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An Overview of the Retinal and Choroidal Changes and Their Influencing Factors after Treatment of Amblyopia

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Abstract

Purpose of Review: Amblyopia is the reduction in the best-corrected visual acuity of one or both eyes and the most common cause of the loss of vision in children. Previously, amblyopia was thought to have no organic lesions. However, the latest "Amblyopia Preferred Practice Pattern" of 2017 points out that in amblyopia, the eye structure is abnormal with a defective eye function, with few differences from the structure of contralateral non-amblyopic eyes. With the development of optical coherence tomography and optical coherence tomography angiography, it has been observed that even the ocular structure of amblyopic eyes is different from that of normal eyes. Here, we review studies investigating the changes in amblyopic eye structure upon treatment. **Review Findings:** The pathogenesis of amblyopia is controversial and not well-understood. The retina, choroid, and blood vessels of amblyopic eyes are different from those of normal eyes. Further, the various types of amblyopia are affected differently upon treatment. Because of the scarcity of studies and long-term follow-up observations, the underlying reason for such differences is unclear. Age, gender, and axial length are the influencing factors of the retina and choroid, and the relationship of these factors with amblyopia needs to be investigated further. **Conclusion:** This review will help us understand the pathogenesis of amblyopia and the underlying mechanism for the changes that occur upon treatment. Further, knowledge of the changes in ocular structure summarized here will be helpful for the diagnosis and treatment of amblyopia.

Keywords

Amblyopia, Children, Retina, Choroid, Optical Coherence

1. Introduction

Amblyopia is an eye disease that seriously endangers the visual function and is the most common cause of vision loss in children [1]. According to epidemiological data, amblyopia is present in approximately 2% - 4% of children [2], with its prevalence in preschool children gradually increasing in recent years [3]. If not treated on time, amblyopia causes lifelong damage to a child's vision. However, proper and timely treatment can completely cure amblyopia. Amblyopia not only results in the decline of vision but also alters visual sensitivity, contrast, and visual function [4]. The sensitive period of visual development is the best period for the treatment of amblyopia [5]. Therefore, timely and appropriate treatment of amblyopia is necessary to avoid permanent damage to an amblyopic child's vision. Although there are several studies on the histological changes of ocular structure in patients with different types of amblyopia [6] [7], there has not been much in-depth exploration of the dynamic changes of indicators after amblyopia treatment. Hence, in this study, we focus on the changes in retinal, choroidal, and vascular density of different types of amblyopia after treatment and integrate these findings with those of previous studies to gain a comprehensive understanding of the treatment of amblyopia.

2. Changes in Retinal Thickness and Retinal Nerve Fiber Layer Thickness (RNFLT) with Treatment

The retina is a soft and transparent membrane and contains visual cells that can be stimulated by light. The optical center of human eyes, the macular region, has the thinnest retina, while the fovea has the highest visual acuity. Changes in the retina are closely related to changes in visual acuity. The thickness of different retinal zones varies with different types of amblyopia, which have been explored in several studies.

Although there are differences in the pathogenesis of various types of amblyopia, they ultimately lead to alterations in retinal thickness and RNFLT, as shown in several studies. Kasem *et al.* [8] showed that the macular fovea in the myopic anisometropic amblyopic group is thicker than in the non-amblyopic group, and there is no significant difference in RNFLT. The foveal retinal thickness, mean retinal thickness, and overall RNFLT of the hyperopic anisometropia amblyopic group are higher than those of the contralateral eyes. In both the astigmatic anisometropia amblyopic and strabismus amblyopic groups, the foveal retina is thicker than that of the lateral eyes. However, there is no significant difference in the overall RNFLT between the astigmatic anisometropia amblyopic and contralateral eyes, while the overall RNFLT of strabismus amblyopia is thicker than those of the contralateral eyes. The macular fovea in form-deprivation amblyopia is thicker than that in the contralateral eye, but the average macular thickness is not different from the overall RNFLT in the contralateral eye. Further, Rajavi *et al.* [9] showed that the macular foveal thickness of anisometropic amblyopia and strabismus amblyopia was thicker than that of lateral amblyopia.

Moreover, in children with hyperopic anisometropic amblyopia, the average RNFLT of the optic disc, the macular fovea, and the thickness of each zone of the amblyopic eye are thicker than those of the contralateral eye [10]. Yong *et al.* [11] showed that the thickness of RNFL and fovea of the optic disc in children with form-deprivation amblyopia was thicker than that in contralateral and normal eyes. Many cones gather in the fovea of the macula. Further, the stimulation of cones is transmitted to 17 areas of the visual center, and the visual sensitivity of the fovea of the macula is the highest. Due to the lack of visual stimulation in the fovea of amblyopic patients, the normal apoptosis of foveal ganglion cells is delayed, and the macula cannot mature normally.

After treatment, the amblyopic eyes received more stimulation, and Henle's fibers accelerated to leave the fovea, which increased the diameter and decreased the thickness of the foveal cone. The retinal thickness and RNFLT in the macular region also changed accordingly. In a prospective controlled experiment by Kavitha *et al.* [12], it was found in the follow-up of children with monocular anisometropic amblyopia upon treatment for up to one year that the macular and foveal thickness of amblyopic eyes decreased with the extension of treatment time and the increase of the best-corrected visual acuity. There was no significant difference in RNFLT between amblyopic eyes, contralateral non-amblyopic eyes, and normal eyes of normal children before and after treatment. Pang *et al.* [13] longitudinally compared the retinal thickness of each macular region in children with myopic anisometropic amblyopia. After 32 weeks of treatment, the macular fovea became thinner, but the thickness of the inner and outer ring macula did not change significantly. However, during the treatment of children with monocular anisometropia, Yoon *et al.* [14] showed that there were no significant alterations in the retinal thickness of nine macular regions after treatment, and the volume of the average fovea decreased. Although the thickness of fovea was not statistically significant before and after treatment, the authors still believed that the decrease in foveal volume was due to the decrease of foveal retinal thickness after the rearrangement of foveal pyramidal cells during treatment, and expanding the sample size might result in statistical significance. Peng *et al.* [15] demonstrated that the fovea became thinner after 24 months of follow-up observation on patients treated for high hyperopic amblyopia. Although the RNFLT became thinner, the change was not as evident as that of the fovea, with no changes until 24 months. The researchers speculated that the reason for the insignificant change of RNFLT after treatment might be because RNFL is not sensitive to light stimulation, and the results need to be verified for a longer time.

Thus, several researchers have recognized the changes in retinal thickness and RNFLT after treatment, but there is still no consensus on which zones are changed and the underlying reason for such changes. Multicenter joint experiments are needed to increase the sample size, integrate different types of amblyopia, and make the dynamic changes in children's retina show more accurate results through the extension of follow-up time.

3. Changes in Choroidal Thickness before and after Treatment

The choroid is a critical eye structure affecting vision. It is rich in blood vessels and provides essential nutrients for the growth and development of the outer layer of the retina. The tan membrane blocks the light penetrating the sclera for clear imaging. As the most sensitive area of the visual eye region, the macular area has the most abundant blood flow, and the thickness of the choroid is significantly greater here than that of other areas. With the development of frequency-domain enhanced depth imaging, researchers can quantitatively measure the choroidal thickness and examine the choroidal difference between amblyopic and normal eyes and the changes before and after treatment.

Only a few studies are present on the changes of choroidal thickness in different types of amblyopia with no conclusive data. Araki *et al.* [16] found that the choroidal thickness of patients with anisometropic amblyopia was significantly higher than that of the healthy side and normal control eyes. However, there was no significant difference in the retinal or choroidal thickness between strabismus amblyopic, healthy, and normal control eyes. They recognized that the increase of subfoveal choroidal thickness (SFCT) was due to the inhibition of ocular compensation and choroidal regulation of hyperopic defocus. Öner *et al.* [17] did not find any significant difference in the foveal choroidal thickness between hyperopic non-amblyopia and hyperopic anisometropic amblyopia, but the choroidal thickness in both the groups was higher than those in the normal eyes. They speculated that the thickness of the choroid is related to the degree of the ocular axis and hyperopia, and amblyopia may not be an independent factor. Further, Yang *et al.* [18] showed no significant difference in the thickness of macular foveal choroid between the eyes of amblyopic children with hyperopic anisometropia and contralateral normal eyes. Wan [19] also found no significant difference in choroidal thickness in most areas of high myopic amblyopia compared with high myopia with the same diopter. Thus, it is speculated that the choroid is not involved in the pathogenesis and development of high myopia and amblyopia. Zhang *et al.* [20] used covariance analysis, and after excluding the influence of eye axis on choroidal thickness, showed that the choroidal thickness in the macular area of amblyopic patients was thicker than that of normal eyes. They also speculated that the choroid was involved in the development of severe congenital ptosis amblyopia.

Choroidal thickness changes with retinal defocus, as studied during myopia development and validated through animal experiments. Rada and colleagues [21] [22] reported that choroidal vascular permeability increased in chicks during recovery from form-deprivation myopia. After myopic or hyperopic defocus in chickens, the change of choroidal thickness brings the photoreceptor of the retina to the focal plane, resulting in forward and backward displacement of the retina, respectively. Choroidal thickness is involved in visual regulation through emmetropia, retinal position adjustment, and scleral growth regulation [23]. Although the visual acuity of children with amblyopia improved after treatment, it is still unclear whether the choroidal thickness changes. Öner and Bulut [24] found that after six months of amblyopia treatment, the vision of patients with anisometropic hyperopic amblyopia improved. However, they did not observe any significant change in choroidal thickness. Since the choroidal thickness was greater than that of the contralateral eye before and after treatment, they speculated that the increase in choroidal thickness caused by amblyopia was irreversible. Likewise, Araki *et al.* [25] also found that the choroidal thickness of amblyopic eyes was thicker than that of contralateral eyes before and after treatment when the experimental follow-up time was as long as 36 months. There was no significant change in choroidal thickness after treatment, but it continued to thicken. A similar study of children with hyperopic anisometropia used multivariate analysis of variance to adjust the axial length and diopter [26]. Although the choroidal thickness in the fovea of amblyopic eyes and that in the nasal and temporal sides 1.5 mm and 3.0 mm away from the fovea became thinner after treatment, the choroid in the fovea was still thicker than in the contralateral and control eyes. Hence, the authors speculated that some areas of the choroid could return to a normal level after amblyopia treatment. Compared with the results obtained by Öner *et al.*, this study showed that the reasons behind a non-significant change were that most of the children missed the best correction period, and the treatment effect was poor. Zhang *et al.* [27] found that the postoperative choroidal thickness of children with form-deprivation amblyopia caused by congenital impairment increased, but there was no statistical significance. It was considered that the choroidal thickness difference was caused by congenital developmental abnormalities.

At present, it is unclear whether the choroidal thickening in hyperopic anisometropic amblyopia is caused by amblyopia or hyperopia. Further, the scarcity of studies makes it difficult to deduce the relationship between choroidal thickness and ocular axis length and hyperopia degree. Hence, more data and long-term follow-up observations are needed from each subtype to reach more reliable conclusions.

4. Changes in Retinal and Choroidal Vessels before and after Treatment

The retinal vascular network [28] is axially divided into four different capillary plexus from inside to outside: nerve fiber layer vascular plexus (NFLVP), shallow capillary plexus (SCP), intermediate capillary plexus, and deep capillary plexus (DCP). The choroid [29] is rich in blood vessels and is divided into five layers from inside to outside: Bruch membrane, choroidal capillary layer, Sattler layer, Haller layer, and suprachoroidal cavity. Optical coherence tomography angiography [30] (OCTA) can provide colored 3D images of retinal and choroidal perfusion vessels. It has the advantages of being non-invasive, fast, convenient, and having high resolution. Currently, it is widely used to measure the ocular blood vessels of amblyopic children.

To date, only a few studies used OCTA to detect the retinal vascular system of amblyopic patients. Further, no special attention has been given to the difference of ocular axis length or diopter of amblyopic eyes in data analysis, even though amblyopic eyes have a large hyperopic diopter and a short ocular axis. Noriko *et al.* [31] used a customized image analysis program to correct the ratio of retinal image to axial length in anisometropic unilateral amblyopic children and anisometropic unilateral amblyopic children with strabismus. The SCP and DCP macular vascular density of amblyopic eyes decreased, and the area of the foveal avascular zone (FAZ) was small. Yilmaz *et al.* [32] provided the research idea earlier. Although the influence of axial diopter was not excluded, it was concluded that the vascular density of SCP and DCP in strabismus amblyopia was lower than that in contralateral eyes and normal eyes of healthy children. Araki *et al.* [33] used OCTA to evaluate the area and vascular density of FAZ after magnification correction of unilateral amblyopia and found that the FAZ area of SCP of amblyopia was smaller than that of the lateral eye, while the FAZ area of DCP of amblyopia was smaller than that of the contralateral eye, with no significant difference in macular vascular density between amblyopic and contralateral eyes. However, their results apply to mild amblyopia, not to medium and high amblyopia. The decrease in vascular density in amblyopia may indicate a reduced demand for blood supply from the retinal artery system. The avascular area of the fovea in amblyopic eyes is smaller, which may reflect the abnormality or delay in foveal development. Gunzenhauser *et al.* [34] compared the blood flow density in the macular area of amblyopia before and after treatment for the first time. They found that the visual acuity of children with anisometropic amblyopia and strabismus amblyopia improved after treatment, and the DCP in the whole image and retinal vascular density in the upper hemisphere increased significantly after treatment. After adjusting the influencing factors such as age, gender, and ametropia, Salerni *et al.* [35] demonstrated that the vascular density and vascular plexus of total macular SCP in amblyopic eyes with normal vision after treatment were significantly higher than that in amblyopic and normal eyes without response after treatment. Further, there was no difference in the vascular density and vascular plexus between amblyopic and normal eyes upon ineffective treatment. The blood vessels of amblyopic eyes with more sensitive treatment are densely distributed, which may be due to the compensatory vascular response in amblyopic patients who experience visual recovery after treatment. Zhang *et al.* [36] adjusted the length of the ocular axis and found that the vascular density of macular SCP and DCP in children with anisometropic amblyopia was lower than that in normal eyes. There was no significant difference in the macular vascular density between amblyopic and normal eyes in SCP and DCP. It shows that anisometropic amblyopia with low macular vascular density can return to the level of healthy eyes after the complete correction of ametropia and occlusion treatment.

There is a lack of prospective longitudinal research on the changes in retinal vessels before and after treatment. The existing research also lacks the understanding of whether the vascular response of children with effective treatment is consistent with that of children with ineffective treatment. Further, the follow-up time should also be extended to observe whether the changes in retinal vascular density and perfusion and the avascular area of the fovea are permanent or temporary.

The increase in choroidal capillary density provides more blood for the thickened outer retina, which is a compensatory response to the decrease of retinal vascular density in amblyopic patients [37]. The authors speculated that the incomplete maturation of the choroidal vascular system might be a separate factor in amblyopia. Terada *et al.* [38] showed that the vascular area of the Haller layer in the amblyopic and contralateral eyes of children was larger than that in healthy eyes. This means that even if the vision of the contralateral eye is normal, there may be anatomical abnormalities. After correcting the magnification error, Araki *et al.* [39] found that although there was no significant difference in choroidal vascular density between unilateral hyperopic amblyopic, contralateral, and normal eyes, combined with the difference in total choroidal volume, the choroidal blood flow of amblyopic eye may be greater than that of contralateral and normal eyes. At present, the ratio of choroidal cavity area to total choroidal area, namely choroidal vascularity, is used to quantitatively measure choroidal vessels. Baek *et al.* [40] used this index in their study and showed that the average choroidal vascularity of amblyopic eyes was greater than that of normal eyes. However, the negative correlation between choroidal vascularity and choroidal thickness of foveal choroid thickness may indicate insufficient blood supply of outer retina and choroid in amblyopic eyes of patients with unilateral anisometropic hyperopic amblyopia. Laser speckle flowgraph is another method for quantitative evaluation of choroidal blood flow. It can reproduce the image depicting the same small area in the eye at different time points. This method was used in the case study of Hashimoto *et al.* [41], and it was found that the choroidal blood flow of two children with anisometropic amblyopia was damaged, and the choroidal blood flow increased after successful treatment.

At present, there are few experimental studies on the changes in choroidal vessels after treatment. We hope that OCT and laser speckle rheogram with high scanning speed and high penetration will be used more frequently in clinics to help us explore the changes in choroidal vessels before and after treatment.

5. Relevant Influencing Factors

5.1. Age and Gender

To date, researchers have studied mostly preschool children [42] with amblyopia and did not find any significant correlation between macular retina and age. The macular thickness of boys is greater than that of girls, similar to that of adults [43]. However, the change of choroidal thickness with age seems to involve two different processes. Read *et al.* [44] suggested that the choroidal thickness of emmetropic children positively correlated with age, while the choroidal thickness of myopic children negatively correlated with age. The choroid thickens with the natural growth of the eye, but the thickening is limited to axial elongation and the development of myopia. In adults, the choroid is thicker in men than in women. The reason is that boys usually start puberty late, but it lasts a long time. In studies involving children [45], the choroidal thickness or choroidal volume of girls was higher than that of boys, but it did not reach statistical significance after adjusting for other relevant factors. As for the relationship between age and gender and choroidal thickness of amblyopic children, more experiments are needed. Group discussion can be carried out according to the age and whether they enter puberty to get more meaningful results.

5.2. Axial Length

Many studies have reported a correlation between retinal thickness, choroidal thickness, and axial length in children. Yi *et al.* [46] found that the longer the ocular axis, the thicker the retina in the macular center, and the longer the ocular axis in other areas, the thinner the retina. In a study of 120 Asian myopic children, Qi *et al.* [47] showed that for every 1 mm increase in axial length, SFCT decreased by 18.95 μm, and the axial length negatively correlated with choroidal thickness. Further, there is little correlation between retinal thickness, choroidal thickness, and ocular axis in hyperopic amblyopic children. Whether the known correlation applies to children with hyperopia and amblyopia needs more research.

6. Summary

The abnormality of ocular structure and the loss of visual function in children with amblyopia are the new directions of our research. We plan to understand how to diagnose the severity of amblyopia through the changes in the retina, choroid, and other indicators. Further, we also seek to observe the treatment process with combined indicators and update and improve the treatment plan. Careful grouping and a large sample size can solve the discrepancies in the results of the current studies. Because of the changes in the eye structure after treatment, we may try to establish a recovery training center for amblyopic children to break the problems of small sample size, single disease type, short follow-up time, and high loss rate of most studies.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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