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Iris transillumination defects in patients with primary open angle glaucoma

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PURPOSE. *To examine the incidence and pattern of iris transillumination defects in patients with primary open angle glaucoma (POAG) with and without vascular dysregulation, in comparison to controls.*

METHODS. *We prospectively examined 24 patients with POAG (M/F 10:14; mean age 59 ± 14, range 21-76 years) and 23 controls (M/F 10:13; mean age 52 ± 15, range 25-86 years). Vascular dysregulation was presumed if patients had a typical medical history of vasospasm and a pathological result in nailfold capillaroscopy. Iris transillumination defects were visualized by video-taped, digitized diaphanoscopy and assessed by two blinded observers.*

RESULTS. *We found significantly more iris transillumination defects in POAG than in controls (54.2% vs. 8.7%; $\chi^2 = 8.85$; df = 1; p = 0.002). The defects in POAG showed a characteristic radially-streaked pattern different from those described, for instance, in pigment dispersion syndrome, pseudoexfoliation syndrome, and acute glaucoma. Glaucoma patients with vascular dysregulation had a tendency to a higher incidence of transillumination defects than non-vasospastic patients, though this finding was not significant.*

CONCLUSIONS. *Patients with POAG have a higher incidence of iris transillumination defects than controls. The underlying mechanisms are not yet clear and call for further investigation. (Eur J Ophthalmol 2003; 13: 365-9)*

KEY WORDS. *Iris transillumination defects, Primary open angle glaucoma, Vascular dysregulation, Diaphanoscopy*

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INTRODUCTION

Besides elevated intraocular pressure (IOP), an additional risk factor for glaucomatous optic neuropathy appears to be hemodynamic insufficiency, which is mainly due to vascular dysregulation and systemic hypotension (1, 2). Both risk factors lead to low perfusion pressure in the eye and therefore predispose the optic nerve head to ischemia and reperfusion damage (3, 4).

Pathological alterations of various other tissues, like glaucomatous parapapillary atrophy (5) and alterations of the choroidal vasculature (6), as well as nerve fiber layer hemorrhages and microaneurysms (7), have been described in glaucoma. However, little is known about the effects of vascular dysregulation or elevated IOP on iris tissue in patients with POAG. Therefore we examined the incidence and pattern of iris transillumination defects in patients with POAG with and without vascular dysregulation, in comparison to controls. Subjects with pigment dispersion syndrome or pseudoexfoliation (PEX) syndrome were carefully excluded. Vascular dysregulation was presumed if the patients presented a typical medical history of vasospasm and a pathological result in nailfold capillaroscopy. Iris transillumination defects were visualized by video-taped, digitized diaphanoscopy and assessed by two blinded observers.

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METHODS

Study population

A group of 24 patients with POAG with and without vascular dysregulation (M/F 10:14) and 23 healthy controls (M/F 10:13) were consecutively recruited at the University Eye Clinic Basel, Switzerland. Vascular dysregulation was defined as a combination of: a) medical history of cold hands and/or feet, and optionally, a tendency to low blood pressure, Raynaud's phenomenon, migraine, and tinnitus, and b) a pathological result in the local cold exposure test in nailfold capillaroscopy (as described below).

The controls were companions of our patients, hospital staff not involved in research, and patients who presented refraction problems.

A detailed medical history was taken, and all participants underwent a complete ophthalmological examination including best-corrected visual acuity, slit-lamp biomicroscopy, gonioscopy, and Goldmann applanation tonometry. Subjects with diseases known to influence iris pigmentation (e.g. pigment dispersion syndrome, PEX syndrome, melanocytic disorders, diabetes mellitus) and any who had already undergone eye surgery (e.g. cataract surgery) were excluded. All participants gave written informed consent for all procedures. The protocol was approved by the Ethical Committee of the University Hospital Basel, Switzerland, and followed the tenets of the Declaration of Helsinki.

Nailfold capillaroscopy - local cold exposure test

Nailfold capillaries were studied using an incident-light microscope attached to a television monitor. Technical details have been described extensively elsewhere (8). For each subject one finger was randomly chosen for evaluation. The examination was conducted in a room with a constant temperature of 23°C. Subjects were acclimatized in the room for 30 minutes before testing. After measuring baseline blood-cell velocity (V1), the subject's hands were warmed in a 40°C water-bath for three minutes, then the second reading (V2) was taken, after which cold CO_2 (temperature approximately -15°C) was directed to the fingertip for 60s. Immediately afterwards, the third measurement (V3) was taken. If the cold induced a flow stop, the duration of blood standstill was measured by a video timer, by averaging the standstill time in seconds of all the capillaries visible in a given microscopic field. In accordance with previous protocols (9, 10), persons with a blood-flow standstill of at least 12 seconds in one or more capillaries were defined as vasospastic.

Iris diaphanoscopy

Iris transillumination defects were visualized using a diaphanoscope consisting of a light source, a fiberoptic and a light probe. After local anesthesia with a drop of proxymetacaine (Alcaine®, Alcon Pharmaceuticals Ltd., Switzerland) subjects were placed in front of a slit lamp, and the light probe was pointed against the temporal conjunctiva (10 mm from the corneal limbus). Picture sequences of 2 min each were recorded by a red-sensitive black-and-white CCD-camera (800 x 600 pixels, 1/4 inch target) attached to the slit lamp, and stored on a Digital Versatile Disk (DVD).

Video sequences were assessed by two experienced ophthalmologists in a masked fashion. Transillumination defects were analyzed as regards area and pattern. In case of disagreement, consent was achieved by discussion.

Statistical analysis

Statistical analysis was done using the statistical package StatView 4.5 (Abacus Concepts, Berkley, CA). The chi-square statistic (2x2 table, contingency table) was used for frequency comparisons (nominal categorized variables). Significances were calculated using Fisher's exact test. Data were expressed as mean ± standard deviation and statistical significance was set at $p<0.05$.

RESULTS

Population characteristics

Patients' mean age did not differ significantly (59 ± 14, range 21-76 years) from controls (52 ± 15, range 25-86 years) ($p = 0.07$). Of the 24 patients with POAG, 17 had vascular dysregulation, compared to none of

the controls. Five patients were under treatment with topical beta-blockers, five with local carbonic anhydrase inhibitors (CAI), six with prostaglandin analogs, and two with alpha-1 agonists.

Iris diaphanoscopy

In comparison to controls, patients with POAG had significantly more iris transillumination defects (54.2% vs. 8.7%; $\chi^2 = 8.85$; df = 1; p = 0.002). Defects in the POAG group showed a characteristic, radially-streaked pattern involving the whole iris, more distinctive in the periphery than in the pupillary border. In ten of the 13 cases the defects were circular, in one case defects could only be found in one quadrant of the iris, and in two cases only in the periphery. Interestingly, the incidence of transillumination defects was even higher in patients with vascular dysregulation (58.8% vs. 42.9%), though this finding did not reach statistical significance.

As brown and green irises contain melanin which can mask defects of the adjacent pigment epithelium layer, we also considered iris colors singly: blue irises were more frequent in the POAG group (n=16) than controls (n=8) ($\chi^2 = 4.78$; df = 1; p =0.04). Interestingly, iris transillumination defects were found in 68.8% of the glaucoma patients with blue eyes, but in none of the blue-eyed controls ($\chi^2 = 11.18$; df = 1; p = 0.001). The iris color did not differ between patients with transillumination defects and those without defects. Details of the color distribution are given in Table I.

DISCUSSION

We investigated the incidence and pattern of iris transillumination defects in POAG and found significantly more of these defects in patients with POAG than controls. Glaucoma patients with vascular dysregulation had a tendency towards an even higher incidence of transillumination defects than non-vasospastic glaucoma patients, though this finding was not statistically significant.

The iris transillumination defects had a characteristic, radially streaked pattern distinct from those seen in other forms of glaucoma like pigmentary glaucoma, PEX glaucoma, and acute glaucoma (Fig. 1). In pigmentary glaucoma, peripheral iris transillumination defects are characteristic “church-window phenomenon” (11, 12), and in PEX glaucoma, pupillary ruff defects and transillumination of the sphincter region have been described (13). In our study, however, subjects with any at least partially mechanical origin of iris tissue loss were carefully excluded.

Our findings are in agreement with those of Wodowosow and Rybnikov, who examined irises of POAG patients and controls by transillumination and fluorescein angiography. They observed typical defects and thinning of the posterior iris pigment layer in 57.7% of the patients, and suggested these morphological changes were secondary to a disturbed iris vessel permeability (14). Donaldson, who photographed all cases of abnormal iris transillumination seen in his clinic over a period of eight years, found variable amounts of iris translucency in a radial-streaked pattern, usually with involvement of the pupillary border in patients with POAG (15). Brooks and Gillies investigated a series of 17 patients with stromal atrophy, hypoperfusion, and microneovascularisation of the iris and found iris atrophy was associated with glaucoma or ocular hypertension in 16 cases. They also noted reduced dye velocity, and a markedly delayed appearance of dye in combination with a long arteriovenous passage time, sectorial hypoperfusion, dye leakage and neovascularisation of iris vasculature, by means of fluorescein angiography (16). Similar alterations have been described within the retinal vasculature of glaucomatous eyes (17).

Interestingly, Brooks and Gillies described one patient with typical glaucomatous iris changes but without elevated IOP (16), and concluded that the vascular alterations in their patients were unlikely to be due to raised IOP only. These results led us to speculate that the iris defects in POAG cannot be explained

TABLE I - IRIS COLOR DISTRIBUTION OF PATIENTS WITH POAG WITH (POAGvasc) AND WITHOUT (POAGnonvasc) DYSREGULATION, AND HEALTHY CONTROLS

	Brown iris	Green iris	Blue iris
Controls (n = 23)	13	2	8
POAGvasc (n = 17)	3	1	13
POAGnonvasc (n = 7)	4	0	3

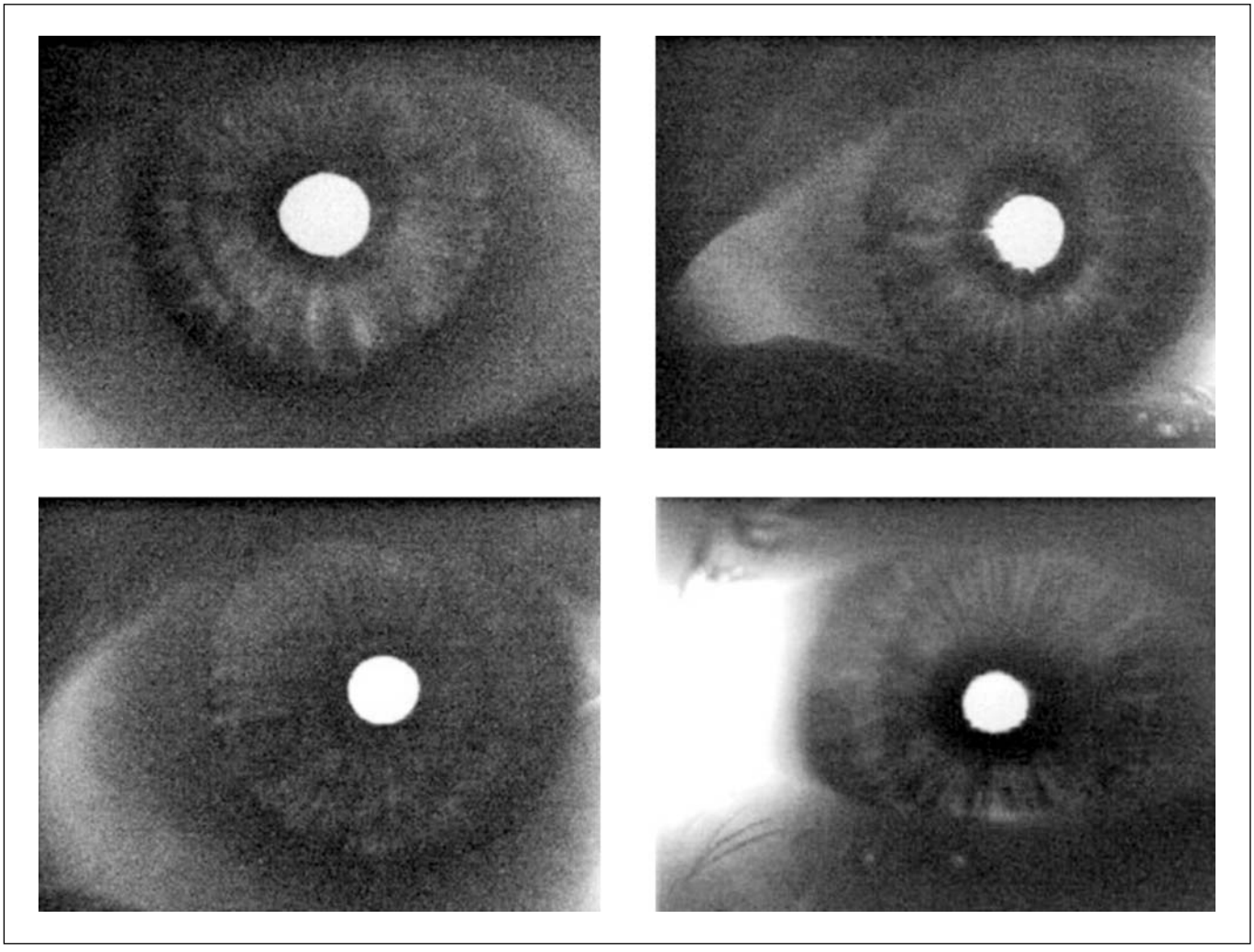

Fig. 1 - *Typical radially-streaked pattern of transillumination defects in four patients with POAG.*

by IOP-induced hypoperfusion alone, but might be at least partly be due to vasospasm-induced ischemia, or reperfusion-damage. However, in our study, glaucoma patients with vascular dysregulation did not have a significantly higher incidence of transillumination defects than non-vasospastic glaucoma patients. We therefore suggest that the changes of the iris in our series cannot be explained by vascular dysregulation, and that other factors such as increased degradation of extracellular matrix might play a role.

Almost thirty years ago, Okamura and Lütjen-Decroll described structural differences in the anterior leaf of the iris stroma and the adventitial sheaths of iris vessels of patients with POAG. In addition, they found the amount of collagen fibers in the inner zone of the adventitial sheath was reduced, and interpreted this as indicating delayed formation and maturation of collagenous fiber material (18). Subsequent studies have shown an increased expression of matrix metalloproteinases (MMP) and tumor necrosis factor-α (TNF-α) in the optic nerve head of patients with POAG. The expression was even more pronounced in patients with NTG (19). This implies a role for MMPs and TNF-α in tissue remodeling and the degenerative changes seen in glaucomatous optic nerve heads.

A similar pathogenic process may be present in glaucomatous irises. The reduced amount of collagen fibers in the inner zone of the adventitial sheath described

by Okamura and Lütjen-Decroll may be due to increased activity of MMPs and TGF-α, resulting in increased degradation of extracellular matrix. Investigation of the expression and activity of MMP and its inhibitors in iris specimens from glaucoma patients will help clear up this question.

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