Decreased choroidal thickness in eyes with secondary angle closure glaucoma

An aetiological factor for deep retinal changes in glaucoma?

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Abstract
A decreased count of retinal photoreceptors all over the fundus and a loss of retinal pigment epithelium cells mainly in the parapapillary region have been reported to be associated with glaucoma. This study addressed the question whether this cell loss in the deep retinal layers may be connected with a change of the choroidal thickness in glaucomatous eyes. Histological sections of 12 eyes with secondary angle closure glaucoma due to a malignant melanoma of the ciliary body and 20 eyes with a malignant choroidal melanoma and normal intraocular pressure were histomorphometrically evaluated. Before enucleation the intraocular pressure was significantly higher in the glaucoma group compared with the control group. Thickness of the choroid was measured at 12 locations from the posterior pole to the fundus periphery. The choroid was significantly thinner in the glaucoma group than in the control group. The decreased choroidal thickness was mainly due to a diminished choroidal vessel diameter. The differences were more marked at the optic disc border than in the fundus periphery. The decreased choroidal thickness in the glaucomatous eyes suggests a reduced choroidal perfusion. It fits with the reported lack of autoregulation of the choroidal blood circulation. Considering the diminished choroidal thickness especially in the parapapillary region, it may be one among other factors explaining the changes of the deep retinal layers in eyes with glaucoma. It indicates that thinning of the choroid, besides the chorioretinal atrophy in the parapapillary region, should be added to the panoply of histological changes in glaucoma.
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Since the first descriptions of parapapillary chorioretinal atrophy to Elschnig et al[1-3] reports are accumulating in number emphasising the correlation between atrophic changes in the intrapapillary region and those in the deep retinal layers in the parapapillary area of glaucomatous eyes.[4-8] Some authors divided ophthalmoscopically the parapapillary chorioretinal atrophy into two zones: a peripheral zone α with irregular pigmentation and a central zone β close to the optic disc border ·with sclera and large choroidal vessels visible upon ophthalmoscopy.[9] Histologically, zone α correlated with an unequal distribution of melanin granules and partial atrophy of the retinal pigment epithelium (RPE) cells.[10] In zone β Bruch's membrane was bared of RPE cells and the photoreceptors were markedly reduced in density or were completely missing (Fig 1).[10] Besides these changes in the vicinity of the optic disc, several investigators have reported a decreased count of retinal photoreceptors for areas all over the fundus in eyes with secondary angle closure glaucoma.[11-13] Extrapolating these findings for eyes with primary open angle

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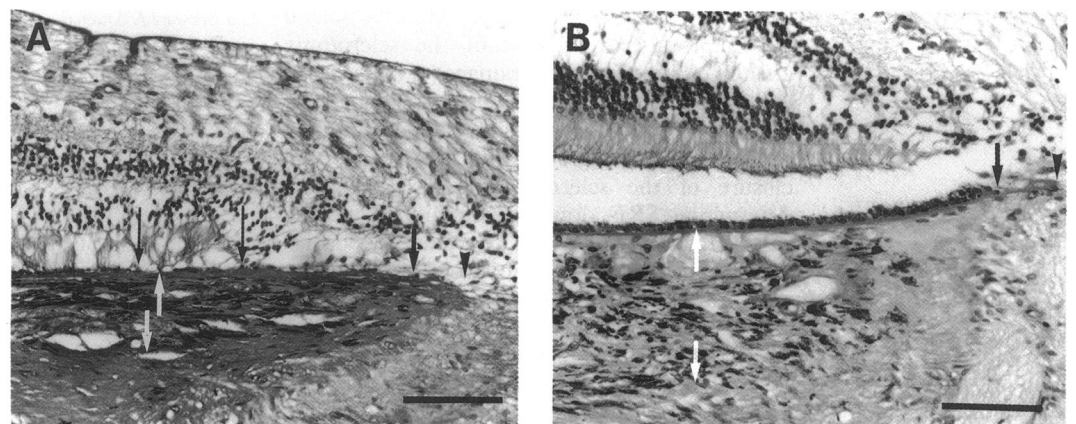Erlangen, Germany.

Figure 1   Histological section through the parapapillary area of an eye with a malignant melanoma in the ciliary body and secondary angle closure glaucoma (A) and an eye with choroidal malignant melanoma and normal intraocular pressure (B). Long thin black arrows: zone α characterised by irregularities in the retinal pigment epithelium (RPE); area between long thin black arrow and short thick black arrow: zone β showing complete loss of RPE cells and incomplete loss of photoreceptors; area between short thick black arrow and black arrowhead: peripapillary scleral ring. The choroidal thickness of the parapapillary area (white arrows) is thinner in the glaucomatous eye than in the non-glaucomatous eye. The photoreceptors are artificially detached from the RPE in B. Bar=100 µm.

Table 1   Choroidal thickness (mean and (SD)) in eyes with malignant ciliary body melanoma and secondary angle closure glaucoma compared with eyes with choroidal melanoma and normal intraocular pressure; p value: significance of difference between the two groups

Temporal side distance (mm) (from the optic disc)	Glaucoma (μm) Mean (SD)	Non-glaucoma (μm) Mean (SD)	p Value	Nasal side distance (mm) (from the optic disc)	Glaucoma (μm) Mean (SD)	Non-glaucoma (μm) Mean (SD)	p Value
0·2	56 (28)	117 (30)	<0·005	0·2	72 (35)	128 (38)	<0·01
0·4	67 (22)	123 (39)	<0·01	0·4	76 (30)	113 (34)	<0·05
0·6	57 (18)	96 (27)	<0·01	0·6	68 (25)	106 (27)	<0·01
0·8	51 (12)	91 (31)	<0·05	0·8	64 (24)	96 (25)	<0·05
1·0	51 (15)	93 (28)	<0·005	1·0	62 (23)	86 (22)	<0·05
1·5	51 (18)	103 (29)	>0·005	1·5	59 (26)	95 (25)	<0·01
2·0	65 (20)	116 (42)	<0·01	2·0	66 (39)	101 (28)	<0·05
3·0	78 (25)	126 (47)	<0·05	3·0	70 (27)	95 (44)	ns
5·0	83 (33)	111 (45)	ns	5·0	62 (24)	95 (28)	<0·05
7·0	91 (31)	100 (40)	ns	7·0	61 (22)	86 (22)	<0·05
9·0	81 (29)	93 (47)	ns	9·0	57 (22)	76 (22)	ns
11·0	81 (20)	79 (34)	ns	11·0	56 (36)	53 (25)	ns

Figure 2   Choroidal thickness in eyes with secondary angle closure glaucoma caused by a malignant melanoma of the ciliary body (□, mean) compared with non-glaucomatous eyes with a malignant choroidal melanoma (×, mean). Mean (SD) is indicated by symbols (lines). The letters indicate the significance between the two groups (a: p<0·005; b: p<0·01; c<0·05; d: not significant; Mann-Whitney test). A: temporal side; B: nasal side.

Distance from the optic disc (mm)

glaucoma, one might assume that some psychophysical defects in glaucoma such as the acquired blue colour deficiency may be caused not, or not only, by a loss of retinal nerve fibres but also by damage to the retinal photoreceptors.

This study was performed to address the question as to whether the glaucomatous alterations in the deep retinal layers and in the RPE are associated with a change in the choroidal thickness. Assuming a correlation between choroidal thickness and choroidal blood flow, it may point towards a pathogenetic role of an altered choroidal perfusion.

Materials and methods
Thirty two eyes enucleated because of a malignant uveal melanoma were included in the study.

In 12 eyes of 12 patients (eight men, four women; mean age 56·3 (SD 20·2); range 10–81 years) the tumour was located in the ciliary body. By blockage of the trabecular meshwork, it had caused a secondary angle closure glaucoma with increased intraocular pressure ranging between 24 and 60 mm Hg.

A second group was composed of 20 enucleated eyes (from 11 men, nine women; age 59·1 (SD 12·3); range 37–77 years) in which the malignant melanoma was located in the choroid without involvement of the trabecular meshwork. The intraocular pressure was less than 22 mm Hg.

Preoperatively all eyes of both groups had received a mean daily radiation of 4 Gy for 5 days preceding the enucleation. Eyes with an axial length exceeding 26·0 mm had been excluded. The intraocular pressure was significantly higher in the glaucoma group (38·3 (SD 14·0) mm Hg) compared with the control group (13·9 (SD 2·3) mm Hg) (p<0·0001). Both groups did not vary significantly in age (p=0·86), side (p=0·52), gender (p=0·59), horizontal globe diameter (p=0·12), vertical globe diameter (p=0·30), and axial length (p=0·70).
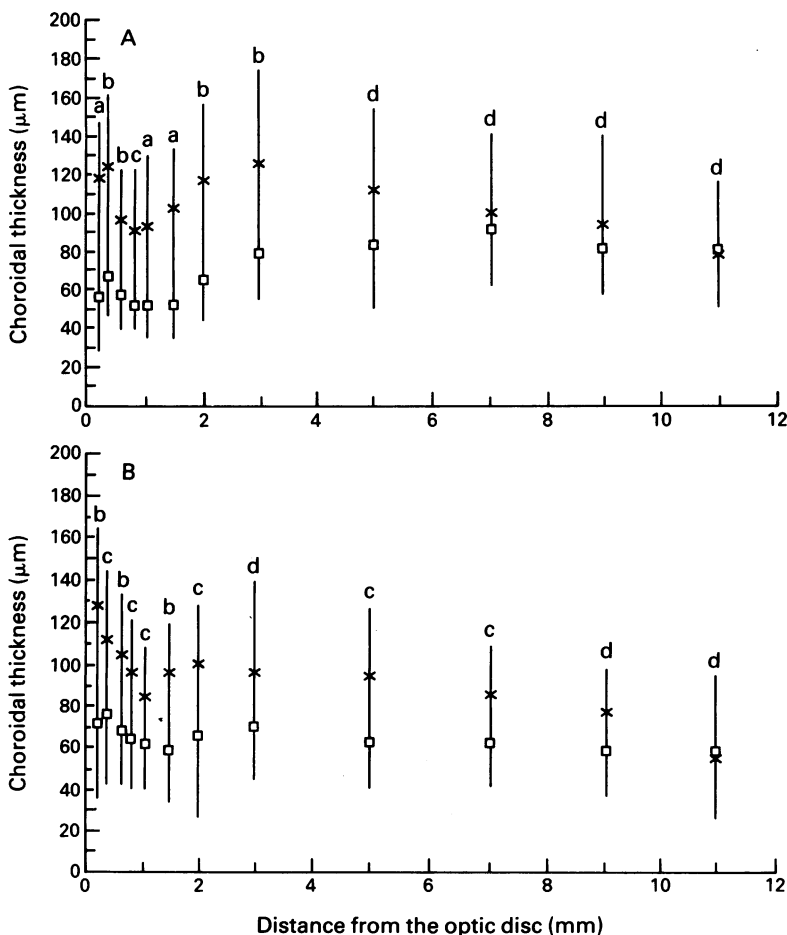
All globes were fixed immediately after enucleation in a solution of 4% formaldehyde/1% glutaraldehyde. Histological sections stained by periodic acid Schiff method and 8 μm in thickness were prepared through the optic disc and pupil. The histological slide going closest through the optic disc centre was selected for evaluation. The meridional orientation of the sections did not differ significantly between the two groups. The thickness of the choroid was measured at 12 locations from the posterior pole to the periphery. To avoid a possible hyperaemic effect by the choroid tumours with secondary choroidal swelling, only the contralateral side to the tumours was evaluated.

To test the significance of differences, the Wilcoxon and Mann-Whitney tests were used.

Results
The choroid was significantly thinner in the glaucoma group compared with the control group. The differences were more marked close to the optic disc border than in the fundus periphery (Table 1, Fig 2). The width of zones α and β as defined histologically[10] (Fig 1) was 0·28 (SD 0·08) mm in the glaucomatous eyes and 0·25 (SD 0·10) mm in the control eyes. Probably

because of the relatively small number of eyes examined, the difference was not significant on the 5% level of error of probability.

Discussion

This histomorphometric study revealed a decreased choroidal thickness in glaucomatous eyes with increased intraocular pressure compared with non-glaucomatous eyes. It confirms a histological investigation of Francois who reported that the choroidal thickness in autopsy eyes with absolute glaucoma was extremely reduced.[14] It contradicts another study in which the choroid measured by radio-frequency signals was 20% thicker in glaucomatous eyes than in normal eyes.[15]

In spite of the statistical significance of its findings there are factors limiting the present study. It included eyes with secondary angle closure glaucoma. This is a special form of glaucoma. Compared with primary open angle glaucoma, it is characterised by a secondary elevation of intraocular pressure, higher intraocular pressure readings, a shorter passage of time until complete optic nerve atrophy occurs, and often unilaterality. It can be considered to be one extreme of the disease process in glaucoma, ranging from eyes with marked elevated intraocular pressure to eyes with so called normal pressure glaucoma. Although representing only a small fraction of all glaucoma eyes, baro-traumatically induced changes observed in eyes with secondary angle closure glaucoma may also occur in eyes with primary open angle glaucoma. Evaluation of secondary angle closure glaucoma may thus offer hints with regard to primary open angle glaucoma. It cannot be excluded with certainty that a possible tumour induced hyperaemia with secondary swelling of the choroid was more marked in the non-glaucomatous eyes than in the glaucomatous ones. To avoid this possible effect of the tumour, we evaluated only the side contralateral to the malignancy. The preoperative radiation was performed for all eyes of both groups. Assuming that the effect of the radiation on the choroid was the same in the glaucomatous and non-glaucomatous group, it may not have affected the significant differences in choroidal thickness between the two groups.

The decreased choroidal thickness was caused by a diminished diameter of the choroidal vessels. Owing to the light microscopic technique it cannot conclusively be determined whether additional changes of the connective tissue were present. The association between decreased choroidal thickness and diminished choroidal vessel diameter suggests a reduced choroidal blood circulation in glaucoma. The choroidal thickness was reduced most markedly in the parapapillary region compared with other fundus areas. It may indicate that the choroidal blood flow too is most affected in the region close to the optic disc border. It fits with the results of experimental studies.[16][19] They demonstrated that the choroid is not fully able to adjust blood flow in conditions with varying intraocular pressure. In laboratory animals with artificially elevated intraocular pressure, the choroidal filling defects were most marked in the parapapillary region compared with other fundus areas. These findings favour the possibility that an impairment of parapapillary choroidal blood circulation may be one among other factors leading to parapapillary chorioretinal atrophy in glaucomatous eyes. It is in agreement with the histology of zones α and β (Fig 1).[10] The hypothesis of an impaired choroidal blood perfusion in glaucoma could also explain recent observations that eyes with secondary angle closure glaucoma might have a decreased thickness of RPE cells[20] and a diffusely diminished count of retinal photoreceptors all over the fundus.[11–13]

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