Current Concepts of Amblyopia: A Neuro-Ophthalmology Perspective


ABSTRACT

Amblyopia can be defined as a developmental disorder in which there is a deficit in visual acuity that cannot be improved by refractive correction and that has no detectable organic cause. It has been recognized as a clinical entity for over 300 years. Amblyopia can no longer be considered a single clinical entity, many subtypes having been recognized.1–9 Early detection and treatment may result in positive outcomes in some subtypes, but others, if not detected early, are not responsive to treatment.

INTRODUCTION

The loss of vision in amblyopia is associated with abnormal visual experience during infancy or early childhood. This deficit in visual acuity cannot be improved by refractive correction and has no detectable organic cause. It is a known developmental anomaly because the same visual conditions causing amblyopia in childhood have no lasting effect on vision when they occur in adults.10

PREVALENCE OF AMBLYOPIA

Amblyopia affects 2–5% of the population, although a prevalence of up to 6% has been reported.6, 10–12 Gender and ethnicity do not seem to be risk factors.11, 12 Untreated amblyopia is also the leading cause of monocular vision loss in the 20–70+ years age group.6

In their large photoscreening study, Donahue and Johnson reported that as many as 67% of suspected cases of amblyopia re-
quired treatment. Flynn et al. reported that 50% of all suspected cases of amblyopia are caused by anisometropia. Attebo et al. reported that 50% of their cases had anisometropia and 25–30% were mixed. Others describe one-third each with strabismic amblyopia, anisometropic amblyopia, and mixed types and only 1% with deprivation amblyopia.

Refractive errors influence the development of amblyopia, with anisometropia being one of the leading causes. Without strabismus or ptosis to draw attention to the problem, these patients are most likely to escape detection.

Kiorpes and McKee found that 40–46% of children with anisometropia and/or strabismus will develop amblyopia. Metz states that amblyopia is caused by two factors: the loss of binocular function in central visual field and blurred imagery in the weak eye. Strabismic-anisometropic amblyopia patients or mixed types are the most challenging to treat as they are affected by both the blurred image and the deviation.

CLASSIFICATION OF AMBLYOPIA

Amblyopia has been recognized as a clinical entity for over 300 years. Considered a form of disuse, the term ex anopsia was used in association with amblyopia. In 1967, von Noorden classified amblyopia as strabismic, anisometropic, organic, or deprivation types. Others recognized the influence of uncorrected refractive errors, especially astigmatic or meridional factors in amblyopia, as well as its known association with strabismus, anisometropia, or both. France expanded the classification of amblyopia into the following types: deprivation, strabismic, anisometropic, ametropic, congenital, and occlusion. Flynn described strabismic, anisometropic, refractive, or deprivation types of amblyopia based on the mechanism causing the loss.

VISUAL DYSFUNCTION IN AMBLYOPIA

Although the word amblyopia is derived from the Greek meaning “blunted sight”, only certain visual functions are affected. Central vision as measured by Snellen or grating acuity is decreased but features such as color vision and critical flicker fusion frequency remain normal in amblyopia patients.

Other functions that may be affected in amblyopia include changes in Vernier acuity, contrast sensitivity, positional uncertainty, motion deficits, and an increase in the crowding phenomenon or contour interaction. There also may be changes in binocular summation and suppression, loss of binocular function, and stereopsis.

Amblyopia is a developmental anomaly of spatial vision. A common finding in most amblyopia patients is some degree of spatial distortion. Hess et al. describe the spatial fidelity of the perceived image within which are spatial distortions and other discontinuities. It is possible to have normal contrast sensitivity yet still experience spatial distortions. These may occur at all orientations and over a wide range of retinal illuminations.

Barrett et al. show some illustrations of visual distortions seen by amblyopic subjects.

RESEARCH INTO SUBTYPES

Extensive research has been conducted into the comparative behavior of the subtypes of amblyopia. Hess and Howell studied threshold contrast sensitivity function in strabismic amblyopia and found two different subtypes that depended upon the level of spatial frequency.

Subtypes of amblyopia have been identified by clinical and laboratory research. Underlying neural mechanisms were studied, a variety of etiologies were recognized and the classification expanded.
Kiorpes and McKee report four proposed neural bases for amblyopia. The first two, abnormal neuronal response properties and poor synchronization of neuronal responses, are supported by findings in neurophysiological experiments in animals. The last two, abnormal topographic representation of receptive fields and undersampling of visual space, are supported by psychophysiological data in humans.

Kiorpes and McKee conclude that there are primary and secondary deficits involved in amblyopia. Amblyopia is primarily a disorder of spatial vision, although most studies of the retina in amblyopes conclude that there is no change at this level. Although anatomical changes in the LGN in monkeys show deprived and shrunken eye layers, there is no apparent correlation in neural signaling.

In amblyopic monkeys, anatomical correlates of abnormal early visual experience have consistently been found in the V1 layer of the primary visual cortex where information from the two eyes is first combined.

THE ROLE OF PSYCHOPHYSICS IN AMBLYOPIA RESEARCH

The most extensively investigated proposals for the neural basis of amblyopia come from human psychophysics.

Visual acuity involves discrimination of very high contrast, stationary stimuli; however, the perception of form is determined to a great extent by the manner in which the visual system discerns contrast. There is psychophysical evidence that the human visual system contains two distinct classes of channels analogous to the sustained and transient cells found in the mammalian visual system.

Channels responding transiently to the onset and offset of stimuli are particularly sensitive to rapid motion and flicker. Channels that respond in a sustained fashion prefer slow moving or stationary stimuli.
ance and is therefore extended in both the nasal and temporal visual fields.\textsuperscript{24}

Their results suggest that the amblyopic defect is a consequence of a retinotopically organized suppression process that eliminates signals that cannot be fused from further processing and thereby prevents the corresponding pathways from maturing normally.\textsuperscript{24} This interpretation is at variance with Ikeda et al. who considered increased prevalence of blurred images on the retina of the deviated eye as a primary cause for the development of strabismic amblyopia.\textsuperscript{20}

Both central suppression and reduced quality of the retinal image contribute to the development of amblyopic deficits, the relative contributions being different in the various forms of amblyopia.\textsuperscript{24}

LARGE CLINICAL STUDIES OF AMBLYOPIA

Another method of investigating the behavior of subtypes of amblyopia is to take large cohort studies, the large sample size improving the ability to detect small differences that may have been unrecognized previously. Some clinical studies involving large numbers of subjects included those by Flynn et al. and McKee.\textsuperscript{8,9,16} Flynn et al. conducted a NEI-supported study that analyzed a retrospective study of pooled data retrieved from 23 studies from between 1965 and 1994. There were 961 anisometropic, strabismic, or mixed types in the grouped studies. They noted that successful results were related to the age that therapy was initiated, the subtype of amblyopia, and the depth of the visual loss.\textsuperscript{16}

Results of the pilot study showed by cluster analysis that there may be a rationale for diagnosing amblyopia on the basis of functional visual loss instead of the traditional classification scheme based on its associated condition (e.g., strabismus, anisometropia, deprivation, etc.).\textsuperscript{16}

In an excellent comprehensive study in 2003, McKee et al. studied the psychophysical functions in a large cohort of 495 patients between the ages of 8–40 years.\textsuperscript{9} They tested multiple psychophysical functions and detected significant differences in subtypes.

The psychophysical testing included a complete clinical eye exam, Snellen visual acuity (Bailey-Lovie logMar chart), gratifying acuity, Vernier acuity, two tests of binocularly including stereoacuity (circles) and an experimental test of binocularly-integrated motion, and two tests of contrast sensitivity, letter contrast (Pelli-Robson chart), and edge contrast detection sensitivity.

McKee's large sample size revealed small differences not previously recognized. These included changes in acuity and contrast in 80\% of all amblyopic patients; however, not to the same extent in each subtype. In deprivation and anisometropic amblyopia, similar changes occurred. In strabismic amblyopia different changes were noted (between acuity and contrast).

Furthermore, in deprivation and anisometropic amblyopia, a decrease was detected in visual acuity and high spatial frequency contrast sensitivity (blurred vision) whereas in strabismic amblyopia, with binocular vision disrupted, visual acuity decreased, but a paradoxical increase was noted in contrast sensitivity. The changes in strabismic amblyopia showed that nonbinocular individuals had better levels of contrast sensitivity than binocular ones. Also that contrast sensitivity appeared to have improved in both eyes, both the fixating and nonfixating eye. They concluded that amblyopia is caused primarily by two factors: loss of binocular function in the central visual field and blurred imagery in the weak eye.\textsuperscript{9}

Donahue, in his discussion of this study in a paper given by McKee at the American Academy of Ophthalmology meeting in 2005, gave the following opinion of the results. He stated that this study was per-
haps the most important investigation of the psychophysical functions of amblyopic individuals to date and certainly the largest and most comprehensive. Donahue considered that when binocularity was disrupted, there was a loss of binocularly driven cortical neurons. He hypothesized that more neurons or synaptic connections may become available for monocular tasks. Donahue also suggested (in a personal communication) that there is a synaptic reorganization in the primary visual cortex after the binocular units disappear.

NORMAL VISUAL PATHWAYS

Light entering each eye stimulates retinal receptors. Impulses pass through the optic nerve to the chiasm. Nerve fibers from the nasally stimulated receptors cross over to the opposite optic tract, while the temporal fibers remain uncrossed. These afferent fibers synapse in the lateral geniculate nuclei and travel to the primary visual cortex.

The lateral geniculate nucleus has several layers; four parvocellular, two magno-cellular, and six koniocellular. The contralateral fibers are received in layers 1, 4, and 6 while ipsilateral fibers are received in layers 2, 3, and 5 (Figure).25

In a normal individual with equal vision, the anatomical stripes seen in the LGN have equal spacing. After a period of deprivation, the dark stripes are greatly narrowed. This unequal spacing is repeated in the striate cortex in the ocular dominance columns after deprivation.25 Again, the normal layers showed stripes with equal spacing while the deprived layers show dark stripes and are greatly narrowed. The arrangement of visual pathway fibers described above results in images from the left visual field being represented in the right primary visual cortex and vice versa. Binocularly driven cells are stimulated by information contributed by both eyes.

NEUROPHYSIOLOGICAL BASIS OF AMBLYOPIA

Hubel and Wiesel, Nobel Prize winners for their pioneering work in the field of visual development, first experimented with deprivation of light into one eye in kittens.26, 27 They documented a decrease in visual acuity with corresponding pathological changes in the visual system. Hubel and Wiesel were able to report abnormalities in the visual pathways and identify the site of amblyopia in the striate cortex. Their description of ocular dominance columns provided the basis for our current understanding of binocular function.26–28

Hubel and Wiesel also recognized critical periods for development of vision and binocular vision in kittens and monkeys. They were able to extrapolate these critical periods to humans, providing clinical guidelines for the early treatment of amblyopia, strabismus, and infantile cataract.26–28 The story of Hubel and Wiesel’s 25-year collaboration has been published recently and comprises all their relevant publications on the brain and visual development, including the Nobel Prize winning lectures.28

Further contributions were made to the field by von Noorden et al. in studies of experimental amblyopia in monkeys with stimulus deprivation and strabismic amblyopia. Results from these studies helped recognize the critical periods in humans.29–31

The critical period for the development of amblyopia correlates with the time period for normal visual development.10 Daw describes three periods in the development of visual acuity and ocular dominance. These are the period of development of visual acuity (birth to 3–5 years of age), the period during which deprivation is effective in causing amblyopia (a few months to 7 or 8 years of age) and the period during which recovery from amblyopia can be obtained (time of deprivation until teenaged years or beyond.).21
Daw states that it is not sufficient to refer to a critical period without defining other parameters. A critical period corresponds to the period during which deprivation is effective, rather than the initial period of development or the period during which recovery can be obtained. Critical periods must be defined for a particular visual property in a particular part of the visual system in a particular species, after a specified form of visual deprivation in an animal with a specified visual history.

Critical periods for the development of deprivation amblyopia occur at slightly different times in the pathways, and in geniculate and cortical structures. Another general principle is that a property processed by higher levels of the visual system has a critical period that lasts longer than a property processed at a lower level. There-
fore, there are different critical periods for the development of acuity, binocularity, and stereopsis. This has important implications for treatment.21

DISCUSSION

From a neurophysiological standpoint, where in the pathways does the defect causing amblyopia occur? Deprivation experiments in animals have shown that there are anatomic changes in the cells of the visual pathways of the retina, LGN, and visual cortex.23

In 1975, Ikeda and Wright described a possible neurophysiological basis for amblyopia, referring to it as a loss of visual acuity at the fovea.20 They agreed that the fovea could not be suppressed as a whole because other visual functions such as color vision and critical flicker-fusion frequency remained normal in amblyopic patients. They studied receptive field organization of the transient (Y) and sustained (X) retinal ganglion cells. Sustained cells were concentrated largely in the area centralis and were capable of fine spatial discrimination, a basis for visual acuity. Sustained and transient cells differed in their response to a defocused image. Transient cells continue to respond, but spatially defused, low contrast stimuli did not constitute an adequate stimulus for the central “sustained” retinal ganglion cells. The authors acknowledged that sustained and transient pathways were known to exist at a higher stage in the visual system.20 Subsequent authors have challenged whether there is retinal dysfunction in amblyopia.23, 32

Many investigators found normal physiological recordings in the LGN, yet histologically the cells in layers 1, 4, and 6 in the eye contralateral to the eye closure and layers 2, 3, and 5 on the ipsilateral side were paler and thinner. An explanation for this paradox of geniculate shrinkage in the presence of normal cell recordings was given as the cortical layers having decreased axons and terminals to support.6

CORTICAL DEFICIT IN AMBLYOPIA

In subjects with amblyopia, anomalous cortical pathologic changes occur as a direct consequence of competition between afferents from the left and right eye. There is a loss of cortical binocularity and a shift in cortical eye dominance from the affected eye. Barrett et al. have shown that there is a susceptibility to develop form deprivation in the ocular dominance columns beginning at birth. They noted that strabismus-induced cortical changes occur later, after stereopsis develops.22

Barnes and Hess et al. studied the cortical deficit in humans with amblyopia.23 They used blood oxygenation level-dependent (BOLD) functional MRI (fMRI) to determine whether the function of any visual area was spared in strabismic amblyopia and to assess whether the nature of any reduced cortical function could be used as a basis for explaining either of the known psychophysical deficits. The results are shown in color in their publication and are worth reviewing with axial, sagittal, and coronal views; the calcarine sulcus showing cortical representation of the fovea; and activation across the visual cortex.33 They found decreased activation in the hemisphere corresponding to the amblyopic eye. This is similar to the findings of Demer using positron emission tomography.33, 34

Blakemore and Vital-Durand show that undersampling of the retinal image and neural blur may contribute to deprivation amblyopia. Anisometropic amblyopia probably has a similar origin and they suggest that those two varieties of amblyopia may collectively be entitled “blur” amblyopia.7

Blakemore and Vital-Durand concluded that neither undersampling nor neural blur are the major cause of strabismic am-
blyopia and that some form of positional uncertainty in the neural representation of the image is likely to be the principal defect. Strabismic amblyopia patients have substantial loss of positional acuity, the ability to judge with precision the relative location of two features (e.g., Vernier acuity). Undersampling is also described in the context of topographical “jitter.”

In further work, Sengpiel and Blake more refine these ideas, stating that the reduction in visual acuity that characterizes amblyopia is due to one or a combination of three different causes. They describe undersampling of the retinal image due to a decrease in the number of sampling channels, converging of signals onto central neurons to decrease neural acuity and scrambling of central representation causing positional uncertainty. The causes may differ depending upon the type of amblyopia so that a neural acuity deficit is more likely in deprivational and anisometropic amblyopia than in strabismic amblyopia.

Hess, Field, and Watt believe that the mechanism causing strabismic amblyopia, which has large absolute distortions with spatial inaccuracies, arises from a combination of elevated internal blur and neural scrambling.

Campbell et al. give a delightful analogy for this phenomenon. If a short-duration photograph is taken of a typical optotype chart placed on the pebbles of a clear shallow stream, the result would show multiple and complex phase distortions due to the rippling on the surface of the water. The contrast between the black and white segments would remain constant so the amplitude information would be maintained, but the positional or phase information would be corrupted.

Campbell et al. realized that understanding the neural basis of amblyopia had an important bearing on developmental theories of sensory function and its application to treatment. The CAM stimulator was designed as a physiologically based treatment for amblyopia using rotating gratings in an attempt to reverse the effects of deprivation. The method enjoyed brief recognition in the treatment of amblyopia but has since fallen into disuse. It did pave the way for the beginning in popularity of minimal occlusion techniques and the return of atropine penalization.

In his 1998 Scobee Memorial Lecture, Mazow outlined the future of amblyopia therapy and discussed the importance of vision screening and its legislation. He reviewed current occlusion practices and the influence of newer outcome studies on the treatment of amblyopia. He talked of concepts including reversing the neuroanatomical changes in the visual pathways and the neuropharmacologic management of amblyopia. He questioned whether the introduction of genetic engineering with future discoveries of loci for strabismus would play a role in the future management of amblyopia.

Flynn, in his 1991 Costenbader Lecture, emphasized the importance of studying the synapses of the visual pathways. He stated that cortical plasticity, the hallmark of the critical period, is mediated by neurochemicals. Understanding the biochemical activity at molecular and synaptic levels would lead to an understanding of amblyopia. The central nervous system is able to adapt to certain insults and reprogram itself to maintain function and so experimental research using biochemical intervention could prolong plasticity.

**NEUROPHARMACOLOGIC TREATMENT OF AMBLYOPIA**

A variety of neurochemical agents have been employed in the treatment of amblyopia. Early experiments used oxygen, strychnine, and alcohol. Beta-blockers have been used to enhance neuroplasticity by activating the norepinephrine system.
Neurotransmitters have been administered to prevent or reverse the anatomical and physiological changes that amblyopia causes in the visual system. Some drugs that have been shown to be influential in treating amblyopia affect dopamine metabolism and include citicoline, levodopa, and carbidopa.6, 37–44 Levodopa has also been used as an adjunct to occlusion in amblyopic children.42

Although levodopa has been shown to be effective, the exact site of its action in treating amblyopia or the stability of improvement has not been determined. Transient effects using levodopa and carbidopa have been reported and there may be beneficial effects in adults with amblyopia.43 Algaze et al. investigated the effects of L-dopa in amblyopic humans using BOLD fMRI. They found visual acuity improved significantly ($P=0.026$) in the amblyopic eye after the administration of levodopa while remaining unchanged in the dominant eye and in the eyes of control subjects. Stereoaucuity and contrast sensitivity did not change significantly. The fMRI activation maps comparing the dominant and amblyopic eyes are well represented in color figures in their article.44

**IMPLICATIONS FOR THERAPY**

Most published studies support early treatment for amblyopia and strabismus. In the various PEDIG studies, outcome comparisons were made between various patching regimens such as full-time versus part-time patching, and atropine versus occlusion.45, 46 However, McKee et al. provided infrastructure suggesting that the response of different subtypes to therapy may depend more on the causative mechanism.9

Metz states that amblyopia is caused by two factors: the loss of binocular function in central visual field and blurred imagery in the weak eye.17 Strabismic-anisometropic amblyopia patients or mixed types are the most challenging to treat as they are affected by both the blurred image and the deviation.17 He concludes that a successful outcome requires early correction of refractive errors to eliminate blurred vision, and early realignment of strabismus to eliminate the disruption to binocularity.17

**CONCLUSION**

Amblyopia cannot be considered one entity—not all amblyopias are the same. Subtypes behave differently in specific testing situations and in their response to treatment. Early detection and treatment may result in positive outcomes in some subtypes, but some, if not detected early, are not responsive to treatment.

An interesting analogy might be made between amblyopia and strabismus in the concept of treatment: In concomitant strabismus, the extraocular muscles are not responsible for the misalignment yet those muscles frequently undergo surgical manipulation to correct the disorder. Current and previous amblyopia treatment modalities are based on restimulating the eye with decreased visual acuity by applying external occlusive and optical methods to the fellow eye.47 The treatment does not address directly the damage that has occurred in the visual pathways. Perhaps pharmacological therapy to influence the neurotransmitters involved in the visual cortex can reverse visual pathway and cortical cell damage and may represent a future approach to the treatment of amblyopia.

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