Amblyopia management

Gladys H Sit[1], MBBS; Emily S Wong[2,3], FRCOpth; Jason CS Yam[2,3,4], FRCOpth
[1]Princess Margaret Hospital, Hong Kong SAR, China
[2]Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China
[3]Hong Kong Eye Hospital, Hong Kong SAR, China
[4]Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, Hong Kong SAR, China

Correspondence and reprint requests:
Dr Jason CS Yam, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong SAR, China. Email: yamcheuksing@cuhk.edu.hk

Abstract

Amblyopia is a reversible neurodevelopmental disorder but can cause vision loss if untreated, especially within critical period of visual neuroplasticity. We review different treatment modalities for amblyopia including refractive correction, occlusion therapy, medication, surgery, perceptual learning, and the more advanced binocular therapy. Binocular therapy can improve both visual acuity and stereoacuity, but whether it is superior to occlusion therapy remains controversial. Future studies to determine the optimal treatment duration, timing of initiation, dosage, and when to step-up treatment when other treatments become refractory are warranted.

Key words: Amblyopia; Vision, binocular; Visual acuity

Introduction

Amblyopia is a neurodevelopmental disorder resulting in abnormal visual acuity (VA) in one or both eyes.[1] Unilateral amblyopia is defined as VA difference of ≥2 lines on Snellen chart between eyes, whereas bilateral amblyopia is defined as VA of worse than 20/50, 20/40, and 20/30 in both eyes in children aged 3 to <4, 4 to ≤5, and >5 years, respectively.[2] Amblyopia is reversible but can cause vision loss if untreated. It affects approximately 1% to 4% of the population.[3] Early detection and management of amblyopia can maximize children's visual development potential.

Neuroplasticity

Early detection enables timely management during the period of greatest plasticity of visual cortex, which is the primary site of visual deficit in amblyopia.[4] Plasticity is a dynamic ability to functionally recognize external stimuli and structurally respond to them. This developmental mechanism relies heavily on the interaction of cortical afferent neurons between both eyes. Reduced connection in the deprived eye was due to competition with the non-deprived eye, rather than the disuse of the deprived eye.[5] Treatment should be started before the age of 7 years and can be extended beyond this age to reverse visual deficits such as reduced VA, stereoacuity, and contrast sensitivity as well as crowding and recurrence.[6-8]

Many patients with amblyopia are affected by reduced fine motor skills and oculomotor skills such as unsteady fixation, delayed initiation of saccades, and inaccurate tracking.[9] Amblyopia reduces the quality of life, as it affects school and career choices, self-esteem, social acceptance, and self-perception.[10]

Treatment

Treatment is guided by thorough history taking and physical examinations to identify any reversible underlying causes. Treatment modalities include optical refractive correction, occlusion therapy, medication, surgery, Bangerter filters, and the more advanced binocular visual stimulation and perceptual learning.

For optical refractive correction, the magnitude of anisometropia correlates with the degree of amblyopia. 20% of patients with a high refractive error develop vision loss secondary to amblyopia.[11] In patients with anisometropic amblyopia (with VA ranging from 20/40 to 20/250) treated with optical refractive correction until VA stabilized or amblyopia resolved, 77% of patients had improvement in VA by ≥2 lines and 27% of patients had resolution of anisometropic amblyopia.[12] However, those with severe amblyopia or higher degree of anisometropic amblyopia did

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not respond well to refractive correction alone.

Occlusion therapy (patching) remains the mainstay treatment in Hong Kong after refractive correction.[13] By occluding the fellow eye, neural signal from the fellow eye is reduced and thus the amblyopic eye is allowed to be fully stimulated and forced to overcome the suppression from the fellow eye and activate its visual pathway. Patching is highly effective, with stable response until at least 15 years of age. In a Pediatric Eye Disease Investigator Group (PEDIG) study of the use of an opaque adhesive patch for 2 to 6 hours per day, with dosage adjusted according to the VA response of patients, visual outcomes were similar between 2 hours and 6 hours of occlusion therapy in children aged 3 to 7 years with moderate amblyopia.[14] VA improved by ≥3 lines after 4 months of patching in 62% of patients in both 2-hour and 6-hour groups. Parents of the 6-hour group expressed more concern over social stigma that may lead to lower compliance. Patching can be used in older children and adolescents, particularly those who are treatment naive.[15] Drawbacks of patching include local irritation, allergy, cosmetic impact, reverse amblyopia, and low compliance. Recurrence amblyopia is common, especially in those with severe amblyopia. Thus, gradual tapering of patching is preferable to an abrupt cessation of therapy.[16]

Medication treatment includes the use of atropine, levodopa, and citicoline. In a PEDIG study of the use of atropine 1% solution on the fellow eye on weekends or once daily, both groups achieved comparable visual improvement.[17] In another PEDIG study of the use of atropine on weekends, improvement in VA was greater in children aged 3 to 7 years than in children aged 7 to 12 years (4.5-5.1 lines vs 1.5 lines).[18] Patching can achieve more rapid initial improvement, whereas atropine can achieve comparable outcome after 6 months,[19] with higher compliance and lower social stigma.[20] Adverse effects of atropine include photosensitivity, conjunctival irritation, dry mouth and skin, tachycardia, and fever. Atropine is not effective for myopia-induced amblyopia.

Levodopa-carbidopa combination therapy has been used to raise retinal dopamine level and exert neuromodulatory effect on visual development.[21] In children with severe amblyopia, patching plus high-dose levodopa resulted in better visual outcomes than patching alone.[22] However, in children aged 7 to 12 years who were refractory to patching, levodopa did not result in greater improvement in VA than placebo plus patching.[23] Levodopa may cause headache and nausea in some patients, but no serious adverse effect such as dyskinesia has been reported.

Citicoline increases the level of neurotransmitters (catecholamines, serotonin, and dopamine) and thus stimulates metabolism of the nigrostriatal dopaminergic system. Its cholinergic effect and neuroprotective effect protect integrity of neuronal cell membrane.[24] Citicoline alone is not more effective than patching, but citicoline plus patching can stabilize the improvement in VA obtained during treatment, whereas patching alone can result in a decrease in VA at 90 days after treatment.[25,26]

Bangerter filters are transparent filters placed in front of spectacles and are for those with mild amblyopia who are not responsive to spectacles alone. The occlusion effect of filters in different densities can change the VA of the fellow eye.[27] Bangerter filters achieve similar results to patching of 2 hours per day in patients with moderate amblyopia.[28]

Surgical treatment should be performed before amblyopia management in patients with structural disturbance along the visual axes (congenital cataract, vitreous hemorrhage, corneal opacities, and ptosis).

Perceptual learning is defined as any relatively permanent and consistent change in perception of stimulus array following practice or experience with this array by a variety of tasks such as vernier acuity, Gabor detection, and positional discrimination.[29] Perceptual learning aims to improve neural processing in visual cortex during the critical period. Perceptual learning can improve VA in the trained eye, but many patients remain to have a broader spatial frequency than normal.[30] However, perceptual learning is not a popular approach for treating amblyopia. The small sample size may overgeneralize the benefits of perceptual learning. More large-scale studies are warranted to determine the effectiveness of perceptual learning on treating amblyopia.

Binocular therapy

Amblyopia was considered to be a monocular visual deficit causing secondary binocular visual deficiency, and thus treatments are mainly monocular without binocular combination of stimuli.[31] However, there is growing evidence to support a binocular deficit secondary to active suppression of the amblyopic eye.[32] The cause of the binocular deficit in suprathreshold tasks in strabismic amblyopia is interocular suppression,[33] and the strength of which is associated with the degree of amblyopia.[34] By varying signal length of the attenuation of amblyopic eye, the binocular contrast summation in strabismic amblyopes can be normalized.[35] Thus, various binocular therapies are developed to improve both VA and binocular function.

Binocular contrast therapy aims to strengthen binocular visual function and reduce interocular suppression by providing high-contrast stimuli to amblyopic eye and low-contrast stimuli to the fellow eye.[36,37] The therapy involves playing videogames that tessellate high-contrast falling blocks to low-contrast stationary base to form a continuous row through goggles that split images between the eyes.[38-40] Other binocular games include the Ping-Pong game, Labyrinth game, and the Balloon game. Both eyes must be used to play the games as each eye does not see the full picture.

Interactive binocular treatment involves presenting dichoptic video or video games without contrast balancing to both eyes but with foreground elements to the amblyopic

Table. Binocular therapy for children with amblyopia

Study	No. of patients	Age, y	Binocular therapy	Outcome
Cleary et al,[42] 2009	12 (refractory to prior occlusion)	6.1-11.4	Interactive binocular treatment (I-BiT): 20 minutes watching video clip and 5 minutes playing interactive driving game for 11 weekly sessions	Sustained improvement in high-contrast visual acuity (VA) in 7 (58%) children and in low-contrast VA in 8 (67%) children
Knox et al,[39] 2012	14	8.5±2.6	Dichoptic perceptual learning by simple computer game, 5 sessions, each 1 hour over a week	VA improvement of the amblyopic eye from 0.51±0.27 to 0.42±0.28 logMAR. Improvement in stereofunction in 3 patients
Herbison et al,[43] 2013	10	5.4	I-BiT: 20 minutes watching video and 10 minutes playing interactive game once a week for 6 weeks	VA improvement in 9 patients
Li et al,[32] 2014	75	4-12	Sham games (n=25) or binocular games (n=50) with red-green anaglyphic glasses for 4 hours/week for 4 weeks	VA improvement from 0.47±0.03 to 0.39±0.03 logMAR in binocular group. No improvement in stereoacuity in both groups
Mansouri et al,[44] 2014	22 (refractory to patching and/or surgery)	5-73	Binocular training with dichoptic random dot kinematograms for 14.5 sessions in 4-6 weeks	VA improvement by 0.34 logMAR
Birch et al,[45] 2015	50	3-6.9	Sham iPad games (n=5) or binocular iPad games (n=45) for 4 hours/week for 4 weeks; 4 and 30 of children in the respective group received additional patching at a different time of day	VA improvement from 0.43±0.03 to 0.34±0.03 logMAR after dichoptic therapy
Webber et al,[46] 2016	20	8.5±1.3	Binocular treatment by dichoptic iPad games for 5 weeks	Improvement in fine motor skills especially in less severe amblyopia
Herbison et al,[47] 2016	75	4-8	I-BiT games using shutter glass technology (n=25), I-BiT DVD footage shown to the amblyopic eye and common background to both, modified shooter game with targets presented to amblyopic eye and background to both (n=25), and non–I-BiT games with both background and foreground presented to both eyes (n=25)	VA improvement by 0.07 logMAR at 6 weeks in three arms
Holmes et al,[52] 2016	385	5-13	16 weeks of a binocular iPad game for 1 hour a day or patching of the fellow eye for 2 hours a day	VA improvement in both groups; primary non-inferiority analysis yielded indeterminate results
Kelly et al,[48] 2016	28	4.6-9.5	Binocular game (n=14) or patching (n=14)	Greater stereoacuity and VA improvement in binocular game than patching (0.15 vs 0.07 logMAR)
Bossi et al,[49] 2017	22	3-11	Balanced binocular viewing therapy: viewing dichoptic movies and gameplay for maximum of 8 and 24 weeks, respectively	VA improvement by 0.27 logMAR after binocular therapy
Singh et al,[50] 2017	68	6-14	Video game for 1 hour/day plus occlusion therapy for 6 hours/day or occlusion alone for 6 hours/day	Greater VA improvement in video game plus occlusion therapy than occlusion alone (0.61±0.12 to 0.40±0.15 vs 0.65±0.09 to 0.48±0.10 logMAR)
Gao et al,[53] 2018	115 (89 had prior occlusion)	7-12, 13-17, ≥18	Case: playing falling-blocks video games with dichotic contrast at home on an iPod Touch for 1 hour/day for 6 weeks. Control: playing placebo video game with identical images to both eyes.	Improvement in visual outcomes was not significantly more in binocular therapy than placebo video game
Manh et al,[54] 2018	100	13-16	Binocular iPad game 1 hour/day or patching of the fellow eye for 2 hour/day for 16 weeks	Binocular therapy was not superior to patching in VA improvement of the amblyopia eye
Rajavi et al,[55] 2019	40	3-10	I-BiT games or patching with placebo video games for 1 month	Both groups achieved similar best-corrected VA improvement
Roy et al,[51] 2019	55	5-15	Dichoptic video game for 2 hours/day or occlusion therapy of 6 hours/day	Improvement in best-corrected VA from 0.70 to 0.49 logMAR in binocular group and from 0.73 to 0.52 logMAR in occlusion group. Improvement in near vision and contrast sensitivity in both groups. Significant improvement in near stereoacuity in binocular group only
Yao et al,[56] 2020	103	3-13	Binocular video game 40 minutes/day, patching 2-6 hours/day, or a combination of patching while playing video games on glasses for 3 months	Improvement in VA of the amblyopia eye and binocularity was less effective in binocular therapy than patching. No superiority in stereoacuity improvement in binocular therapy
Gao et al,[57] 2021	105	7-17	Active treatment or placebo videogame 1-2 hours/day for 6 weeks on iPod Touch device	Younger age groups showed lower adherence to binocular treatment

eye only. The key element is only seen by the amblyopic eye, but both eyes must be used to watch/play the video game. For instance, the non-amblyopic eye receives peripheral stimuli and the amblyopic eye receives moving stimuli. Images can even be moved towards different directions to correct the angle of strabismus.[41]

The **Table** summarizes outcomes of various binocular therapies for children with amblyopia.[32,39,42-57] Most binocular therapies involve home-based dichoptic video games or movie watching for several hours a day over few months. Binocular therapy can replace occlusion therapy or can be an adjunct when the patient is refractory to conventional amblyopic treatment. In some studies, binocular therapy is effective in improving VA in amblyopic children and is superior to the conventional occlusion therapy.[32,39,42-51] In other studies, binocular therapy is not superior to patching.[52-56] Acceptability to binocular therapy is generally high among children with amblyopia,[47] compared with patching that has cosmetic concern on self-esteem. No major complication or risk is caused by binocular therapy. Nonetheless, compliance varies in different localities with different cultural and social backgrounds. Low compliance to binocular video game playing or watching may affect the outcome. Some studies are limited by the short treatment duration, short follow-up period, and small sample size; more comprehensive randomized controlled trials are warranted.

Optimal treatment duration and dosage as well as screening and surveillance

Amblyopia treatment is more effective in the first 6 months of treatment. For refractive correction, improvement is maximal in the first 400 hours of patching.[58] The Monitored Occlusion Treatment of Amblyopia Study attempted to determine the dose-response relationship of patching, but there was difficulty in measuring the actual dose received and in ensuring compliance to the prescribed therapy.[59] Statistical modeling has been used to determine the personalized dosage of treatment for maximal visual improvement.[60] Screening amblyopia at young age enables timely management within the critical period. However, screening too early may result in high false-positive results, whereas delayed screening may result in poor visual outcome. Surveillance is required to detect recurrence of amblyopia within 52 weeks of treatment cessation. About 25% of patients have recurrence within the first year of treatment cessation, especially when treatment is stopped abruptly rather than gradually.[16] Improvement in VA can deteriorate in long run. Thus, follow-up is important, especially in those with poor initial VA. There is no consensus on the optimal treatment duration, timing of initiation, dosage, screening, and surveillance of amblyopia. Further studies are warranted.

Conclusion

Amblyopia is a reversible neurodevelopmental disorder but can cause vision loss if untreated, especially within critical period of visual neuroplasticity. Apart from conventional treatment modalities (refractive correction, occlusion therapy, medication, surgery, and perceptual learning), the more advanced binocular therapy is increasingly popular. Binocular therapy can improve both VA and stereoacuity, but whether it is superior to occlusion therapy remains controversial. Future studies to determine the optimal treatment duration, timing of initiation, dosage, and when to step up treatment when other treatments become refractory are warranted.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, JCSY was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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