reflected in amplitude more than in latency of the signals.

In a study by Zadnik et al.[24],the concordance between cycloplegic auto refraction at 95% confidence interval were ± 0.32 diopters, 3 times less than that for manual cyclo plegicretinoscopy, ± 0.95 D. Cycloplegic retinoscopy was reported to be appropriate and accurate method to determine refractive error during a comprehensive eye examination in preschool children.[25] Studies with f-MRI in anisometropic amblyopia have depicted reduced level of activation, in the calcarine cortex at higher spatial frequencies, in the lateral geniculate nucleus and in the visual cortex corresponding to the anisometropic eye.[26, 27]

Teller charts and Bailey-Lovie-Ferris charts are used to test the sensitivity of spatial contrast at low and high frequency respectively, anisometropic amblyopia being characterized by higher differences at high spatial frequencies and smaller differences at low spatial frequencies caused by optical magnification differences between the eyes, the loss of high spatial frequency contrast sensitivity resulting into both stereoacuity and summation defects.[28, 29]

Anisometropic amblyopia are related to anomalous parvo cellular visual pathways, causing defect in the dorsal layers of the lateral geniculate nucleus, which reflect foveal visual function and greater defects in central field of vision, as supported by diminished multifocal visually evoked potentials in the region, compared to the peripheral field of vision.[30,31]

5. TREATMENT

The treatment protocol for anisometropic amblyopia comprises rectification of refractive error followed by improvement of visual acuity. Further treatment involves atropine penalization of the better eye, occlusion with patching of the better eye or contact lenses, and combined atropine and spectacle therapy.[32, 33] Treatment success is expected to be associated with the magnitude of anisometropia and the extent of the amblyopiogenic factors.

Refractive correction alone with spectacles resolved amblyopia of children 3 to <7 years old with moderate (20/40 to 20/100) untreated anisometropic amblyopia causing improved visual acuity indicated by an average 3-line improvement in visual acuity that may lower the burden of subsequent amblyopia therapy for those with denser levels of amblyopia.[34] The interocular acuity difference (log minimum angle of resolution) in diopters, corrected and uncorrected, is represented in Figure 1 for anisometropic cases of spherical and cylindrical myopia and hyperopia.[13] In children with mild to moderate anisometropic amblyopia, a 1-2-4 rule can be considered, such that in hyper metropic anisometropia of +1.0 D, astigmatism of 2.0 D or myopia of -2.0 D or a hypermetropia of +4.0 D, spectacles are required in presence of 2.0 D astigmatism or myopia, and not a must if the uncorrected visual acuity is satisfactory.[35]High anisometropic amblyopia is challenging to treat; Roberts and Adams[36] used contact lenses to improve visual acuity in myopic anisometropia of up to 9 dioptres, since contact lenses provide better quality of vision and contrast sensitivity compared to spectacles.

Treatment with atropine penalization involves the use of 1% atropine that works by obstructing parasympathetic innervation of the pupil and ciliary muscle in the preferred eye leading to pupillary dilation and temporary loss of accommodation. The obscuring of vision due to atropine usage is higher in hyperopic eyes caused by loss of accommodation.[37]It has been suggested that atropine works best in patients with visual acuity ≥ 20/100 in the amblyopic eye since atropine use generally causes blurring of image by decreasing visual acuity to 20/200.[38]

Megbelayin [39] reported reversal of myopic anisometropic amblyopia with occlusion therapy in a 25 year old. The Pediatric Eye Disease Investigator Group reported, compared to atropinisation, significant

improvement with 10 or more hours of patching in the range of 20/80 (6/24) to 20/100 (6/30) and an insignificant improvement by 6 months, in children between 3 and 7 years with moderate amblyopia[40] while 2 hours of daily patching to be equally effective as 6 hours of daily patching [41], however 6 hours of daily patching was found to be equally effective as full-time patching in severe amblyopia with a range of 20/100 (6/30) to 20/400 (6/120).[42] The vision may not be completely restored after atropinization and penalizaion or there may be recurrence after abrupt cessation of treatment without weaning in patients after 6 or more hours of daily patching to 2 hours of patching.[43, 44]

Table 1: Prevalence of anisometropia, amblyopia, anisometropic amblyopia

Population	No	Age	Technique	Prevalence			Reference
				Anisometropia	Amblyopia	Anisometropic amblyopia	
Patients	200	1-30 year	Cycloplegic refraction	—	—	72% (< 12 y), 28% (>12 y)	[2]
Individuals	1024	5-46 year	Cycloplegic refraction, visual acuity	2%	—	47.6%	[12]
Children	120000	Up to 7 year	Photoscreening	0.22%	—	0.37%	[18]
Children	1356	<13 year	Cycloplegic streak retinoscopy	2%	67%	1.3%	[22]
Patients	85	7-50 year	Cycloplegic refraction, best corrected visual acuity	64.7%	1.2%	100%	[54]

Table 2: Morphological changes in the retina in anisometropic amblyopia

Method	Morphological changes	Reference
Optical coherence tomography (OCT) image segmentation for the assessment of morphological changes in the retina in amblyopia	Significant difference in thickness of outer nuclear layer in central region using linear mixed model and insignificant difference in interocular thickness of macular layers	[55]
Scanning laser ophthalmoscope microperimetry to evaluate amblyopic patients	Presence of scotoma in the amblyopic eye and in fellow non-amblyopic contralateral eyes	[56]
Spectral-domain OCT to investigate the choroidal thickness in amblyopes	Chorodial thickness was more in amblyopic eyes; differences in choroidal thickness in both eyes of amblyopes compared with normal vision	[57]
Spectral-domain OCT to compare the macular retinal thickness and characteristics of optic nerve head parameters in amblyopic and fellow eyes in patients with unilateral amblyopia	Macular retinal thickness parameters such as circumpapillary retinal nerve fibre layer thickness, macular full retinal thickness, and macular outer retinal thickness were greater in the amblyopic eyes. The optic nerve hyperplasia parameters, such as, the rim area was larger and the cup-to-disc area ratio was smaller in the amblyopic eyes.	[58]
Spectral-domain OCT to compare the retinal and choroidal thickness before and after optical correction in eyes of children with anisohypermetropic amblyopia.	Corrective plus lenses improved visual acuity but did not cause choroidal or retinal thinning. Different choroidal thickness in both eyes of amblyopes compared with normal vision that did not alter after one year of optical correction	[59]
Spectral-domain OCT to evaluate unilateral anisometropic amblyopia.	Mean macular thickness was greater in amblyopic eyes	[60]
Ophthalmic examination and microperimetry with analysis of retinal sensitivities and fixation patterns with red cross of 2° as the fixation target, white background illumination of 4 asb, Goldman III stimuli with a projection time of 200 ms, and a grid of 68 stimuli around 10° centered on the fovea. Fixation was assessed with evaluation of behavior contour ellipse area.	Unchanged fixation and reduced macular sensitivity in amblyopia.	[61]

Lee and Kim[45] reported a case of abruptly developed large esotropia combined with superior oblique muscle palsy after full time occlusion therapy in anisometropic amblyopia. Occlusiontherapy is an essential method for treatment of amblyopia, but it can disrupt certain peripheral fusion, which may control a latent component of the existing strabismus[46], hence stereopsis and fusional ability should be evaluated before a full time occlusion that could result in a disruption of fusion.[45]

Refractive surgery including laser in situ keratomileusis (LASIK), laser epithelial keratomileusis (LASEK) and photorefractive keratectomy (PRK), may be an alternative in patients where conventional modalities have failed that can be carried out under regional anesthesia with self-fixation, along with the usage of midazolam or diazepam anxiolytic agents in uncooperative children.[47] Autrata and Rehurek [48]

reported 78% gain of binocular vision and improvement of mean BCVA from 20/95 to 20/26 along with a rectification of anisometropic amblyopia in 4 to 7 year children using PRK and LASEK with a respectively mean spherical equivalent (SE) of -8.3 D and-1.6 D, pre- and post- operative value after a 24 months follow-up. Chipont et al.[49] reported a case of reversal of myopic anisometropic amblyopia(spherical equivalent refraction of right eye:-14 -3 x 100^0, left eye: -5 -3.25 x 90^0) in a 8 year old boy with -15 D Artisan iris claw phakic anterior or chamber intraocular lens implantation, which after surgery, treatment of amblyopia and spectacle correction of -4D cylinder at 85^0 in the right eye and -3.5 D cylinder at 90^0 in the left eye was required.

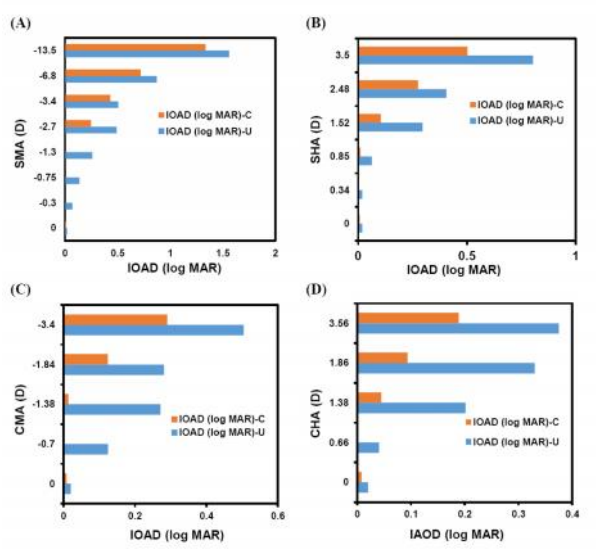

Figure 1: Interocular acuity difference (log Minimum Angle of Resolution) corrected and uncorrected; IOAD (log MAR)-C and IOAD (log MAR)-U in
[A]Spherical myopic anisometropiain diopters; SMA (D)
[B]Spherical hyperopic anisometropiain diopters; SHA (D)
[C] Cylindrical myopic anisometropiain diopters; CMA (D)
[D]Cylindrical hyperopic anisometropia in diopters; CHA (D)
(Data table partly converted to figure from Weakly[13])

According to Hennessey,[50] moderate amounts of anisometropic amblyopia have been effectively treated with non-surgical modalities including refractive adaptation through appropriate correction, six hours of everyday patching, weekend-only usage of atropine and a combination of atropine with optical penalization. The prevalence and depth of amblyopia were markedly reduced by screening 4–5 year olds in a cohort of 3126 Swedish children indicating that early treatment of amblyopia in childhood after a screening programme would result in a better final visual acuity.[51]

Careful follow‑up is essential for early detection and management of recurrence of amblyopia after stopping therapy for which, older age, better best corrected visual acuity (BCVA) after stopping therapy and greater magnitude of improvement in BCVA contribute as important risk factors.[52]

Use of medication such as levodopa, carbidopa and citicoline that increase dopaminergic neuro transmission have also been applied to treat amblyopia in adults and children.[47]

LASIK surgery is suggested in all types of anisometropic amblyopia in whom traditional management have failed, who are intolerable to glasses or contact lenses, with amblypoia management being continued postoperatively, along with assessment of factors affecting anisometropic amblyopia management by LASIK, such as age, refraction, depth of amblyopia and response to conventional therapy.[53]

The prevalence of anisometropia, amblyopia, anisometropic amblyopia in a population of patients of different age groups is indicated in Table 1.[2,12,18,22,54]

The morphological changes in the retina associated with anisometropic amblyopia using different diagnostic modalities is shown in Table 2.[55-61]

Techniques such as photoscreening, photorefraction, and non cycloplegic autorefraction, help to evaluate younger children in very large numbers, however further development of such technology for earlier detection of the disease is of any value or not, remains to be explored. Prospective studies are necessary to explain the mechanistic differences behind the fraction's ability to induce amblyopia. Final visual

outcome is correlated with initial visual acuity, and comparable acuity improvement in all refractive groups warrants the standard of care treatment for all anisometropicamblyopes. It is essential to carry out large-scale multi-centric randomised clinical study at the regional level, in order to completely explore the benefits of amblyopia therapy.

6. CONCLUSION

Anisometropic amblyopia is the consequence of persistent formation of defocussed image on the fovea causing anomaly in the binocular vision and towards sensitivity to the high spatial frequency contrast. The relationship between amblyopia depth and anisometropia magnitude depends on the refractive basis of the amblyopia, with deeper amblyopia being associated with larger amounts of anisometropia in hyperopic amblyopia. Patients of all ages with anisometropic amblyopia must be encouraged to enter a management programme with frequent follow ups to monitor progress. Children with anisometropic refractive error are less likely to have amblyopia if they are detected at a young age. Treatment becomes difficult with high magnitude of anisometropia, when visual acuity is ＜20/40, and difference in BCVA is ≥4 line between the amblyopic and non-amblyopic eye. Amblyopia is generally treated well with either glasses or occlusion therapy or both and refractive surgery is used for the treatment of patients who cannot tolerate spectacle or contact lenses.

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