ABSTRACT

Amblyopia is a unilateral or bilateral reduction of visual acuity secondary to abnormal visual experience during early childhood. It is one of the most common causes of vision loss and monocular blindness and is commonly associated with strabismus, anisometropia, and visual deprivation (in particular congenital cataract and ptosis). It is clinically defined as a two-line difference of best-corrected visual acuity between the eyes. The purpose of this study was to understand the neural mechanisms of amblyopia and summarize the current therapeutic strategies. In particular, the authors focused on the concept of brain plasticity and its implication for new treatment strategies for children and adults with amblyopia. [J Pediatr Ophthalmol Strabismus 2014;51(2):78-86.]

INTRODUCTION

Amblyopia is a unilateral or bilateral reduction of visual acuity, without apparent cause, that can be resolved with appropriate therapy. It is the most common cause of monocular blindness, affecting approximately 3% to 5% of the population worldwide. It is clinically defined as a two-line difference of best-corrected visual acuity between the two eyes. It is caused by abnormal brain stimulation during critical periods of visual development, the so-called “plastic period.” Plasticity refers to the dynamic ability of the brain to reorganize its functional and structural connections in response to environmental changes. Experimental studies in animals, clinical experiences, and electrophysiological studies have shown that this period lasts from birth to 7 to 8 years of age. At the end of this period, plasticity is dramatically reduced and amblyopia cannot be treated or prevented. Recent studies demonstrate that a reduction of GABAergic inhibition would be able to restore plasticity in the visual system. In fact, intracortical inhibitory circuitry seems to be the key factor in defining the limits of cortical plasticity. Pharmacological treatment with antidepressants (eg, fluoxetine, a selective serotonin reuptake inhibitor) and anticonvulsants (eg, valproic acid) would reduce intracortical inhibition, restoring the plasticity of the visual system.

The most common predisposing conditions for amblyopia are strabismus, anisometropia, and form-deprivation. These subtypes of amblyopia are associated with distinctive patterns of loss of acuity and contrast sensitivity. Strabismus and amblyopia are associated with moderate acuity loss and better contrast sensitivity; anisometropic amblyopia is associated with moderate acuity loss but worse contrast sensitivity. These different types of amblyopia may be caused by deprivation of pattern vision or abnormal binocular interaction.

The mainstays of treatment are occlusion and penalization. These have a good therapeutic response that ranges from 60% to 80%, depending on patient compliance. Other therapeutic options are prism therapy and instrumental treatment.

In this review, we summarize the main causes and neural mechanisms characterizing amblyopia. We analyzed neuroanatomical, neurophysiological, and electrophysiological studies in the literature to...
better understand actual treatment regimens and evaluate new therapeutic possibilities.

CAUSES OF AMBLYOPIA

Amblyopia includes several clinical entities due to different levels of visual system impairment.

Strabismic Amblyopia

Amblyopia occurs in 35% to 50% of people affected by strabismus. It is unilateral and is caused by an active inhibition of the visual system. The deviated eye is not used to focus images, so the brain areas that do not receive any signal from this eye undergo failure of normal visual development. Amblyopia is the result of ocular deviation, not the cause. Among the different types of strabismus, exotropia is the one most frequently associated with amblyopia. Short duration and intermittent ocular deviations do not cause the disease. There is no relationship between the degree of deviation and the severity of amblyopia.

Anisometric Amblyopia

A difference in refractive error between the two eyes (anisometropia) is a common cause of amblyopia, being present as the only identifiable amblyogenic factor in 37% of cases. It causes the inability of the cortex to fuse different sized retinal images (it is commonly considered impossible to fuse images with dimensions that exceed 5% of the difference between the two eyes or with a refractive difference greater than 3 diopters). That inability involves the suppression of the image that comes from the more ametropic eye. It is more common in hyperopic than myopic deficit.

Deprivational Amblyopia

Deprivational amblyopia includes all of the conditions characterized by a reduction of retinal stimulation caused by organic changes. The most common causes are represented by nystagmus, ptosis, ocular media opacities, and congenital cataracts. The visual stimulus can be reduced unilaterally or bilaterally. No significant changes were found in the retina. There was evidence of changes in cell morphology in the lateral geniculate nucleus, but they were not sufficient to explain the behavioral changes in humans with amblyopia. Significant anatomical and functional abnormalities occurred in V1. The pioneering work of Wiesel and Hubel16,17 and many subsequent works18-23 demonstrated that abnormal visual experience (reduction of spatial resolution and binocular stereoscopic vision and increased binocular suppression) results in alterations of functional properties and anatomic architecture in V1.

Recent studies also suggest that extrastriate areas are involved. Li et al.24 reported a reduction in the activation of extrastriate areas in children with anisometric amblyopia when using functional magnetic resonance imaging. This would result in deficits of spatial information such as global form perception,25,26 global contour processing,27 crowding,28 visual acuity,29 and contrast sensitivity. Deficits of spatiotemporal information were also observed, including global motion integration,30 second-order motion detection,31 complex motion detection,32 and motion-defined form.33 Deficits in higher cognitive functions,34 in addition to sensory deficits35 and deficit of motor functions36 (including the initiation and execution of saccadic eye movements37 and planning and execution of reaching and coordination movements38), have been reported. Many studies with positron emission tomography,39,40 functional magnetic resonance imaging,41-45 and magnetoencephalography44 were performed to understand these mechanisms. The differences among these studies may result from different techniques and stimuli used and from different characteristics (eg, amblyopia subtypes) of the patients included.

It is now generally agreed that visual alterations occur in both striate and extrastriate areas. Recent studies also suggest later specialized cortical area abnormalities, such as a progressive reduction of activity in the fusiform gyrus,45 parahippocampal area, visual cortical areas V4+/V8, and lateral occipital complex46 in the middle temporal complex and the anterior intraparietal sulcus.47 Moreover, modern neuroimaging techniques allow better understanding of brain activity in vivo, both in healthy people and during several pathologies, and in particular the fundamental concept of brain plasticity. The term plasticity refers to the dynamic ability of the brain to reorganize its connec-
sions functionally and structurally in response to environmental changes. This period lasts from birth to 7 to 8 years of age; plasticity dramatically declines later. Recently, several studies evaluated the possibility of functional recovery of the visual pathways by sensory stimulation. Li et al. demonstrated that video game play, both action and non-action games, can result in a substantial improvement of amblyopic visual acuity, positional acuity, spatial attention, and stereoaucity. They postulated that the intense sensory-motor interactions while playing video games might stimulate brain functions, enabling the visual system to learn on the fly and to recalibrate and adjust itself, providing the basis for functional plasticity.

**TREATMENTS**

The traditional treatment of amblyopia is characterized by occlusion and penalization of the better-seeing eye, and forcing use of the amblyopic eye. The success of this treatment depends on many factors, such as the patient’s age and compliance, type of amblyopia, and degree of visual acuity reduction. Despite the “dogma” that amblyopia is an untreatable pathology in adults, recent studies challenged that, providing exciting evidence that several strategies can boost brain plasticity in adulthood and may allow the reinstatement of visual functions in amblyopic patients.

**Surgical Correction of Strabismus, Cataracts, and Ptosis**

All amblyopic factors should be removed. It is important to remove all causes that occlude vision so the patient can get a clear image, well focused on the retina. For example, the visual prognosis is better if the congenital cataract is removed in the first 2 months of life. If not treated promptly, amblyopia may persist even after the opacity is removed. Ptosis or some other problem that physically occludes a child’s vision (eg, hemangiomas) should be treated early. It has been conservatively estimated that 17% of patients with amblyopia will undergo alignment surgery, 1.5% require cataract extraction, and 1.5% require ptosis surgery.

Strabismus surgery could be considered before or after the treatment of amblyopia. In most cases it is considered after amblyopia has been treated. Lam et al. suggested that performing corrective surgery in children with esotropia before full resolution of amblyopia was safe and efficient if the amblyopia therapy was continued after surgery.

**Refractive Correction**

The second step is represented by refractive correction. Correction of any underlying refractive error has long been established as critical to treat amblyopia. Refractive deficits need to be identified fully and in a timely manner. In some cases, the correction of refractive errors alone might result in significant improvement of amblyopic visual acuity. This leads to the conclusion that refractive adaptation prior to occlusion or penalization therapy can have many important benefits.

**Occlusion and Penalization**

Occlusion is the oldest, simplest, and one of the most effective methods to treat amblyopia. It has a dual purpose: to improve the visual acuity of the amblyopic eye and remove the inhibitory stimuli of the fixing eye on the contralateral eye. These characteristics make it the treatment of choice for amblyopia. Patching can be total or partial. Younger children usually need shorter periods of occlusion during the day. However, the duration of the occlusion must be proportionate to the severity of amblyopia. Each case must be assessed individually, although there are schemes standardized on the duration and length of treatment. The most recommendable occlusion is always to cover the fixing eye. Patching on lenses has the disadvantage of allowing vision from the side of the eyeglasses and the possibility for the child to take it off. Pharmacological or optical penalization is another therapeutic possibility for amblyopia. Pharmacological penalization is obtained by the use of cycloplegic drugs such as atropine. Optical penalization requires wrong lenses deliberately worn on the good eye to encourage the use of the amblyopic one and has a good therapeutic efficacy in mild to moderate amblyopia.

**Perceptual Learning**

Modern research has shown that the brain is plastic and dynamic and therefore capable of structural changes following exposure to new learning experiences. Each experience forces the brain to reorganize itself by creating new functional connection. This phenomenon is called perceptual learning. Some software and visual training exercises have been developed to stimulate the visual system and improve the neuronal connections responsible for this process.

The Cambridge Stimulator treatment, described in the 1970s, might be considered the first...
application of perceptual learning theory. It consists of a patient’s passive stimulation by slowly rotating stripes during monocular viewing with the amblyopic eye. However, the effectiveness of this treatment has been challenged by severe negative studies. Several new studies have shown visual improvement resulting from the use of perceptual learning. Hussain et al. concluded that perceptual learning can reduce the deleterious effects of crowding in patients with amblyopia. Polat et al. and Chen et al. found that patients who underwent perceptual learning showed substantial improvement in visual acuity, letter-recognition tasks, and contrast sensitivity.

Transcranial Magnetic Stimulation (TMS)

TMS is a noninvasive and safe method for stimulating the human brain. It is based on a brief magnetic field generated by a plastic-coated coil of wire placed on the head. The magnetic field induces a weak electrical current that stimulates cortical areas. Repetitive TMS is a technique based on a series of pulses delivered to a cortical region to temporarily alter the neural excitability of the stimulated region. It is used for the treatment of depression, strokes, and other conditions.

Thompson et al. demonstrated a transient contrast sensitivity improvement after repetitive TMS stimulation in adult humans with amblyopia. Hess and Thompson suggested that repetitive TMS may enhance the effects of current amblyopia treatments.

Binocular Treatment

Binocular treatment is a computer-based virtual reality treatment that avoids occlusion of the nonamblyopic eye. The virtual reality system offers a stereo image of a three-dimensional virtual environment by presenting an image separately to each eye. This treatment encourages the two eyes to work together to assimilate two separate images into a coherent image. It is based on strengthening binocular fusion at the expense of suppression with the goal of restoring binocular vision. No side effects were observed during the experiments, but improvements in stereopsis and visual acuity were at significant levels.

DRUG THERAPIES

Carbidopa-levodopa

In 1993, carbidopa-levodopa was described as a possible drug to treat amblyopia. Levodopa (L-DOPA [3,4-dihydroxy-l-phenylalanine]) is an intermediate in the biosynthetic pathway of dopamine used to treat adults with Parkinson’s disease and children with dopamine-responsive dystonia. Carbidopa is a peripheral decarboxylase (DDC) inhibitor that prevents peripheral conversion of levodopa to dopamine, a neurotransmitter that does not cross the blood–brain barrier (Figure 1). L-DOPA is converted into dopamine within the peripheral nervous system, causing many adverse side effects (eg, hypotension, arrhythmias, nausea, gastrointestinal bleeding, and disturbed respiration). To bypass these effects, it is co-administered with a peripheral DOPA DDC inhibitor such as carbidopa, which prevents the peripheral synthesis of dopamine from L-DOPA, thus allowing more levodopa to cross the blood–brain barrier and requiring less concentration.

Dopamine is stored in vesicles released through synapses after a process known as exocytosis, triggered by a different kind of stimuli. Once in the synapse, dopamine binds to and activates postsynaptic dopamine receptors.

Adults with Parkinson’s disease can tolerate a dose of levodopa higher than 30 mg/kg of body weight. Chronic dosing of levodopa for dopamine-responsive dystonia treatment in children is approximately 4 to 5 mg/kg for each dose, although a dose of 20 mg/kg/day may be needed. Several studies reported significant visual function improvement in the amblyopic eye thanks to this treatment. Some of these studies used levodopa at a relatively high dose (range: 67 to 10 mg/kg/day), but for shorter periods (range: 1 day).
day to 1 week). Other studies used much lower doses of 1.5 mg/kg/day for a longer duration (7 weeks) and low doses for a short period (25 to 50 mg/day for 3 weeks). Several researchers tested levodopa at a relatively high dose (6 to 9 mg/kg/day) for a relatively short duration (3 weeks) or lower doses (1.86 and 2.36 mg/kg/day) for a longer duration (4 weeks). As stated by Yang et al., levodopa is an effective and safe option for the treatment of amblyopia and can be considered as a first-line treatment. Moreover, higher weight-adjusted doses of levodopa (6.25 to 8.3 mg/kg for 6 weeks) may represent an additional tool for occlusion to expand both the age limit for treatment (older than 12 years) and the range of severity of amblyopia that can be successfully treated.

The reason for this improvement can be explained by the constrictive effect of dopamine on the receptive field size of horizontal cells, thus increasing their spatial frequency sensitivity. Changes in the retinal receptive field increase visual acuity in both amblyopic and dominant eyes. This is further supported by the finding that the reduced retinal function is improved by levodopa in patients affected by Parkinson’s disease.

Levodopa probably acts on dopamine receptors (D1 and D2) widely expressed by the retinal pigmented epithelium, photoreceptors, amacrine, and horizontal cells. According to Witkovsky, dopamine is released by a unique set of amacrine cells and activates D1 and D2 dopamine receptors distributed throughout the retina, where it plays as a chemical messenger for light adaptation and multiple trophic capabilities. These findings were supported by Huemer et al., who indicated that dopamine has a distinct effect on retinal vessel diameters, which implies a role of dopamine in retinal blood flow hemodynamics. However, other studies show that the effect of dopamine would take place mainly at the cortical level. A recent study by Sun and Zhang detected levodopa action in the visual cortex of rats on N-methyl-D-aspartate receptor-1. Oral levodopa increased N-methyl-D-aspartate receptor-1 expression in rats and may be related to the improvement of visual function.

Moreover, the effectiveness of levodopa in the treatment of amblyopia is proven by electro-functional changes on electroretinogram (ERG) and visual evoked potential (VEP). It is well known that amblyopia is related to changes of the retina, the visual pathway, and the visual cortex. Therefore, ERG evaluation allows analysis of amblyopia retinal abnormalities, whereas VEPs help to evaluate visual pathway alterations. Patients with amblyopia or Parkinson’s disease (dopaminergic deficit) showed a decrease in the amplitude of both flash and pattern ERG. In particular, they had a reduction of ERG b-wave. The administration of levodopa in humans induces an increase of the scotopic ERG b-wave amplitude in agreement with other studies performed with other dopamine agonists or antagonists in patients with Parkinson’s disease. Therefore, it has been found that the conventional VEP pattern in amblyopia and Parkinson’s disease is also abnormal.

Because amblyopia affects the striate, extrastriate, and probably other cortical areas, the simultaneous evaluation of multiple areas is needed. For this reason, Joosse et al. made an electroencephalographic recorder with eight electrodes applied to the skull: three to the occipital area, three to the parietal area, and two to the temporal area. They measured the activity of these visual cortical areas during stimulation of each eye under monocular and binocular viewing conditions with hemi-sinusoidal light pulses stimulus and found an electrophysiological suppression of the non-dominant eye in all areas. Other evidence of the efficacy of treatment with levodopa is supported by Basmak et al., who argued that levodopa can improve visual acuity and the VEPs.

**Phenylethylamine**

Phenylethylamine is an endogenous amine produced physiologically in the brain. It is biosynthesized from the aminoacid phenylalanine by enzymatic decarboxylation as a result of the bacterial enzyme tyrosine decarboxylase (expressed by gastrointestinal flora). Phenylethylamine is usually metabolized by monoamine oxidase (MAO) into phenylacetic acid because of extensive first-pass metabolism. MAO is a family of enzymes that catalyze the oxidation of monoamines. They belong to the protein family of flavin-containing amine oxidases. In humans there are two types of MAO: MAO-A and MAO-B. The latter is necessary to inactivate monoaminergic neurotransmitters (serotonin and melatonin are mainly metabolized by MAO-A and phenylethylamine by MAO-B). Both forms break down dopamine, tyramine, adrenaline, and noradrenaline. Some studies showed how the inhibi-
tion of MAO may increase the effects of phenylethyl-
amine. It is known that the levels of dopamine
and phenylethylamine increase after the administra-
tion of selegiline (a selective inhibitor of MAO-B).

The same result could be achieved using phycoc-
cyanin, a pigment-protein complex from the light-
harvesting phycobiliprotein family, extracted from algae and in particular from Aphanizomenon Flos Aguae that contains both phycocyanin and phenylethylamine. It is characterized by the association of proteins of the phycobiliprotein family and of photosynthesis water-soluble pigments of the phycobilins family, the phycocyanobilin. Antioxidant, anti-inflammatory, and anti-cancer effects have been experimentally attributed to phycocyanin. Moreover, it is hypothesized that phycocyanins are able to inhibit MAO-B; this characteristic would make them particularly useful in combination with phenylethylamine to allow absorption and avoid monoamine oxidation. Furthermore, Rimbau et al. demonstrated the ability of phycocyanins to cross the blood–brain barrier and be active in the central nervous system after oral administration.

**Citicoline**

Citicoline is a complex organic molecule that acts as an intermediate in the biosynthesis of cell membrane phospholipids. It is also known as cytidine diphosphate choline (CDP-choline [cytidine 5'-diphosphocholine]). CDP-choline belongs to the group of biomolecules in living systems known as "nucleotides" that play important roles in cellular metabolism. CDP-choline is composed of ribose, pyrophosphate, cytosine, and choline. Animal experiments and human clinical trials provide evidence of its cholinergic and neuroprotective actions.

CDP-choline has been used for many years as a support treatment in traumatic, ischemic, and degenerative pathologies, both neurological and ophthalmological. Due to its activity on phospholipid metabolism, citicoline was hypothesized to prevent nerve cell damage by acting directly on cell membrane and maintaining its anatomical and functional integrity, essential for cell survival. Moreover, CDP-choline has the property to increase the synthesis of the main neurotransmitters (acetylcholine, dopamine, norepinephrine, and serotonin) in some areas of the brain. Choline is the physiological precursor of acetylcholine and could explain its cholinergic activity. Otherwise, the possible mechanisms that could lead to an increase of other neurotransmitters are not clear. It has been hypothesized that an increase in the synthesis of acetylcholine can cause a release of dopamine.

The most used oral dosage is 500 to 2,000 mg/day, corresponding to 7 to 28 mg/kg/day in adults. In children the recommended dosage is 80 mg/kg. The daily dose should be 800 mg for patients weighing between 10 and 20 kg and 1,200 mg for those weighing between 20 and 30 kg. Several studies suggested that oral administration of citicoline combined with patching contributes to obtaining more stable effects on the treatment of amblyopia compared to patching alone.

**Bicuculline**

Another therapeutic option is the use of bicuculline, a selective blocker of GABA. The loss of binocular responsiveness of V1 neurons would be reversible with the removal of suppression. The use of microiontophoretic bicuculline would be able to block the GABAergic inhibition and therefore reduce that suppression.

**CONCLUSIONS**

The visual cortex undergoes an important period of development during the first years of life, enabling the maturation of visual functions. This process is driven by the dynamic interplay between sensory input and brain plasticity. Amblyopia is caused by inadequate visual stimulation leading to alterations in cortical plasticity and function, with monocular or binocular deficit that will be permanent if not properly treated. Identifying the underlying mechanisms of amblyopia and the development of new treatment possibilities may reduce the incidence of amblyopia and improve the visual acuity of patients with this disease. Through neuroimaging techniques and functional studies, it was possible to acquire additional information on the concepts of brain plasticity and the factors that can control the beginning and the end of this process. These new skills can lead to an improvement of visual function in both children and adults with amblyopia by using specific treatments: levodopa, citicoline, and phenylethylamine. All of these substances would be able to promote the recovery of visual function in partially sighted patients and to make a more stable and long-lasting treatment. Further research is needed to improve the knowledge of these substances and their possible use in the treat-
ment of amblyopia. In particular, studies based on the evaluation of the effectiveness of these substances by electro-functional tests such as ERG and VEPs would be useful to improve the therapeutic achievement reached by these new treatment possibilities.

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