

Iris neovascularisation in eyes with pseudoexfoliation syndrome

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SUMMARY The iris vascular bed of eyes with pseudoexfoliation syndrome has been studied with electron microscopy. Two of the eyes suffered from painful glaucoma, whereas the third showed normal intraocular pressure. The following changes were observed: (1) deposits of pseudoexfoliation material lying adjacent to the endothelial wall; (2) thin vessel basement membrane, sometimes even interrupted; (3) extreme reduction of vessel lumina through increased volume of the endothelial cells; (4) fenestration of the endothelial wall. It is suggested that the iris neovascularisation in eyes with pseudoexfoliation syndrome is due to an obstruction of iris vessels causing tissue hypoxia.

The pseudoexfoliation syndrome (PE syndrome) is characterised mainly by the presence of specific pathological material in the eye. Deposits of such material are found on the anterior lens surface, on the posterior and the anterior iris surface, on the ciliary processes, on the zonules, and the anterior hyaloid membrane. PE material is also seen adjacent to iris vessels, in the trabecular meshwork, and in the conjunctival connective tissue.¹

However, other lesions are also present in such eyes. Fluorescein angiography has shown that neovascularisation of the iris stroma may be considered as part of the syndrome. The endothelium in normal iris vessels is of the nonfenestrated type, with cells connected through tight junctions.² Consequently they do not usually leak fluorescein except at the pupil margin, particularly in elderly people.³ In contrast to this, the iris vessels of eyes with PE syndrome are leaky, as shown by increased permeability of fluorescein in the anterior eye segment⁴ and more specifically by the abnormal passage of fluorescein through the vessel wall.³ The increased permeability of the iris vessels is probably the cause of the abnormal aqueous humour in such eyes.⁵

The neovascularisation of the iris and its leaky vessels has been previously studied by fluorescein angiography and light microscopy. The purpose of the present work was to see if a more detailed morphological examination of the abnormal vascular bed could elucidate the pathophysiology of the iris in this syndrome.

Material and methods

This study was based on electron microscopy of 3 different eyes, all showing by slit-lamp examination PE material along the pupillary margin and on the anterior lens surface. Two eyes were enucleated because of painful glaucoma (70- and 74-year-old men). These eyes showed moderate ciliary injection, partly closed anterior chamber angle, some aqueous flare, cataract, light perception over some few metres, and increased intraocular pressure (IOP). Both had been treated with pilocarpine and epinephrine eye drops in recent years. The third eye was removed because of a malignant choroidal melanoma in the macular region with gradual loss of vision (71-year-old woman). Apart from the intrabulbar tumour and the presence of PE material this eye appeared normal in all respects, including the IOP.

Immediately after enucleation the bulbi were opened along the equator, and the anterior segments were fixed for 1–2 h in 1% OsO₄ adjusted to pH 7.2 with phosphate buffer. Tissue blocks were dissected from the central, intermediate, and peripheral parts of the iris, dehydrated in graded acetone solutions, and embedded in Araldite. Sections were made with an LKB Ultratome, stained with aqueous solutions of uranyl acetate followed by lead citrate, and examined in Siemens Elmiskop 1A and Philips EM 400 instruments.

Results

The iris vessels showed striking changes in all 3 eyes as an extreme narrowing of the vessel lumen,

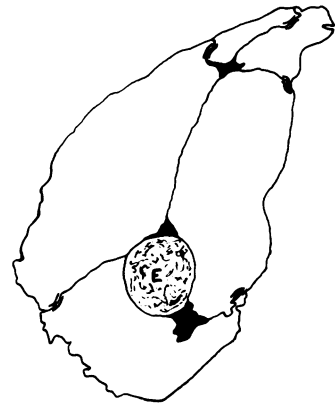
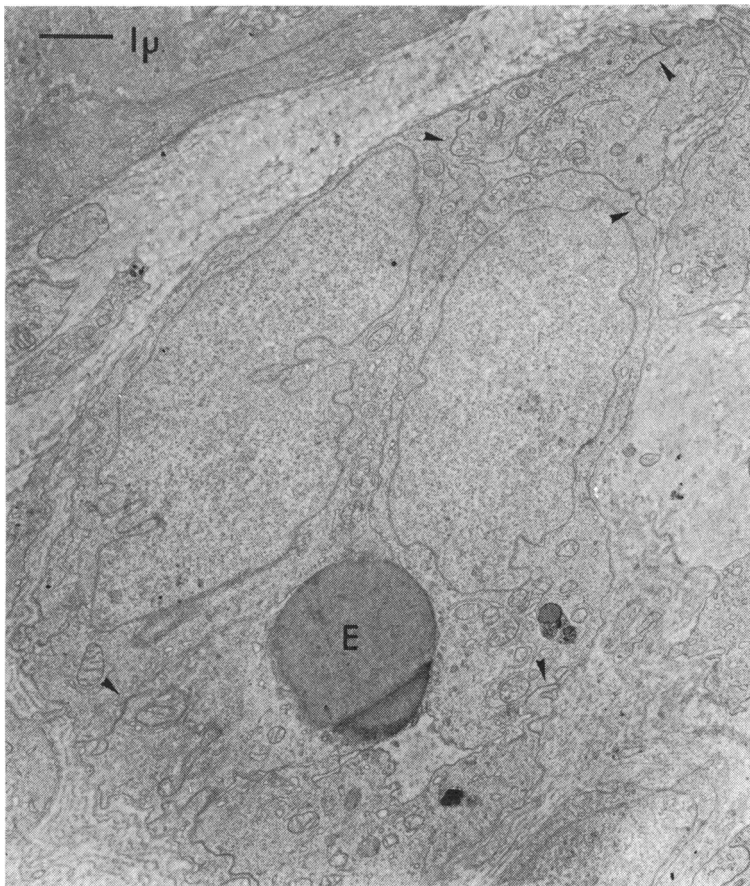


Fig. 1 *Electron micrograph of iris vessel with a narrow lumen marked black in the drawing. Intercellular junctions are shown with arrows and tripled lines, respectively. E = erythrocyte.*

caused by a large increase in volume of the endothelial wall (Fig. 1). The lumen was frequently reduced to a slit less than 100 nm across. In such cases the structures were identified as true vessels by the surrounding basement membrane and by tight junctions being present between neighbouring endothelial cells. In some instances an erythrocyte or a few thrombocytes could be found indicating the lumen.

Both capillaries and larger vessels were involved in this kind of pathological change. However, no distinction between arterioles and venules could be made in this material. All eyes showed in addition to normal appearing vessels some that were in different stages of pathological alteration.

The increase in volume of the endothelial cells seemed to involve both the cytoplasm and the nuclei. The usual cytoplasmic components were present, no abnormal content of the cells could be found, and no irregularities were observed at the intercellular junctions. The abnormal endothelial cells had no crypts filled with PE material such as

have been described for iris pigment epithelial cells,⁶ though such material was sometimes found close to the endothelial wall.

In accordance with a previous description⁷ the endothelial basement membrane was rather thin, in some places even broken up into crumpled, interrupted bands forming an irregular, multilayered structure, partly intermingled with PE material (Fig. 2).

The 2 eyes enucleated because of severe glaucoma had iris vessels with fenestrated endothelium (Fig. 3). The fenestrae were roughly 60–80 nm in diameter, and they were closed by a diaphragm. The fenestrated vessels were lined by a continuous, thin basement membrane towards the surrounding tissue. Such vessels were not observed in the third, non-glaucomatous eye.

Discussion

Under the electron microscope the iris vessels showed 4 different pathological changes in eyes with

Fig. 2 Electron micrograph of capillary surrounded by an abnormal basement membrane showing a spongy structure (curved arrows). Intercellular junctions between endothelial cells are marked with arrows. L = vessel lumen.



PE syndrome. (1) Deposits of PE material are found adjacent to the endothelial cells and the endothelial basement membrane. (2) The endothelial basement membrane may be thin and may be broken up into crumpled, interrupted bands forming an irregular multilayered structure. (3) The lumina of the vessels may be reduced to a narrow slit because of a large increase in volume of the vessel endothelium. (4) In some eyes with PE syndrome the endothelial cells are fenestrated. This phenomenon may be restricted to vessels formed by neovascularisation.

It is apparent from angiography that 2 processes are occurring in iris vessels in eyes with PE syndrome; firstly, a reduction of the number of radial vessels, and, secondly, the formation of new vessels. According to Vannas,³ however, it is impossible to decide from such studies which of the changes developed first. Since both of them are frequently encountered in normotensive eyes with PE syndrome,³ they are obviously not caused by the increased IOP.

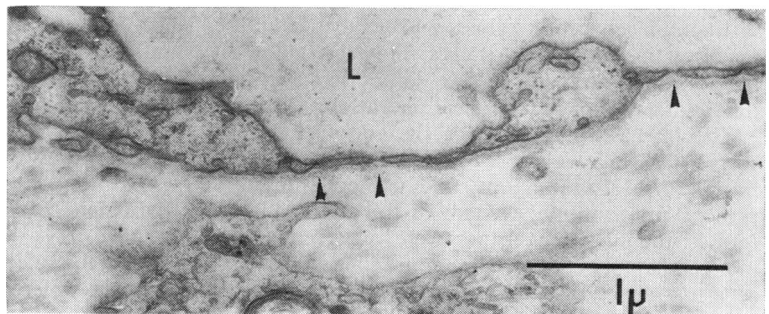
It seems reasonable to suggest that the angiographic finding of a reduced number of radial vessels reflects the morphological narrowing of vessel lumina, which was first described in light microscopic sections,⁸ According to the present

study the narrowing of the vessel lumina is not due to thrombosis or other obstruction through deposits of extracellular material, but it is brought about through an increase in volume of the endothelial cells themselves.

As to the second phenomenon, it is seen that the leakage of fluorescein is mainly localised to the regions with neovascularisation.³ In general, increased vascular permeability is attributable to gaps in the interendothelial junctions⁹⁻¹³ or to endothelial fenestration. The present work indicates that the leakage of iris vessels in the PE syndrome is due to the latter cause. This is obviously a common mode of vascular reaction when the iris vessels are stimulated to neovascularisation.^{14 15}

New vessel formation of the iris occurs in many different pathological conditions.^{16 17} In most cases the neovascularisation is caused by diseases elsewhere in the eye rather than by a local process in the iris itself.¹⁸ Consequently iris rubeosis is frequently the result of occlusive vascular disease of the posterior segment of the eye, and it may be that the resulting hypoxia may lead to the formation of vasoproliferative factors which reach forwards to the iris by diffusion.¹⁹ The present work shows that in eyes with PE syndrome the lumen of some

Fig. 3 Electron micrograph of capillary endothelium with fenestrae (arrows). Note continuous, tenuous basement membrane outside the cell wall. L = vessel lumen.



iris vessels is transformed into a narrow slit. Probably this transformation leads to reduced blood flow and hypoxia, which would indicate that in the PE syndrome the iris neovascularisation is due to vascular changes in the iris itself.

As judged by fluorescein angiographic studies, the blood flow through the posterior ciliary circulation is also impeded in cases of capsular glaucoma, and the peripapillary underfilling of the vessels is more pronounced in advanced stages of glaucoma. Furthermore, irregularities of the perilimbal vascular pattern are rather common.²⁰ It seems, therefore, that the obstructive vascular process in such eyes may affect very different regions simultaneously. Whether or how this process is linked to the abnormal synthesis of extracellular components (PE material and basement membranes) remains to be clarified.

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