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Abstract

Nine eyeballs were enucleated from nine patients with excessive myopia, secondary retinochoroidal atrophy, absolute glaucoma, uveal malignant melanoma, Behcet's disease and sympathetic ophthalmia. The retina and choroid were studied with light and electron microscopes. The results were: In excessive myopia, marked blockade of choriocapillaries was accompanied by progressive retinal degeneration. In secondary retinochoroidal atrophy induced by retrobulbar fibrosis, the choriocapillaries were partially blocked and the retina had markedly degenerated. In Behcet's disease, exudative inflammation was recognized in the choroid extending to the retina and causing retinal detachment, though the choriocapillaries remained morphologically normal. In sympathetic ophthalmia, both the choriocapillaries and the retina remained normal, though marked inflammation was recognized in the outer layer of the choroid. In absolute glaucoma, the fine structures of the choriocapillary were well preserved in spite of bulbar hypertonia. In uveal malignant melanoma, the ultra structure of the choriocapillary near the tumor was well preserved. The choriocapillaries were normal even when the retina had degenerated. Retinal degeneration was recognized when changes such as blockage, disappearance, dilatation and increased permeability were found in the choriocapillaries. Damage to the choriocapillaries might play an important role in inducing and developing retinochoroidal atrophy.

KEYWORDS: retinochoroidal atrophy, electron microscope, choriocapillaries, Bruch's membrane, retinal pigment epithelium

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ELECTRON MICROSCOPIC STUDIES ON RETINOCHOROIDAL ATROPHY IN THE HUMAN EYE

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Abstract. Nine eyeballs were enucleated from nine patients with excessive myopia, secondary retinochoroidal atrophy, absolute glaucoma, uveal malignant melanoma, Behçet's disease and sympathetic ophthalmia. The retina and choroid were studied with light and electron microscopes. The results were: In excessive myopia, marked blockade of choriocapillaries was accompanied by progressive retinal degeneration. In secondary retinochoroidal atrophy induced by retrobulbar fibrosis, the choriocapillaries were partially blocked and the retina had markedly degenerated. In Behçet's disease, exudative inflammation was recognized in the choroid extending to the retina and causing retinal detachment, though the choriocapillaries remained morphologically normal. In sympathetic ophthalmia, both the choriocapillaries and the retina remained normal, though marked inflammation was recognized in the outer layer of the choroid. In absolute glaucoma, the fine structures of the choriocapillary were well preserved in spite of bulbar hypertonia. In uveal malignant melanoma, the ultra structure of the choriocapillary near the tumor was well preserved. The choriocapillaries were normal even when the retina had degenerated. Retinal degeneration was recognized when changes such as blockage, disappearance, dilatation and increased permeability were found in the choriocapillaries. Damage to the choriocapillaries might play an important role in inducing and developing retinochoroidal atrophy.

Key words: retinochoroidal atrophy, electron microscope, choriocapillaries, Bruch's membrane, retinal pigment epithelium.

Retinochoroidal atrophy, which has various etiologies, leaves irreversible visual defects. Knowledge of its etiology and course is of major importance in prevention and treatment. Both light and electron microscopic observations were made of the retina and choroid of human eyeballs enucleated for various reasons in the hope that comparison of the choroid and the retina of eyes that are blind or almost blind would clarify the role played by the choroid in the pathogenesis of retinochoroidal atrophy.

MATERIALS AND METHODS

Case Studies

The eyeballs used in this study were obtained from 9 patients with 6 different diseases:

3 had excessive myopia, 1 had absolute glaucoma, 1 secondary retinochoroidal atrophy, 1 malignant melanoma of the uvea, 2 Behçet's disease and 1 sympathetic ophthalmia.

Case 1 was a 62-year-old woman who had suffered a sudden reduction in visual acuity 2 weeks earlier, after having had a visual defect of the right eye for 3 years. Her visual acuity was reduced to only being able to recognize a hand moving in front of her face. Exophthalmos was 16 mm for the right eye and 10 mm for the left. The intraocular pressure was 7.1 mm Hg. Funduscopy revealed a tigroid retina with a tumor-like mass on the temporal side. There was no observable pattern on the electroretinogram. Enucleation of the eyeball was performed because of the suspected tumor, ocular pains and cosmetic requirements. The eyeball, when cut in half, had pronounced intraocular hemorrhage and marked retinal detachment. The anteroposterior diameter was 31 mm.

Case 2 was a woman aged 64 who had excessive myopia and secondary glaucoma caused by herpetic keratitis of the left eyeball. The intraocular pressure was 75 mm Hg. Enucleation of the eyeball was performed to relieve ocular pains. The eyeball had an anteroposterior diameter of 31 mm and posterior scleral staphyloma. When the eyeball was cut in half, the retina was found to be detached completely.

Case 3 was a 57-year-old man. His left eye had excessive myopia with refraction of more than $-20D$. There was retinochoroidal atrophy of myopic origin in the posterior pole of the eyeball with advanced cataract. The left eye was exotropic and widely affected with filamentous keratitis. Its visual acuity was *sensus luminis*. Enucleation of the eyeball was performed for pain and cosmetic requirements. Posterior scleral staphyloma was present in the eyeball, which had an anteroposterior diameter of 36 mm.

Case 4 was a 51-year-old woman who had suffered an injury 27 years previously, leading to secondary, then absolute, glaucoma of the right eye. This necessitated enucleation of the eyeball. The intraocular pressure preoperatively was 69.3 mm Hg.

Case 5 was a man aged 41 who had a history of orbital periostitis. The patient developed exophthalmos with a visual acuity of zero and retrobulbar fibrosis. Enucleation of the affected eyeball was performed because of pains caused by keratitis, lagophthalmos, and cosmetic requirements.

Case 6 was a 12-year-old girl who underwent enucleation of the right eyeball because of malignant melanoma of the uvea. Her preoperative visual acuity was *sensus luminis*. The tumor was found growing out of the eyeball and proved by light microscopy to be of epithelioid type.

Case 7 was a 33-year-old woman with Behçet's syndrome manifested by uveitis 4 years earlier, then by secondary glaucoma, requiring trephination 3 years later. Enucleation of the affected right eyeball was performed to relieve pain. The visual acuity of the right eye was zero.

Case 8 was a 40-year-old man with Behçet's syndrome of complete form. He had elevated intraocular pressure for 4 years with hypopyon developing 5 months before enucleation of the eyeball.

Case 9 was a 55-year-old woman who had been injured in the left eye by bamboo 1 month earlier, leading to laceration of the sclera and prolapse of the uvea. Enucleation of the injured eye was performed because of the later development of sympathetic ophthalmia. The visual acuity of the left eye was *sensus luminis*.

The enucleated eyeballs were fixed in 2.5 percent glutaraldehyde and sectioned with a razor-blade into small pieces. The pieces were postfixed in 1 percent Osmium tetroxide, dehydrated in graded ethanols and embedded in epon. The thick sections were stained

with azure II, then examined with a light microscope (Venox, Olympus, Tokyo). The thin sections were stained with uranyl acetate followed by lead citrate, then examined with an electron microscope (HS-9, Hitachi Ltd, Tokyo).

RESULTS

Cases in Which the Choroid Underwent Changes

A study was made of the significance of microscopic findings of excessive myopia with posterior scleral staphyloma in Case 1. Light microscopy demonstrated that the retina was devoid of the pigment epithelium through the external nuclear layer and retained the inner layers from the internal nuclear layer. The choroid was thin with vessels present in some regions but completely absent in others (Fig. 1). Electron microscopy indicated that the layers of pigment epithelium and visual cells were completely absent in the retina, having been replaced by Müller's cells. In devascularized areas of the choroid, these layers had undergone fibrotic changes or had been replaced by fibroblasts and collagen fibrils (Fig. 3). Electron microscopy of a vascularized portion of the choroid showed that the vessel was not fenestrated but contained smooth muscle cells, suggesting that it was an arteriole. The vessel was located just beneath the boundary between the retina and the choroid, a site where the choriocapillaries must lie under normal conditions. This suggests disappearance of the choriocapillaries and the possibility of capillaries being obstructed and disappearing earlier than the other choroidal vessels under the conditions of excessive myopia (Fig. 4).

In Case 2 with excessive myopia and posterior scleral staphyloma, there was fibrosis of the choroid and disappearance of choriocapillaries as in Case 1. Bruch's membrane retained its elastic fibers (Fig. 5), but the choroid was markedly thin. In one region near the site of such changes, the fenestration of choriocapillaries was well preserved. This suggests that the choriocapillary obstruction associated with excessive myopia may occur in a lobulated fashion.

In Case 5 with retrobulbar fibrosis, there was light microscopic evidence of retinochoroidal degeneration with secondary retinochoroidal atrophy, a decrease in choriocapillaries, and lymphocytic infiltration. Electron microscopic observation of the site of such changes showed that choriocapillaries were still preserved in some regions, with lymphocyte infiltrates in the adjacent area (Fig. 6). In other choriocapillaries, there were some lipid deposits in the endothelial cells but other fine structures were well preserved. In this case compression of the eyeball from behind was considered responsible for partial obstruction of the choriocapillaries which, in turn, led to serious retinal changes. Some disorder of the retina per se also was probably involved.

In Case 7 (Behçet's syndrome), there was light microscopic evidence of dilatation of choroidal capillaries and veins with infiltration of the choroid by lym-

phocytes, monocytes and plasma cells. Electron microscopy revealed dilatation of choroidal capillaries with the presence of amorphous material suggestive of exudate in the adjacent area, but normal fenestration, endothelial cells and basement membrane. No abnormalities were observed in the fine structure of choroidal arterioles. The layer of pigment epithelium of the retina contained lymphocytes and amorphous substance presumably consisting of exudate. The basement membrane was only continuous to part of the base of the pigmented epithelial cells (Fig. 7). In places, some of these cells were completely detached from the basement membrane. This indicated that lymphocytes and exudate probably of choroidal origin caused serious damage to the retina.

In Case 8 with Behçet's disease there was monocyte infiltration around the choriocapillaries, where an amorphous substance, probably exudate, was also observed. Monocyte infiltration was also present just beneath the basement membrane of the retinal pigment epithelium (Fig. 8). These findings indicate that in Behçet's disease, too, monocyte infiltration of the retinal pigment epithelium occurs, with exudative inflammation spreading from the choroid to the retina. In Case 8, there was perivascular exudative inflammation of the choroid with monocyte infiltrates around the arterioles, but no changes were observed in vascular endothelial or smooth muscle cells or in the basement membrane.

In Case 9 with sympathetic ophthalmia, there were no changes in the retina other than lipid deposits seen in large numbers in pigment epithelial cells. The outer segment of visual cells was well preserved. In the external layer of the choroid, eosinophils, lymphocytes, plasma cells and macrophages were seen along with some epithelioid cells (Fig. 9). The choriocapillaries were normal. Monocytes were present in large numbers in and outside the lumen of the choroidal venules. The choroid was markedly inflamed but the retina was not affected.

Cases in Which the Choroid was Hardly Involved

Observations were made of the posterior pole of the eyeball in Case 3 with excessive myopia. Light microscopic observation showed that visual cells were completely absent in some areas but preserved in others. The choroid was thin and atrophied but still vascularized (Fig. 2). Electron microscopy demonstrated dilatation of choriocapillaries with distinct fenestration, features which were seen irrespective of the presence or absence of visual cells. More extensive studies are needed. Such capillary dilatation may be compensatory in nature (Fig. 10).

In Case 4 with absolute glaucoma there was light microscopic evidence of the visual cells having disappeared, with the retina undergoing severe degeneration and the choriocapillaries being well preserved. Electron microscopically, Bruch's membrane was seen to have undergone changes due to aging but the choriocapillaries remained normal. No changes were observed in fenestration, the basement membrane or endothelial cells, or in the arterioles (Fig. 11). These findings indicate that the fine structure of choriocapillaries was kept intact despite elevated intraocular pressure. It is hence suggested that retinal atrophy

in this case was not secondary to the changes in the choroid.

In Case 6 with malignant melanoma of the uvea there were marked deposits of melanin in the retinal pigment epithelium with dilatation of choroidal veins, as demonstrated by light microscopic observation of the boundary between involved and noninvolved areas. Electron microscopy showed that the choriocapillaries remained normal with hemorrhage seen at places in the adjacent region (Fig. 12). Arterioles in the proximity of the tumor were normal, indicating that the fine structure of choroidal vessels there was well preserved.

DISCUSSION

A list of disease entities or conditions presenting with retinochoroidal atrophy or degeneration is given in pertinent books (1, 2). Retinochoroidal atrophy associated with excessive myopia, circulatory disturbances, inflammation, trauma, glaucoma or angioid streaks of the retina is often encountered in routine practice and unfortunately frequently results in blindness because of resultant irreversible visual defects. The mechanism of pathogenesis and development of the condition has yet to be elucidated. The close relationship, both anatomic and physiologic, of the pigment epithelium of the retina, Bruch's membrane and the choroid, which is implicated in the condition as well, led us to make an electron microscopic pathologic study of eyeballs affected by retinochoroidal atrophy of different origins.

Comparison of three cases of excessive myopia presenting with scleral staphyloma showed that pronounced choriocapillary obstruction was accompanied by more serious degeneration of the retina. This indicated that choriocapillary obstruction was involved in the retinal atrophy associated with excessive myopia. In this connection, Chonan (3) reported light microscopic studies which showed that retinochoroidal atrophy of myopic form originated in the choriocapillaris, that changes in the retina were secondary to changes in the choroid, and that choroidal atrophy of the myopic eye was a major factor in the elongation of the ocular axis.

Secondary retinochoroidal atrophy due to retrobulbar fibrosis may be attributed to partial obstruction of the choriocapillaries subjected to pressure from behind, which, in turn, can lend to the development of severe degeneration of the retina. In addition, some disorder of the retina per se may be involved. Of interest in this connection is the fact that the fine structure of choroidal vessels was well preserved in absolute glaucoma in which abnormal pressure is exerted on the eyeball from inside in the form of elevated intraocular pressure. Hayashi (4) stated that in glaucoma the retina presents marked sclerotic changes in vessels whereas the choroid does not, being generally atrophied. In glaucomatous eyes, Uchizono (5) observed a gradual decrease of capillaries in the choroid in contrast to changes such as degeneration of nerve fibers and gangli-

onic cells and obstruction of capillaries seen in the retina even early in the course of the disease. It is difficult to identify the particular site where a mechanical agent such as pressure causes damage and to determine whether the nerve or the vessel is damaged first. In explaining the difference between the retinochoroidal lesions of secondary retinochoroidal atrophy and absolute glaucoma, consideration should be given not only to differences in the direction of pressure being exerted but also the differences in the location or mode of the ensuing circulatory disturbance. In glaucoma, the circulatory disturbance is in the optic disk or retinal vessels in contrast to the posterior ciliary arteries and pressure on the wall of the eyeball in secondary retinochoroidal atrophy.

In malignant melanoma of the uvea, the fine structure of choroidal capillaries and arterioles in the vicinity of the tumor was well preserved. Whether this was due to choroidal vessels not being readily injured or to the necessity of maintaining blood supply to the tumor remains to be investigated.

In Behçet's disease, there was an amorphous substance, probably representing exudate, in the choroid along with perivascular cellular infiltration. Infiltration by lymphocytes and monocytes (probably of choroidal origin), together with exudation, resulted in serious damage or detachment of the retina. This showed that exudative inflammation originating in the choroid will extend to the retina. On the other hand, the fine structure of choroidal capillaries, although dilated, remained normal, that of arterioles. Sugiura *et al.* (6) stated that the incipient intraocular lesions of Behçet's disease may be summed up as degeneration and disappearance of capillaries, including changes in choriocapillaries. In advanced stages of the disease, the venular and arteriolar walls become involved in the retina but hardly ever in the choroid for unknown reasons.

In sympathetic ophthalmia, there was marked inflammation of the choroid but no morphological changes in the choriocapillaris, Bruch's membrane or pigment epithelium of the retina; features which correspond to those reported by previous investigators (7). The difference between the retinal lesion of Behçet's syndrome and that of sympathetic ophthalmia may be explained by differences in the stage of disease when enucleation of the eyeball is performed. More importantly, Behçet's disease represents chronic nonspecific inflammation involving the uvea and retina whereas sympathetic ophthalmia is specific inflammation which arises in melanocyte-containing areas of the eyes, skin, meninges or internal ear derived from the neural crest and which centers around the melanocyte (8, 9). It is only natural, therefore, that retinochoroidal lesions proceed in different ways in these two conditions.

Our present study showed that in retinochoroidal atrophy, whether inflammatory or non-inflammatory in nature and which occurs as the ultimate result of various diseases, degeneration of the retina may sometimes be present in the absence of damage to choroidal capillaries. It is invariably present whenever disturbances of choroidal vessels has occurred, particularly when the capillaries

are obstructed, absent or excessively permeable. It has been shown in laboratory studies that circulatory disturbances in the choroid give rise to changes in the pigment epithelium of the retina (10). Diseases of the retina due to impairment of the blood-retinal barrier have also been recognized clinically. It is therefore important in the prevention of retinochoroidal atrophy to keep choroidal circulation as intact as possible.

With the intention of elucidating the process of obstruction and disappearance of choroidal vessels as well as the physiology of normal choroidal circulation, further study is under contemplation concerning circulation disturbances of the choroid including those vascular lesions so far reported which are associated with the retinopathy of hypertension (4, 11, 12) or diabetes mellitus (13, 14).

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EXPLANATION OF FIGURES

- Figs. 1-2 Light micrographs of the retina and the choroid.
- Fig. 1 Case 1 : excessive myopia. The retinochoroid of posterior scleral staphyloma. The choroid has become thin. The arrows show choroidal vessels. R : retina.
- Fig. 2 Case 3 : excessive myopia. The retinochoroid of the posterior pole area. The visual cells are well preserved in some parts (thick arrow) but they disappeared in other parts (thin arrow).
- Figs. 3-12 Electron micrographs of the retina and the choroid. The bar in each figure represents 1 μ .
- Fig. 3 Case 1 : excessive myopia. Fibroblasts (F) and collagen fibrils (cf) have increased where choroidal vessels have disappeared. BM : basement membrane, M : Müller's cell \times 4,500
- Fig. 4 Case 1 : excessive myopia. A choroidal arteriole is seen near the retinochoroidal boundary area where the choriocapillaries is normally present. Choriocapillaries have disappeared. Increase of collagen fibrils (cf) is seen around the arterioles. BM : basement membrane, S : smooth muscle cell \times 6,000
- Fig. 5 Case 2 : excessive myopia. The choroidal vessels have disappeared and fibrosis is seen. F : fibroblast, PE : pigment epithelium. \times 5,700
- Fig. 6 Case 5 : secondary retinochoroidal atrophy induced by retrobulbar fibrosis. The choriocapillaries (cc) are still partially present and infiltration of lymphocytes (L) is seen. PE : pigment epithelium \times 1,600
- Fig. 7 Case 7 : Behçet's disease : Lymphocytes (L) and amorphous substance (A) are seen in the pigment epithelial layer (PE) and the basal portion of the pigment epithelium is partially in contact with the basement membrane (BM). \times 5,100
- Fig. 8 Case 8 : Behçet's disease. Monocytes (Mo) are seen under the basement membrane (BM) of the pigment epithelium. cc : choriocapillary, A : amorphous substance \times 4,800
- Fig. 9 Case 9 : sympathetic ophthalmia. The choriocapillaries (cc) are normal, though cellular infiltration is marked. PE : pigment epithelium, E : eosinophils. \times 1,600
- Fig. 10 Case 3 : excessive myopia. The choriocapillaries (cc) are dilated. BM : basement membrane. \times 4,800
- Fig. 11 Case 4 : absolute glaucoma. No changes are recognized in the choriocapillaries (cc), the fenestration (arrows) or the basement membrane (BM). cf : collagen fibril. \times 4,800
- Fig. 12 Case 6 : uveal malignant melanoma. Many melanin granules (mg) are seen in the pigment epithelium (PE). The choriocapillaries (cc) are normal. Arrows show fenestration. BM : basement membrane. R : blood red cell. \times 4,800





