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Management of Abnormal Visual Developments

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Abstract

When human beings recognize the external world, more than 80% of the information come from visual function and visual system. Normal visual development and normal binocularity are the fundamental of good visual acuity and visual functions. Any abnormal visual experience would cause abnormality, such as refractive error, strabismus, amblyopia and other diseases. The patients with abnormal visual developments were reported to have abnormal, lonely, and other psycho problems. In this chapter, we will describe the normal developmental of visual function, summarize the abnormal developments and the correction or treatment.

Keywords: abnormal visual function, abnormal visual development, myopia, strabismus, amblyopia

1. Introduction

The main anatomical structure development of the visual organs was completed prenatally, then the visual system development after birth mainly includes macular differentiation, vision, and visual function development.

Unlike other perceptual systems, the visual system undergoes significant changes after birth, with the most significant changes occurring during the first year of life [1]. Newborns can perceive changes in brightness and distinguish between static and dynamic objects in the visual field. With the development of eye structure, such as the elongation of cone and rod cells, the growth of the eye axis, etc., the vision and visual function of infants will be prominently improved [2].

1.1 Visual acuity (VA)

Visual acuity (VA) develops at the rate of 0.46 octaves per month between 34 and 44 weeks of gestational age [3]. Then VA starts poor after birth and gets better over time. Both genes and the environment can significantly impact VA development [4, 5]. The newborn infant's visual system is not mature, the VA could reach 0.05 logMAR. At 2 months of age, the VA is about 0.15 logMAR. Four-month-old babies have a VA of about 0.33 logMAR. Before 3 years old, infants' vision is in an uneven exponential growth process. Studies in human VA support separate and

Vision		0~2 months	2~6 months	6 months ~2 years old	3~4 years old	5 years old	6~7 years old	8~9 years old
Pupil light response		Exist						
VA(logMAR)		0.05~0.15	0.33		0.5 The difference between the two eyes < two rows	0.6~0.7 The difference between the two eyes < two rows	0.7~1.0 The difference between the two eyes < two rows	
Dioptor(D)		+2.00~ + 3.00(neonate)	Little change between birth and 3 months	+0.50~ + 1.50 (Emmetropization in 3~9 months, 1or 2 years old)	Relatively high myopia prevalence rates in children from nonwhite ethnic groups			-0.50 ~ + 0.50
Axial length(mm)					22.00~22.50		22.50~23.00	23.00~23.60
Stereopsis			Begin to develop (3 months)	Mature rapidly (8~12 months), improve gradually(until 3 years old)				
Eye position		Usually external oblique, rarely internal oblique	Alignment, a few external oblique, but esotropia is abnormal	Alignment				
Eye movement	Fixation	Occasional	Central					
	Pursuit	Occasional	Accurate binocular smooth pursuit, asymmetrical single eye smooth pursuit	Accurate, smooth eye pursuit movement				
	Saccades	Irregular	Complete development					
	Optokinetic nystagmus(OKN)	Present at birth already but with limited slow-phase velocity	Accurate					
	Accommodation	Dynamic accommodation appear to be present by 8 weeks of age	Appropriate to visual target(4 months)					

Table 1.
The critical normal visual developmental milestones of children.

distinct critical periods for development (e.g. birth to 3–5 years of age), [6] susceptibility to disruption (e.g. 2 weeks to 7 or 8 years of age), [7] and restoration of function (e.g. 2 weeks to 9 years or later) [8, 9].

1.2 Binocular vision

Depth perception, like vision, is not fully developed at birth. After receiving the appropriate visual stimulation postnatally, the convergence, vergence movement ability, and vision get improved, then stereopsis of infants will develop rapidly.

For binocular vision (e.g. fusion and stereopsis), the critical developmental milestone is well defined; after an abrupt onset at about 3 months of age, [10, 11] there is a rapid period of stereo acuity maturation until 8–12 months of age, [12] followed by a continued gradual improvement in stereo acuity until at least 3 years of age [13]. Much less is known, however, about the critical periods for susceptibility and restoration of human binocularity. Early studies suggest that the onset of the critical period of susceptibility overlaps with the critical period of development [14, 15]. Optimal binocular vision development requires sensory fusion of concordant retinal images during the formative postnatal critical period, which can extend up to 8 years of age [16].

1.3 Other visual functions

Newborns have amazing facial recognition skills, and they can recognize their mothers' faces as early as 2 weeks after birth. The cone cells in the retina of the human eyes elongate, and color vision shows a steady increase during the first year of life. A newborn baby has a higher threshold of light sensitivity up to 50 times than an adult. As the development of photoreceptor cells in the retina, the threshold of light sensitivity decreases significantly in the first 2 months of life.

The normal developmental milestones of binocular visual function are shown in [17–21] **Table 1**.

2. Abnormal visual development

Most children are born hyperopic, with a normal distribution of refractive errors. During the first year or two after birth, the distribution narrows, with a mean in the hyperopic range of +1 ~ +2 dioptres (D). This change indicates that there is an active process shaping the distribution of refraction, known as emmetropisation [22]. Increased axial length coupled with decreased corneal and lenticular power (axial length change most significant [23]). Emmetropia is the refractive state of an eye in which parallel rays of light entering the eye are focused on the retina, creating an image that is perceived as crisp and in focus, and this process needs a normal visual system, normal visual environment, and normal eye development. The absence of any one of them could cause abnormal visual development.

2.1 Refractive error

Refractive error is an optical defect in an unaccommodating eye, parallel light rays are not brought to a sharp focus on the retina, producing a blurred retinal image, poor visual acuity, and can be corrected by optical methods or other methods. Most of the eye problems present in this population are caused by or complicated by refractive error. As for the types of refractive error, we can divide it into four parts: hyperopia, myopia, astigmatism, and anisometropia.

2.2 Hyperopia

Hyperopia (farsightedness) is a condition of the eye in which parallel rays are focused behind the retina. Most infants and children are hyperopic (average + 2.00D), because the axial length of the eye is short. But the children born with high hyperopia ($\geq + 5.00\text{D}$) sometimes can cause amblyopia [22, 24].

2.3 Myopia

Myopia (short-sightedness or near-sightedness) is a condition in which the visual images come to a focus in front of the retina, and is often regarded as a benign disorder because it can be corrected with frame glasses, contact lenses, and refractive surgery. High myopia ($\leq - 6.00\text{D}$) if not fully corrected (uncorrected or under-corrected refractive error) is a major cause of visual impairment. People with high myopia are at a substantially increased risk of potentially blinding myopic pathologies. The average myopic progression is -0.50 D per year, stabilizes during late teens and females tend to develop myopia earlier and stabilize sooner than males [25].

2.4 Astigmatism

Astigmatism is a condition in which the eyes aren't completely sphere. Astigmatism occurs when either the front surface of the eye (cornea) or the lens, inside the eye, has mismatched curves. Astigmatism ($>1.00\text{ D}$) is common in infants and toddlers. Magnitude decreases over the first 3 years of life, with adult levels ($<0.50\text{ D}$) being reached at about 3.5 years. In the age of 5 months to 3 years old, astigmatism above 2.00D would be considered abnormal, as for 3 years old to 5 years old children, above 1.50D would be considered abnormal [22].

2.5 Anisometropia

Anisometropia refers to that two eyes have different refractive power, so there is unequal focus between the two eyes. Anisometropia may onset age 0 ~ 5 years. It may decrease, increase, or be unchanged for 0 ~ 5 years. It is believed that hyperopic $>1.00\text{D}$ difference or astigmatic $>1.50\text{D}$ difference or myopic $>3.00\text{D}$ difference, would be considered as anisometropia [22]. The uncorrected or undercorrected anisometropia could cause abnormal binocularity and amblyopia.

2.6 Strabismus

Strabismus describes any binocular misalignment. Prevalence of strabismus is about 0.8% to 6.8%, uncorrected strabismus could cause server vision function loss. Strabismus in horizontal: one eye deviates inward (esotropia) or outward (exotropia), in vertical: one eye is higher (hypertropia) or lower (hypotropia) than the other. Normally the treatment of strabismic patients is various vision therapies and strabismic surgery.

2.7 Amblyopia

Amblyopia is caused by an abnormal visual input early in life. Amblyopia is a unilateral or, less often, bilateral reduction of best-corrected visual acuity (BCVA) that usually occurs in the setting of an otherwise normal eye. It is a developmental disorder of the central nervous system that results from the abnormal processing of

visual images, which leads to reduced visual acuity and abnormal binocular vision. Prevalence estimates from population-based studies in children age 6 to 71 months range from 0.7% to 1.9%, whereas school-based studies of older children typically report higher rates (range: 1.0% to 5.5%) depending on the population studied and the definition used [26].

In later chapters, we are going to discuss ametropia, strabismus, amblyopia, and their treatments.

3. Refractive error and management

3.1 Overview

When parallel rays of light from infinity are focused on the retina after passing through the refractive system of the eye with accommodation at rest, it is called emmetropia. Conversely, when parallel rays of light from infinity are not focused on the retina after passing through the refractive system of the eye with accommodation at rest, it is known as ametropia or refractive error. Ametropia may be due to some causes, such as abnormal length of the eyeball, abnormal curvature of the cornea or the lens, abnormal refractive indices of the media, and abnormal position of the lens. There are three types of ametropia: myopia, hyperopia, and astigmatism. Different types of ametropia have their characteristics [27].

3.2 Myopia

Myopia is that parallel rays of light from infinity are focused in front of the retina after passing through the refractive system of the eye with accommodation at rest. Genetic and environmental factors are closely related to the occurrence and development of myopia. It can be recognized from animal and human experiments that changes in the gene and protein may occur after the onset of myopia and they may be involved in the regulation of eye growth [28–33].

Myopia can be divided into axial myopia and refractive myopia. Axial myopia owing to the ocular axial length is abnormal long. Refractive myopia owing to the excessive refractive power of the cornea or the lens. According to refraction, myopia can be divided into mild myopia ($\geq -3.00\text{D}$), moderate myopia ($< -3.00\text{D}$ but $> -5.00\text{D}$) and high myopia ($\leq -5.00\text{D}$). Physiological myopia occurs in adolescents and refraction stabilizes gradually with age. Pathological myopia was originally described as high myopia accompanied by characteristic degenerative changes in the sclera, choroid, and retinal pigment epithelium, with compromised visual function.

3.3 Hyperopia

Hyperopia is that parallel rays of light from infinity are focused behind the retina after passing through the refractive system of the eye with accommodation at rest. Can be divided into axial hyperopia, refractive hyperopia, and index hyperopia. Axial hyperopia owing to the ocular length is abnormally short. Refractive hyperopia owing to the curvature of the refractive system is flat. Index hyperopia owing to the index change of crystalline lens which occurs most in old people. According to the refraction, hyperopia can be divided into mild hyperopia ($> 0.50\text{D}$ but $< +3.00\text{D}$), moderate hyperopia ($\geq +3.00\text{D}$, but $< +5.00\text{D}$), and high hyperopia ($\geq +5.00\text{D}$). Uncorrected high hyperopia would contribute to amblyopia at the procession of visual development.

3.4 Astigmatism

Astigmatism is that parallel rays of light from infinity would not be imaged in a focus point but focused lines. Astigmatism occurs when the curvature of the cornea or lens may vary in different meridians. The mode of delivery may affect the formation of astigmatism [34]. Astigmatism can be divided into regular astigmatism and irregular astigmatism. In regular astigmatism, the direction of greatest and least curvature is 90° apart at any point on a curved surface. According to the axial of astigmatism, it can be divided into with-the-rule astigmatism, against-the-rule astigmatism, and oblique astigmatism. If the steepest curve of astigmatism lies near $90^\circ \pm 30^\circ$ meridians, then it is called with-the-rule astigmatism. And if the steepest curve of astigmatism lies near $180^\circ \pm 30^\circ$ meridians, then it is called against-the-rule astigmatism. If the steepest curve of astigmatism lies near $45^\circ \pm 15^\circ$ or $135^\circ \pm 15^\circ$ meridians, then it is called oblique astigmatism.

According to the position of the two focus lines formed by the parallel rays from infinity about the retina, astigmatism can be divided into simple myopic astigmatism, simple hyperopic astigmatism, compound myopic astigmatism, compound hyperopic astigmatism, and mixed astigmatism.

Simple myopic astigmatism: one line is in front of the retina, the other is on the retina. Simple hyperopic astigmatism: one line is behind the retina, the other is on the retina. Compound myopic astigmatism: two lines both in front of the retina but at two different locations. Compound hyperopic astigmatism: two lines both behind the retina but at two different locations. Mixed astigmatism: one line is in front of the retina the other is behind the retina.

In irregular astigmatism, the curvature varies from one point to another in the same meridians or the orientation of principal meridians changes from one point to another. When the curvature and refractive power are markedly irregular leading to multiple focal points, producing a completely blurred image on the retina. The irregular astigmatism is caused by situations like a corneal scar, penetrating injuries of the eye, keratoconus, dislocation of the crystalline lens, pterygium, and so on.

4. Correction of refractive error

4.1 Correction for myopia

The primary principle of myopia correction is to determine the degree of myopia after accurate optometry and to apply a suitable concave lens to spread the light so that it can be focused on the retina. The goal of correction is to ensure the best visual acuity while providing comfort and longevity to the patient. The achievement of this goal is influenced by a variety of individual factors, such as age, refractive error, individual habits and requirements, past prescriptions, and the state of accommodation and convergence of the eyes.

The common methods of myopia corrections including spectacle lenses, contact lenses, and surgery.

4.2 Spectacle lenses

Spectacle lenses are the most common myopia correction method, including single vision spectacle lenses and peripheral defocus glasses. The material of spectacle lenses prefers using plastic which is more lightweight and can be tinted in a wider array of colors. The spectacle lenses are more safety and easy to achieve. For patients with high myopia, the spectacle can cause differences between image

magnification and actual objects, restricted visual fields, distortion of objects in the peripheral field of vision, and prismatic effects, resulting in poor visual quality.

4.3 Contact lenses

There are two types of contact lenses: rigid and soft, which have different corrective effects due to differences in materials and design, including, soft contact lenses, rigid gas permeable (RGP) contact lenses, and orthokeratology (Ortho-k).

Soft contact lenses are a kind of lenses made of soft, oxygen-permeable polymer materials that act on the cornea. They can correct myopia up to -12.00D. Studies found that the wearers of soft contact lenses had limited knowledge about using and care of contact lenses. More education on standard lens wear and care should be provided to wearers [35, 36].

RGP is a kind of lenses made of rigid, oxygen-permeable polymer materials that act on the cornea. They can correct myopia up to -25.00D.

Compared to soft contact lenses, RGP can offer better oxygen permeability, fewer corneal complications, better-corrected vision, and visual quality. However, they are more expensive, more difficult to fit, and less comfortable. A study found that margin reflex distance, palpebral fissure height, and levator function were significantly greater after than before lens removal [37].

Ortho-k is a custom-designed rigid contact lens, which can reshape the cornea to reduce refractive error and allow clear unaided vision during the day. Generally, orthokeratology can correct upwards of -6.00D of myopia.

It can lead to better vision-related quality of life in children, compared with those wearing single-vision spectacles [38]. Ortho-k is a well-accepted option in children to avoid having to wear spectacles in the daytime [39, 40]. Improvements in accommodative function, stereopsis, and ocular motility; and a decrease in the binocular horizontal vergence range can also be found after switching to ortho-k [41]. But after overnight orthokeratology wearing for adult myope, tear film stability and tear secretion decreased. They seem easy to suffer corneal injury after overnight orthokeratology wearing [42]. The cleaning of accessories is also very important for the safe use of orthokeratology [43, 44].

Contact lenses and spectacle lenses have the same principle of correct myopia correction. But due to the different vertex distances, there are differences in the prescription.

4.4 Surgery

Surgical treatment is divided into two categories, one is corneal refractive surgery, like laser-assisted in situ keratectomy (LASIK), laser-assisted subepithelial keratomileusis (LASEK), and small incision lenticule extraction (SMILE), the other is intraocular refractive surgery, like implantable Collamer lens (ICL). Corneal refractive surgery is the use of excimer laser on the myopic patient's cornea indicates a precise central stromal cutting, so that the cornea becomes flat to reduce the refractive power of the cornea. Intraocular refractive surgery involves adding an artificial lens to the patient's eye or replacing the original lens to change the refractive state of the entire eye.

4.5 Myopia control

In the case of underage myopic patients, the growth of myopia should also be monitored and, if necessary, appropriate myopia control should be given to prevent the rapid growth of myopia into high myopia causing serious ocular complications such as myopic maculopathy [45, 46], glaucoma [47, 48], cataracts [2], retinal

detachment [49, 50], etc. Each additional 1 D of myopia is associated with a 58%, 20%, 21%, and 30% increase in the risk of myopic maculopathy, open-angle glaucoma, posterior subcapsular cataract, and retinal detachment, respectively [51].

Myopia control can be achieved by increasing outdoor time to slow the onset of myopia and using interventions like atropine and orthokeratology to slow the progression [52–56]. A study shows that DIMS lenses resulted in a significantly different peripheral refraction profile and relative peripheral refraction changes, and significant myopia control effects compared with single vision spectacle lenses [57]. Soft multifocal contact lenses have the effect to control myopia. It results in a 50% reduction in the progression of myopia during 2 years compared with single vision contact lenses [58]. However, there is a lack of large-scale random clinical trials and large sample size validation. Ortho-k lenses show a significant effect in controlling the progression of myopia. And the progression was reduced by 45% [59].

4.6 Correction for hyperopia

The primary principle of hyperopia correction is to determine the degree of hyperopia after accurate optometry and to apply a suitable convex lens to converge the light so that it can be focused on the retina. The goal of hyperopia correction is similar to that of myopia correction, which still requires the best visual acuity while allowing the patient to feel comfortable and use the eye for a long time.

Prescriptions are often based on factors such as the degree of hyperopia, children's physical hyperopia, visual acuity, eye position [60], whether visual fatigue is present, and whether it affects the development of the visual function. Since accommodation plays an important role in the correction of hyperopia, and since accommodation is closely related to age, the prescription needs to be adjusted accordingly.

The common methods of hyperopia corrections including spectacle lenses, contact lenses, and surgery.

4.7 Spectacle lenses

Spectacle lenses are the most common method of correction for their convenience and economic advantage in children. For patients with high hyperopia, the spectacle can cause a difference between image magnification and actual objects, restricted visual fields, distortion of objects in the peripheral field of vision, and prismatic effects, resulting in poor visual quality.

4.8 Contact lenses

Contact lenses are based on the same principle as spectacle lenses but require attention to the vertex distance. Prescriptions of contact lens are often higher than that of spectacle lenses for the same hyperopic patients. The image created by RGP and SCL is closer to the actual object, without affecting the field of view and without distortion. The inconvenience is that all contact lenses with replacement schedules longer than daily must be maintained. At each step of their use, the lenses may be contaminated.

4.9 Surgery

Refractive surgery uses an excimer laser to cut the cornea or implant an IOL to produce a 'convex lens' effect. Such as hyperopic LASIK, hyperopic LASEK, hyperopic SMILE and intraocular procedures, etc.

5. Correction for astigmatism

The purpose of astigmatism correction should be to improve visual acuity and relieve symptoms without destroying the visual function of both eyes.

5.1 Regular astigmatism

All forms of regular astigmatism can be corrected by cylindrical lenses or sphere-cylindrical lenses.

Spectacles and different types of corneal contact lenses can be selected according to the source of astigmatism. Such as toric soft contact lenses or RGP.

Moderate to large degrees of astigmatism can be managed by refractive surgery.

When patients have high corneal astigmatism and mixed astigmatism, the final prescription should be based on the topography and the refraction result under the natural pupil [61].

5.2 Irregular astigmatism

Irregular astigmatism varies widely among individuals, and treatment is usually individualized according to the actual situation. It can be managed by wearing RGP lenses and scleral lenses, which produce tear lenses that compensate for the irregular shape of the corneal surface. For keratoconus patients, appropriate correction with RGP lenses may contribute to the good vision-related quality of life [62]; however, as the disease progresses to a steep keratometric value of more than 52 diopters (6.50 mm), RGP lenses did not guarantee a relatively good vision-related quality of life. New-generation hybrid contact lenses, piggyback contact lenses and scleral lenses can provide a viable alternative for visual rehabilitation of irregular astigmatism in selected eyes with RGP intolerance or RGP failure [63]. Keratoplasty and refractive surgery for patients with indications can also achieve better results.

6. Strabismus and management

6.1 Background

When normal eyes viewing, the image of the target with slight differences projecting onto the fovea of each eye, the brain could integrate monocular information and produce a combined perception, which is the basic process of the high level of binocular vision such as stereopsis. The projecting route from the target to the fovea is called the visual axis.

Strabismus or squint, the misalignment of visual axes of the two eyes, is a common visual disorder in humans. It affects approximately 3% of the population across the world. Strabismus usually leads to a series of binocular vision losses, which may persistently exist even after successfully surgical correction. Misalignment of the visual axes can cause diplopia or confusion since the objects are projected onto noncorresponding retinal locations of the two eyes. To offset these abnormal perceptions, suppression or abnormal retinal corresponding occurs in the visual system when the eyes are misaligned. In addition, strabismus may be associated with amblyopia if it occurs in early childhood.

6.2 Classification

Strabismus can be categorized in various ways, usually based on causes or age of onset. According to our clinical practice experience and previous literatures [64, 65],

we recommend the classification below. It should be noted that phoria, referring to one kind of strabismus, can be corrected by binocular fusion. Many people may have asymptomatic phoria and require no treatment. In contrast, tropia, referring to various kinds of strabismus, cannot be corrected by fusion and needed external interventions. Esotropia and exotropia are the most common types of tropia.

6.3 Esotropia

The visual axes intersect before the target.

6.4 Infantile Esotropia

Infantile esotropia occurs within 6 months after birth, usually with a large deviation, and is unable to be treated by optical correction. It is usually accompanied by other kinds of strabismus, such as the inferior oblique overaction, disassociated vertical deviation (DVD), and nystagmus. It may be associated with congenital dysplasia of motor fusion.

6.5 Concomitant Esotropia

Concomitant esotropia has a similar angle of deviations in different visual directions, usually presents after age 6 months.

6.6 Accommodative Esotropia

Accommodative esotropia is related to overconvergence due to increased accommodation or abnormally high accommodative convergence to the accommodative ratio (AC/A ratio).

Refractive Accommodative Esotropia with a normal AC/A ratio is caused by increased accommodation induce by uncorrected moderate to high hyperopia (+2.00D ~ +6.00D).

Nonrefractive Accommodative Esotropia with a High AC/A Ratio is caused by the abnormal effect of accommodation and accommodative convergence. The esodeviation at near fixation is larger than that at distance.

Partially accommodative esotropia is not only caused by accommodative factors. Patients with partially accommodative esotropia may have some improvement of their esodeviation when they wear corrective glasses for the hyperopia, but they may still have residual esodeviations (≥ 10 prism diopter (PD)).

6.7 Non-accommodative Esotropia

The esotropia degrees remain unchanged after refractive correction. This type of strabismus can be classified as basic, convergence excess, and divergence insufficient type.

6.8 Other types of concomitant Esotropia

Micro-strabismus, cyclic esotropia and acute concomitant esotropia, etc.

6.9 Secondary Esotropia

Consecutive Esotropia can occur after surgery for exotropia.

Sensory Esotropia is linked with monocular poor vision.

6.10 Non-concomitant Esotropia

Paralytic esotropia can be caused by cranial nerve VI palsies.

Restricted Esotropia may happen in Duane Syndrome, Moebius Syndrome, Thyroid-associated ophthalmopathy, etc.

6.11 Nystagmus blockage syndrome

The patients may have a variable angle of esotropia and are accompanied by nystagmus, which is most obvious in the abduction and decreased or absent in adduction.

6.12 Exotropia

The visual axes intersect behind the target.

6.13 Congenital Exotropia

Congenital exotropia could happen after birth and is usually accompanied by other kinds of strabismus, such as the inferior oblique overaction, DVD, and nystagmus.

6.14 Concomitant Exotropia

The similar angle of exodeviation in different visual directions.

6.15 Intermittent Exotropia

Intermittent exotropia, characterized by an intermittent outward deviation of one eye, is the most common form of exotropia in children. At the early stage of the disease, patients with intermittent exotropia may experience an alternating exophoria and exotropia at distance fixation. Manifest exotropia can be induced by fatigue, visual inattention, or covering one eye. It can be classified as basic, divergence excess, convergence insufficiency, and pseudo-divergence excess.

6.16 Constant Exotropia

Patients with constant exotropia have a constant angle of exodeviation in different directions of gaze. It is mainly related to the imbalance between the convergence and divergence functions, and the abnormal mechanical and anatomic factors.

6.17 Secondary Exotropia

Consecutive Exotropia can occur after surgery for esotropia.

Sensory Esotropia is linked with monocular poor vision.

6.18 Non-concomitant Exotropia

Paralytic exotropia can be caused by cranial nerve III palsies.

Restricted Exotropia may happen in Duane Syndrome, congenital fibrosis of the extraocular muscles, etc.

6.19 A-V pattern strabismus

A-V pattern strabismus is characterized by a change in the amount of horizontal deviation from the primary position towards upgaze and downgaze. The A pattern describes a difference of at least 10 PD, while the V pattern describes a difference of more than 15 PD. The pattern strabismus is mainly caused by oblique muscle dysfunction.

Vertical Strabismus and *Cyclotropia* are mainly caused by oblique muscle under-action or overaction.

6.20 Other kinds of strabismus

DVD, Congenital Fibrosis of Extraocular Muscles, Duane Retraction Syndrome, Moebius Syndrome, Brown Syndrome

6.21 Treatments of strabismus

The main goal of treatment for strabismus is to achieve satisfactory ocular alignment and restore binocular vision. The principle is to reverse the binocular abnormalities (suppression, paracentral fixation, abnormal retinal correspondence) caused by misalignments. Corrections for strabismus consist of a variety of non-surgical and surgical methods.

6.22 Timing of treatment

The timing of surgery for exotropia patients is influenced by children's neuro-developmental status and their ability to control eye position. For children with esotropia, treatments should be considered for all types of esotropia. Since younger children lose binocular vision rapidly, establishing binocular alignment as soon as possible is advised. For constant infantile exotropia, surgical treatments at an early age are indicated to improve sensory outcomes, although the normal binocular function is difficult to achieve. Patients with intermittent deviation and good fusion control should be followed up. When the deviations are present frequently or there are significant binocular vision impairments, treatments are usually required. Early strabismus surgery may contribute to the recovery of stereoscopic vision [66].

6.23 Non-surgical treatment

6.23.1 Amblyopia treatment

Amblyopia treatment is expected to initiate before surgical treatment of strabismus because this may alter the angle of exodeviation [67], and/or increase the likelihood of obtaining good binocular vision postoperatively. The presence of amblyopia may reduce the success rate of esotropic surgery [68]. For patients with exotropia, amblyopia treatment can improve fusion control, reduce the angle of exodeviation, and/or improve postoperative success rates of strabismic surgery.

6.24 Optical treatment of strabismus

6.24.1 Refractive correction

The first step in the treatment of strabismus in children is refractive correction [69]. For patients with accommodative esotropia, glasses or contact lenses,

determined by cycloplegia, are successful to achieve binocular alignment in most cases.

For patients with exotropia, any clinically significant refractive error should be corrected as the improved retinal-image quality could improve the control of the exotropia [70]. However, patients with intermittent exotropia are not recommended to correct mild to moderate amounts of hyperopia because reduced accommodative convergence may worsen the control or angle of the exodeviation. Overcorrecting myopia or undercorrecting hyperopia is recommended to stimulate accommodative convergence [71].

6.24.2 Prism therapy

Prism therapy may help improve binocular vision in some patients with acquired esotropia with diplopia. For patients with a small angle of residual esotropia, the prismatic correction was also reported to be feasible [60]. However, prisms are rarely useful in infantile esotropia, because the angle of deviation is usually too large to correct with prisms alone. Patients with intermittent exotropia do not typically have diplopia, thus prisms are rarely prescribed.

6.24.3 Botulinum toxin injection

Botulinum toxin is a potent neurotoxin that blocks the release of acetylcholine at the neuromuscular junction of cholinergic nerves [72]. Botulinum toxin injection is an alternative to surgery for a variety of esotropia subtypes. It is as effective as surgery in acute onset esotropia. Compared with standard strabismus surgery, botulinum toxin injection possesses several advantages: less anesthesia exposure; lower risk of overcorrections; muscle preservation; earlier treatment; relatively painless postoperative period; and minimally invasive procedure. However, the following drawbacks limit the practice of botulinum toxin injection: lower success rate overall compared to surgery; less precision and less efficacy in large-angle strabismus; transient postoperative exotropia and ptosis; and lack of standardized botulinum toxin dose recommendations based on the angle of deviation [73–75].

6.24.4 Orthoptics

Orthoptics can be used to supplement and reinforce the effects of treatment. For example, convergence exercises can improve fusional control for children or adults with convergence insufficiency and with small- to moderate-angle exodeviation (i.e., 20 PD or less) [76].

6.25 Extraocular muscle surgery

6.25.1 Methods of surgical treatment

Surgery for correcting strabismus is performed based on strengthening or weakening the extraocular muscle. There are various types of strabismus surgery, including rectus muscle recessions, resections, and plications [39, 40, 77], rectus muscle transpositions, inferior oblique recessions, rectus muscle posterior fixations, and so on. The amount of surgery and the choice of surgical technique may vary. Surgeons should be aware of the effects of oblique muscle weakening on horizontal deviation and pattern collapse when planning and performing strabismus surgery [43, 44]. Multiple factors determine the choice of surgical muscle. The deviation of the primary position of eyes should be considered first, as well as the difference

between the deviations at near and distance fixations should be noted. The medial rectus muscle has a greater corrective effect for the patients with a greater angle of deviation at near fixation, and the lateral rectus muscle is more effective for the patients with greater angle deviation at distance fixation.

Surgery can only correct the eye position mechanically. Many factors can affect the correction results, such as the nature of muscle, the relationship with surrounding tissues, and different nerve impulses. Overcorrection and undercorrection are relatively common problems that occur after surgery for strabismus [78], therefore it may take more than one operation to get satisfactory results.

6.25.2 Minimally invasive strabismus surgery

Minimally invasive strabismus surgery (MISS) provides a valuable option to minimize tissue trauma, postoperative corneal complications, and patient discomfort [77]. However, this technique faces a technical challenge, due to a longer surgical time and increasing risk of scleral perforations. Therefore, surgeons should be paying more attention when performing this technique.

6.26 Adjustable sutures

The application of adjustable sutures is an effective auxiliary method for strabismus surgery, which can be used to improve motor outcomes. It is especially effective for patients with restrictive diseases or requiring multiple operations. It is usually difficult for pediatric patients to cooperate, therefore, the effect of adjustable sutures on children needs further research [79].

6.27 Prognosis

After strabismus surgery, some patients may achieve normal alignment, while others may present with oblique overaction or postoperative adduction limitation, which could cause consecutive exotropia [80].

6.28 Follow-up

To prevent the risk of amblyopia, binocular function defects, and recurrence of strabismus, follow-up is necessary for patients whether their initial treatment results are good or not, especially for children [81]. Unstable postoperative outcomes may indicate the need for more frequent follow-up visits.

7. Amblyopia and management

Amblyopia is a developmental visual disorder characterized by reduced corrected visual acuity in one or both eyes without obvious abnormality of the visual pathway. It is thought to result from a disturbance of normal visual input during the critical period of visual development [82]. Factors commonly associated with amblyopia include strabismus, stimulus deprivation such as cataracts or ptosis, and those caused by anisometropia or ametropia. A substantial burden is potentially placed on patients and health care resources as the visual defect of amblyopia can last a lifetime. The estimated prevalence of amblyopia is between 2% and 3%, depending on the diagnostic criteria used and the population selected [83]. The diagnosis basis of amblyopia is defective central visual processing. Zhao used visual event-related potential (ERP) techniques to assess the late-stage cognitive dysfunction in

anisometropic amblyopes then found that the latency of P3a ERP was delayed in the amblyopes compared with normal subjects, with P3a amplitude showing a significantly compensative effect [84]. Wang has concluded that both the amblyopic eye and fellow eye exhibiting the longer latency of P3b components as well as the larger amplitude of novelty P300 and P3b. The above researches demonstrate abnormal neural responses of the amblyopic eye at the middle and late stages of cognitive processing, indicating that the amblyopic eye needs to take more time or integrate more resources to process the same visual task [85].

The conventional management of amblyopia includes optimum refractive correction, occlusion therapy (patching the good eye) [86] and atropine occlusion [87, 88].

8. Optical treatments

The basis of amblyopia treatment is an optical correction. Wearing suitable spectacles is the first step to resolving amblyopia or improving visual acuity. Stewart described the visual response to spectacle correction for young children with unilateral amblyopia over 18 weeks, which suggested that all children with unilateral amblyopia and a significant refractive error will benefit from a longer period of refractive adaptation before any other treatment, such as occlusion, atropine penalization or Bangerter filters, which in some cases would no longer be necessary [89]. Cotter reported data on the response of 12 patients with previously untreated strabismic amblyopia to refractive adaptation [90]. 9 patients (75%) improved their visual acuity by ≥ 2 lines from spectacle-corrected baseline acuity. The improvement lasted up to 25 weeks. Amblyopia Treatment Studies (ATS) have shown that there is no need to begin patching at first. Spectacles alone can aid VA (visual acuity) progression in 3-year-old to less than 7-year-old children [91, 92]. In conclusion, children 3–7 years with amblyopia, especially anisometropic amblyopia, can improve or even resolve with spectacle correction alone. Additional treatment can be prescribed after appropriate 4 months or even half a year when VA stabilized with spectacle correction alone.

9. Patching/occlusion

When refractive correction alone is not useful for amblyopic patients, or VA stops improving, occlusion therapy is another well-known and commonly practiced way of treating amblyopia. Occlusion increases visual stimulation to the amblyopic eye and visual cortex, thus aiming to recreate and enhance neural connections. The forms of occlusion are part-time patching, atropine penalization, or Bangerter filters.

After the visual acuity has stabilized with refractive correction alone, there should be at least 2 hours of daily patching of the designated eye for patients with moderate to severe amblyopia. Wallace and Pediatric Eye Disease Investigator Group (PEDIG) conducted a prospective randomized clinical trial on 180 children with amblyopia [93]. It was found that the VA of the daily patching group (combined with 1 hour of near work) improved average 1.1 lines, while the improvement in VA of the control group (wearing spectacles alone) improved by 0.5 lines. It shows that after wearing correct spectacles, 2 hours of daily occlusion combined with 1 hour near work can better improve VA for moderate to severe amblyopia in pre-school children. Although Timothy found that a higher percentage of amblyopic patients treated with full-time occlusion achieved better VA over a short period of occlusion [94], the final goal of treatment is not only to achieve normal corrected vision but also to establish a binocular vision, especially stereopsis.

Atropine penalization is an alternative to occlusion therapy. The recommended dosage was one drop of 1% atropine sulfate ophthalmic solution daily to the fellow eye. It can make a cycloplegic effect on the dominant eye, blur the near images. Patients who have a hyperopic prescription in the dominant eye are ideal candidates for this treatment. PEDIG investigators compared patching to atropine in 419 children 3 to 7 years of age with moderate amblyopia (20/40 to 20/100) at 6 months of treatment [95]. There was no statistical difference in outcomes between the two groups. The results showed that the two ways were similar in improving VA, indicating both methods were suitable for children with mild amblyopia aged 3–7 years. Two years after enrollment, a follow-up study re-evaluated 188 patients [96]. Although the residual mean amblyopic eye acuity was 0.17 logMAR (approximately 20/32), it was noted that the VA improvement achieved in amblyopic eyes remained. No difference was noted between the patching and atropine groups, validating the effectiveness of both treatments and the sustainability of gains.

Not correcting the hyperopia of the dominant eye can strengthen the effect of atropine penalization, which is equivalent to atropine therapy combined with optical penalization [97]. Significantly, adverse amblyopia or decreased vision in the sound eye may happen due to noncompliance [98]. Side effects of atropine include constant blur at distance and near, especially for hyperopic patients. If this case occurs, it should not persist immediately.

Occlusion is a gold-standard treatment for amblyopia. However, patching the fellow eye will destroy the binocular vision, affecting life and learning. Besides that, it also affects the appearance and may cause ridicule by peers. Bangerter filter (Ryser Optik, St. Gallen, Switzerland) is a translucent filter, which is attached to the back surface of the spectacle lens of the sound eye. Patients need to wear it partially or full-time. It can scatter light through microelements with eight levels, and produce localized image distortions. The VA of the non-amblyopic eye is lower than the amblyopic eye, and as acuity improves, the filter is switched to one with less degradation. Rutstein compared the visual acuity improvement between Bangerter filters and patching [99]. The improvement in visual acuity was similar for the two treatments, and a lower burden of treatment was found in the Bangerter filters group. Hence, he recommended Bangerter filter treatment is a reasonable option for initial treatment of moderate amblyopia. Chen, Z approved Bangerter filters can immediately reduce suppression of amblyopic eye and promote binocular summation for mid/low spatial frequencies in observers with amblyopia [100].

10. Pharmacological therapy

Levodopa is the immediate metabolic precursor of dopamine, which can be transformed into dopamine in the brain. Levodopa can increase the levels of dopamine in the human brain and improve visual function. Gottlob and Stangler-Zuschrott were the first to use levodopa in the treatment of amblyopia [101]. They found that levodopa improved contrast sensitivity of amblyopic eyes for a short period. Yang combined the results of 6 clinical trials by using standard meta-analytic methods to address the efficacy and tolerance of levodopa on amblyopia [102]. He concluded the use of levodopa is an effective and safe option for the treatment of amblyopia.

Carbidopa is a peripheral dopamine decarboxylase inhibitor, which inhibits the decarboxylation of levodopa outside the brain, makes more levodopa enter the brain to decarboxylate into dopamine. Pandey reported the effect of amblyopic therapy for three weeks with levodopa and carbidopa in children and adults [103]. They found patients receiving higher dosages of levodopa and carbidopa had better improvement in VA and contrast sensitivity.

The use of levodopa/carbidopa is an effective option for the treatment of amblyopia. It is considered an adjunct to conventional therapy because it may enhance compliance for occlusion. However, due to the side effects, it cannot become the first-line treatment of amblyopia.

11. Perceptual learning

Perceptual learning is considered a potential treatment for amblyopia, especially for adults who retain sufficient plasticity. It is an important research content in the field of perception, involving cognitive psychology, psychophysics, neurophysiology, and other disciplines. Different from the traditional treatment of amblyopia, perceptual learning is a process of active participation. Researchers use mobile terminals or computers to present visual stimulation with different characteristics, and subjects need to complete different visual tasks. Since 1996, Levi and Polat first applied perceptual learning in adult amblyopia [104]. They found that the VA of adult amblyopia can still be improved after training. Zhang compared the efficacy of Internet-based perceptual learning and conventional treatment in amblyopia [105]. The VA improvement of the perceptual learning group is larger than the conventional treatment group. In addition, perceptual learning can shorten the cure time of amblyopia. Several findings have indicated that optical quality is an important factor in visual perceptual learning [106, 107]. Li compared the difference of VA and contrast sensitivity thresholds of 10 amblyopes before and after correcting higher-order aberration. The VA of amblyopic eyes was improved after correcting high-order aberrations (mean 0.16 times). Meanwhile, the contrast sensitivity threshold decreased after correction of higher-order aberrations in lazy eyes (mean 0.34 times) [108]. Liao corrected high-order aberrations (HOA) of anisometropic amblyopes, using an adaptive optics perceptual learning system (AOPL), and trained adult amblyopia with contrast detection task [29]. Surprisingly, the improvements in visual function could be found in the trained eye and untrained eye.

Recently, several studies suggest that perceptual learning can improve visual function. It has achieved positive clinical results in the treatment of amblyopia. Perceptual learning may change the current clinical amblyopia treatment so that patients can achieve better visual function by vernier acuity, positional acuity, and contrast sensitivity tasks. Of course, before perceptual learning is widely used in the clinic, there are still some problems to be solved, such as the need for a large sample of clinical research to determine the dose–response relationship and the relationship between prognosis and the type or degree of amblyopia.

12. Non-invasive brain stimulation

Emerging evidence suggests that inhibitory neural pathways which utilize γ -aminobutyric acid (GABA) as a neurotransmitter play an important role in the regulation of visual cortex plasticity. The GABAergic inhibition level of the visual cortex is low at birth, and when its development reaches a certain threshold, the critical period opens. External environmental stimuli influence the function and structure of the neurons and synapses in the visual cortex during the critical period. With the continuous maturation of the inhibitory pathway, it reaches the second threshold and triggers the closure of the critical period [109–111]. It has been concluded that the reduction of inhibition in the visual cortex is the core to restore the plasticity of adult amblyopia after the critical period. Studies on animal models

have shown that reducing GABAergic inhibition with pharmacological treatment such as blockers of GABA synthesis or GABA receptor antagonists or environmental paradigms which contain environment enrichment and dark exposure can increase plasticity in the adult brain, enabling ocular dominance plasticity and favoring recovery from amblyopia [112–114]. New research has found that transplanted embryonic inhibitory neurons from the medial ganglionic eminence reinstate ocular dominance plasticity in adult amblyopic mice, with the recovery of both visual cortical responses and performance on a behavioral test of visual acuity [115].

Non-invasive brain stimulation (NIBS) techniques allow painless and safe modulation of neural processes in the brain [116], which mainly contains two certain methods: transcranial magnetic stimulation (TMS), which is based on principles of electromagnetism, and transcranial electrical stimulation (tES), which harnesses weak, painless electrical currents applied to the scalp, and these mechanisms remind us NIBS maybe a potential treatment for amblyopia by changing excitation-inhibition balance in visual cortex. Thompson presented data showing that both 1HZ and 10HZ repetitive transcranial magnetic stimulation (rTMS) of the visual cortex can temporarily improve contrast sensitivity in the adult amblyopic eye [117]. Similarly, continuous theta-burst stimulation (cTBS), a specific type of rTMS, may improve adult amblyopic eye contrast sensitivity to high spatial frequencies, and the improvements were stable over up to 78 days, indicating that rTMS can produce long-lasting effects on the amblyopic visual cortex [118]. Moreover, another study showed a transient improvement in adult amblyopic eye contrast sensitivity for at least 30 minutes after anodal transcranial direct current stimulation (a-tDCS) [119]. Notably, few subjects were included in the above preliminary researches, suggesting that NIBS techniques deserve further investigation as a potential tool to improve visual function in amblyopic adults.

Generally, it was believed that amblyopia could only be reversed if treatment was initiated before the critical period of visual development, 6 to 8 years old [120]. While 73–90% of amblyopic children show improvements in visual acuity with these interventions alone or in combination [121–125]), successful interventions are not generally seen in adults.

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