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Iris fluorescein angiography and iris indocyanine green videoangiography in pseudoexfoliation syndrome

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ABSTRACT: Background. *Precise evaluation of the iris vascular pattern in pseudoexfoliation syndrome (PXS) may be difficult with iris fluorescein angiography (IFA) because of the frequent presence of a heavily pigmented iris and conspicuous late leakage. However, iris indocyanine green videoangiography (IICGV) can precisely visualize details of the iris vascular pattern. This study analyzed the utility of IICGV in detecting microvascular changes in PXS and compared these findings with those of IFA.*
Methods. *Twenty-eight patients with PXS in both eyes underwent an ophthalmic examination including IFA and IICGV. IICGV was done with the IMAGEnet system H1024.*
Results. *IICGV gave better visualization of iris hypoperfusion and anastomotic vessels whereas iris microneovascularisation was far more clearly visible on IFA. IICGV also detected iris pigment epithelium defects.*
Conclusions. *IICGV can be considered a useful tool for evaluation of the iris vascular pattern in PXS. Iris hypoperfusion did not appear to contribute to the development of iris microvascular changes. (Eur J Ophthalmol 1999; 9: 284-90)*

KEY WORDS: Pseudoexfoliation syndrome, Iris fluorescein angiography, Iris indocyanine green videoangiography

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INTRODUCTION

Pseudoexfoliation syndrome (PXS) is clinically characterized by grayish-white material in the anterior ocular segment, mainly on the anterior lens capsule, and at the pupillary border. Iris fluorescein angiography (IFA) serves to detect the iris microvascular abnormalities such as hypoperfusion, microneovascularisation and anastomotic vessels in PXS (1-7). Nevertheless, precise evaluation of these changes may be difficult when there is a heavily pigmented iris and conspicuous late leakage (5).

Iris indocyanine green videoangiography (IICGV) helps visualize details of the iris vascular pattern better especially as regards hypoperfusion and capillary dilatation (8-10). The spectral absorption and emission in the infared wavelengths makes for better transmission through the iris pigmentation, and the almost complete protein binding minimizes dye leakage. We analyzed the utility of IICGV in detecting microvascular changes in PXS and compared these findings with those of IFA.

METHODS

In a prospective study patients with PXS observed in the outpatient department of the Eye Clinic of Trieste between January 1996 and January 1997 were enrolled. The inclusion criterion was the diagnosis of classic PXS, defined by the presence of deposits of typical PXS material at the pupillary margin and/or on the anterior lens capsule, visible on slit-lamp examination, with intraocular pressure (IOP) less than 21

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mmHg, measured three times in miosis. The exclusion criteria were: other ocular diseases, topical myotic therapy, previous laser or surgical treatment, capsular glaucoma, diabetes mellitus. We examined a control group of healthy subjects with no ocular or systemic pathology, to rule out iris microvascular changes detectable in a normal population.

All patients gave informed consent and underwent a complete ophthalmologic examination including IFA and IICGV, performed using an IMAGEnet System H1024 (Topcon Corp.) as previously described (8-10). A solution containing 25 mg of indocyanine green in 5 ml of aqueous solvent was injected intravenously and IICGA images were taken at 1-5 second intervals for 5-10 minutes. Afterwards, a 5-ml dose of a 20% solution of fluorescein was injected intravenously to perform IFA. The two examinations were done by the same examiner (EB). Each angiogram was evaluated in masked fashion by two of the authors (MBP, SS), with agreement in 96% of cases. A third (GR) was consulted to define uncertain cases.

The main aspects considered in assessing the degree of iris vascular impairment were: hypoperfusion, microneovascularisation and anastomotic vessels (5). Iris hypoperfusion was revealed by: 1) reduction of the number of radial arterioles, slight (13-15 arterioles), moderate (10-12 arterioles), or marked (< 10 arterioles); 2) sectorial filling defects, slight (2 clock hours), moderate (3-4 clock hours), or marked (> or = 5 clock hours); and 3) attenuation of radial arterioles, slight (< 3 arterioles), moderate (3-10 arterioles), or marked (> 10 arterioles). Microneovascularisation was classified as: 1) tufts in the iris stroma, slight (< 3 tufts), moderate (4-10 tufts), or marked (> 10 tufts); 2) more complex plexuses of fine new vessels, slight (< 2 plexuses), moderate (4-10 plexuses), or marked (> 10 plexuses); 3) tufts in the peripupillary area, internal to the collarette of the iris, classified as slight (< 3 tufts), moderate (4-10 tufts), or marked (> 10 tufts); and 4) tufts at the pupillary margin, slight (< 3 tufts), moderate (4-10 tufts), or marked (> 10 tufts).

Anastomotic vessels were classified as: 1) peripheral loops which extended a variable distance towards the pupil, assessed as absent or present; 2) pronounced lesser circle of the iris, absent or present; 3) obliquely or circumferentially running vessels distinct from the lesser circle, absent or present.

Statistical analysis was done by the chi-square tests.

RESULTS

Twenty-eight patients fulfilled the inclusion and exclusion criteria. All the patients were caucasian, 12 of them having a dark pigmented iris (24 eyes). The mean (±SD) age was 64.7 ± 7.7 years (range 50-87) with 15 females (53.5%) and 13 men (46.4%). Fourteen healthy volunteers with no ocular or systemic pathology were used as a control group. All were caucasian, 8 having a heavily-pigmented iris (16 eyes). The mean age was 63 ± 10 years (range 53-82), with 8 men (57%) and 6 women (43%).

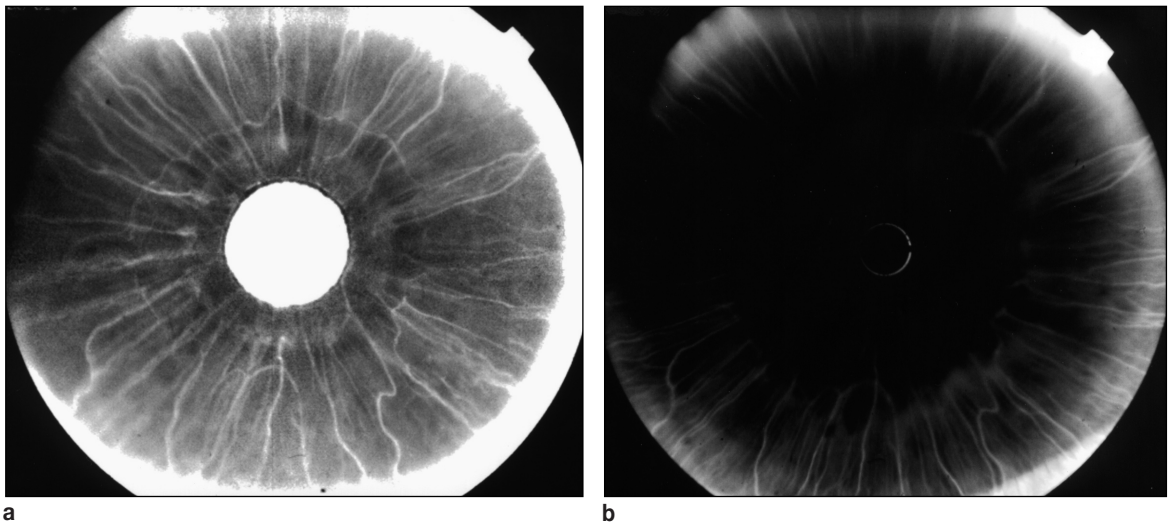
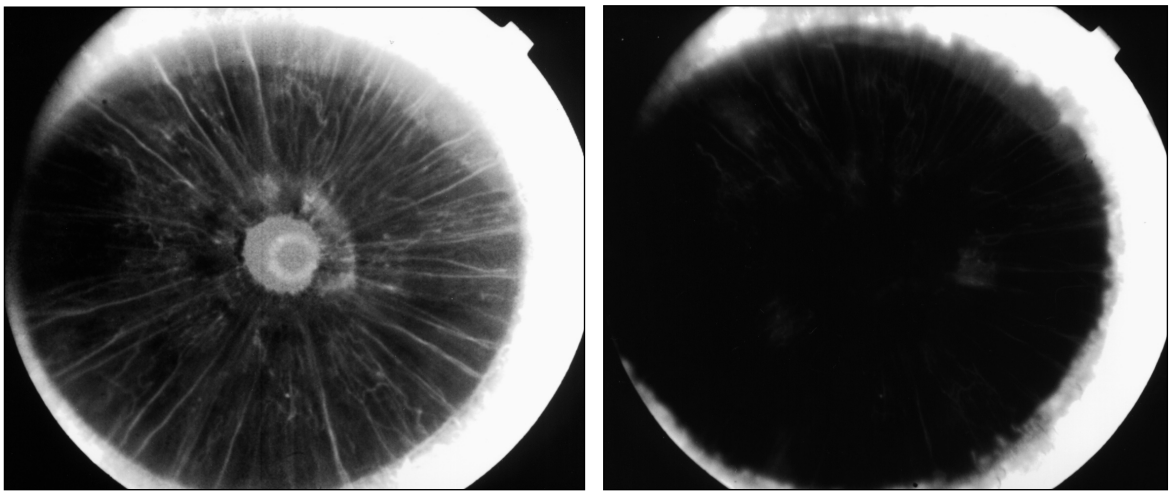


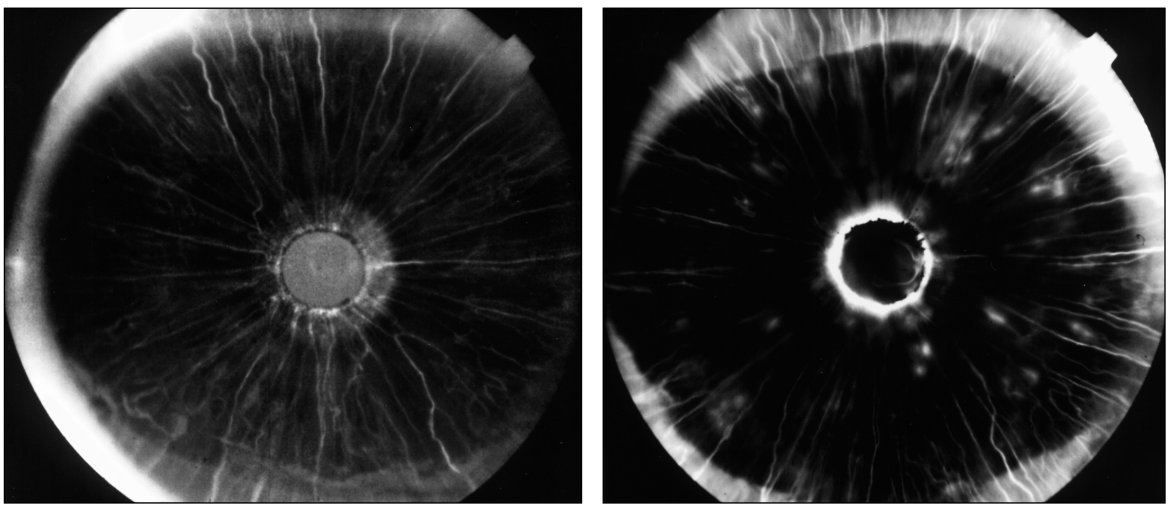
Fig. 1 - *Control eye.* ***a)*** *IICGV frame showing a normal vascular pattern.* ***b)*** *Same eye examined by IFA.*

a **b**



a **b**

Fig. 2 - *PXS eye.* ***a)*** *IICGV frame (45 seconds) showing several microvascular abnormalities with iris hypoperfusion. The hyperfluorescent ring in the peripupillary area corresponds to an iris pigment epithelium defect.* ***b)*** *IFA frame (50 seconds) showing slight peripupillary and stromal leakage, but no clear evidence of iris hypoperfusion.*



a **b**

Fig. 3 - *PXS eye.* ***a)*** *IICGV frame (1 minute and 30 seconds). A hypoperfused iris sector is visible at 9 o'clock. The hyperfluorescent peripupillary ring is related to the iris pigment epithelium defect.* ***b)*** *IFA frame (1 minute and 37 seconds) not clearly showing the hypoperfused sector because of the dark pigmented iris.*

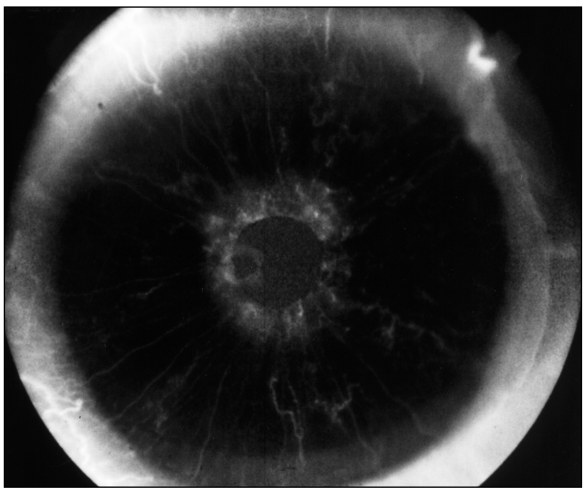


Fig. 4 - *PXS eye. IICGV frame (1 minute and 45 seconds) showing a hypoperfused sector at 3 o'clock and several patchy areas of attenuated arterioles.*

The pupillary diameter appeared larger on IICGV than IFA, even using the same flash power. This feature is related to the infrared activity of IICGV, with a different pupillary reaction.

The control group showed a regular vascular pattern in IFA, except for 16 eyes (57.1%) with a heavily pigmented iris, in which the vascular details were not visible. The 12 evaluable eyes (42.8%) had no evidence of hypoperfusion, microneovascularisation, or anastomotic vessels. In 20 eyes (71.4%) mild peripupillary leakage was evident, compatible with the patient's age. On IICGV examination the same eyes showed a regular vascular pattern, easily detectable even in the heavily pigmented iris cases, without any evidence of hypoperfusion, microneovascularisation, anastomotic vessels, leakage, or iris pigment epithelium defects (Fig. 1).

IFA examination of PXS patients did not permit a precise

TABLE I - IRIS HYPOPERFUSION IN PXS EYES

Iris hypoperfusion	Nil	Slight	Moderate	Marked	Total*
Iris fluorescein angiography					
Reduced radial arterioles	4 (8%)	16 (28.5%)	4 (7.1%)	0	24
Sectorial filling defects	13 (23.2%)	8 (14.2%)	1 (1.7%)	0	24
Attenuated arterioles	6 (10.7%)	12 (21.4%)	6 (10.7%)	0	24
Iris indocyanine green angiography					
Reduced radial arterioles	13 (23.2%)	25 (44.6%)	18 (32.1%)	0	56
Sectorial filling defects	18 (32.1%)	29 (51.7%)	6 (10.7%)	3 (5.3%)	56
Attenuated arterioles	8 (14.2%)	19 (33.9%)	22 (39.2%)	7 (12.5%)	56

* On iris fluorescein angiography only the 24 eyes without heavily pigmented iris were evaluable

TABLE II - IRIS MICRONEOVASCULARISATION IN PXS EYES

Iris microneovascularisation	Nil	Slight	Moderate	Marked	Total
Iris fluorescein angiography					
Stromal tufts	12 (21.4%)	13 (23.2%)	19 (33.9%)	12 (21.4%)	56
Plexuses	9 (16%)	19 (33.9%)	16 (28.5%)	12 (21.4%)	56
Peripupillary	8 (14.2%)	31 (55.3%)	10 (17.8%)	7 (12.5%)	56
Pupillary tufts	0	9 (16%)	23 (41%)	24 (42.8%)	56
Iris indocyanine green angiography					
Stromal tufts	36 (64.2%)	15 (26.7%)	5 (8.9%)	0	56
Plexuses	12 (21.4%)	21 (37.5%)	14 (25%)	9 (16%)	56
Peripupillary	25 (44.6%)	27 (48.2%)	4 (7.1%)	0	56
Pupillary tufts	9 (16%)	32 (57.1%)	15 (26.7%)	0	56

evaluation of the vascular pattern in 24 eyes (42.8%), because of a heavily pigmented iris. In the remaining 32 eyes (57.1%) iris hypoperfusion was detected in 20 eyes (35.7%) (Figs. 2, 3). The results are summarized in Table I. On IICGV, iris hypoperfusion was detected overall in 48 eyes (85.7%) (Figs. 2-4), and it was manifest as set out in Table I.

Statistical analysis showed a significant difference between IFA and IICGV for the detection of iris hypoperfusion ($p < 0.001$).

IFA showed iris microneovascularisation (Figs. 2, 3) in all the 56 eyes (100%), thanks to the typical dye leakage, manifested as set out in Table II. IICGV recognized iris microneovascularisation overall in 47 eyes (83.9%). In no case did we observe dye leakage. The lesions are listed in Table II.

Statistical analysis showed a significant difference between IFA and IICGV as regards the detection of iris microneovascularisation ($p < 0.05$).

Dye leakage from iris vessels without neovascularisation secondary to blood-acqueous barrier breakdown was detectable in 40 eyes (71.4%) only on IFA. Anastomotic vessels turned out to be detectable only in 7 eyes (12.5%) on IFA and on IICGV, anastomotic vessels were detected overall in 31 eyes (55.3%) (Tab. III). Statistical analysis indicated a significant

TABLE III - IRIS ANASTOMOTIC VESSELS IN PXS EYES

Iris anastomotic vessels	Absence	Presence	Total*
Iris fluorescein angiography			
Peripheral loops	21 (37.5%)	3 (5.3%)	24
Lesser circle	22 (39.2%)	2 (3.5%)	24
Oblique vessels	17 (30.3%)	7 (12.5%)	24
Iris indocyanine green angiography			
Peripheral loops	37 (66%)	19 (33.9%)	56
Lesser circle	36 (64.2%)	20 (35.7%)	56
Oblique vessels	25 (44.6%)	31 (55.3%)	56

On iris fluorescein angiography only the 24 eyes without heavily pigmented iris were evaluable

difference between IFA and IICGV regarding the detection of anastomotic vessels ($p < 0.001$).

On IICGV examination 31 eyes (55.3%) showed hyperfluorescent lesions, which were visible before the iris vascular filling. Transscleral illumination indicated that the transillumination defects corresponded perfectly with these hyperfluorescent lesions, meaning they were simple iris pigment epithelium defects, detectable by a retroillumination mechanism related to the retinochoroidal fluorescence. Iris pigment epithelium defects were not visible on IFA examination, and they were especially located in the pupillary border in 31 eyes (55.3%), and in the peripupillary area in 23 eyes (41%) (Figs. 2, 3). The defects did not appear to be correlated with hypoperfusion, microneovascularisation, or anastomotic vessels.

Overall, the vascular impairment was symmetrical with no particular difference between right and left eye of the same patient.

DISCUSSION

The PXS syndrome is clinically characterized by the presence of greyish-white fibrillo-granular material in the anterior segment of the eye. Histological studies indicate that the exfoliation material involves the iris vessels, randomly causing a wide spectrum of vascular impariment (11-17). The ultrastructural changes may range from focal accumulation of exfoliation material without any evidence of cellular degeneration, to progressive damage to vascular supporting and endothelial cells, or even vascular deposition of exfoliation material with secondary closure of vessels (ghost vessels) (17).

The variability of the histological findings is reflected in the different angiographic features on IFA examination, which include hypoperfusion, microneovascularisation with fluorescein leakage and anastomotic vessels (1-7). Moreover, angiographic evaluation of microvascular abnormalities may be difficult, either because of a heavily pigmented iris or because of fluorescein leakage (5).

ICGV gives better imaging of the iris vascular pattern since infrared wavelengths penetrate the iris pigmentation better, and because dye leakage is minimal on account of strong protein binding of the dye and the conseqeunt large protein complex (8-10).

As expected, IICGV permitted imaging of the iris vascular pattern in all patients, whereas IFA failed in 42.8% of cases, because of heavy iris pigmentation. Hypoperfusion and anastomotic vessels were detected better by IICGV, whereas microneovascularisation was imaged better by IFA.

Iris hypoperfusion was evident in 35.7% of eyes on IFA, in comparison with 85.7% on IICGV. The hypoperfused areas corresponded in cases in which they were detected by both examinations, though hypoperfusion areas were more clearly outlined on IICGV.

The most common appearance of iris hypoperfusion in PXS, seen as patchy areas of attenuated arterioles, may be related to the histological findings with the typical irregular microvascular involvement, and it differs from cases with diabetic iridopathy, where iris hypoperfusion generally appears as a hypoperfused sector (9).

Microneovascularisation was far more clear on IFA, thanks to the profuse dye leakage, and was most frequently represented by pupillary tufts, detectable on IFA in all cases. Fluorescein can leak from iris neovascularisation or from increased permeability of originally present iris vessels, detectable on IFA in 71.4% of eyes, secondary to the blood-aqueous barrier breakdown. This breakdown depends on the ultrastructural changes to the vascular structures involved in PXS (11-17) and has a clinical correlate in the aqueous flare and cells (18, 19).

It is interesting that IICGV did not show dye leakage in any eye affected by PXS, contrasting with 8.3% of eyes with proliferative diabetic iridopathy (9). This may mean that diabetic iridopathy causes even more marked breakdown of the blood-aqueous barrier than PXS. The better imaging of anastomotic vessels on IICGV can be ascribed to the more precise detection of the iris vascular structure typical of IICGV (8-10).

Iris translucency is commonly associated with PXS (20-22), and is found in about 45% of these eyes; it is related to degeneration of the iris pigment epithelium (23, 24). In diabetic iridopathy IICGV shows hyperfluorescent areas corresponding to iris translucency (8). Transscleral illumination demonstrates the correspondence between transilumination defects and hyperfluorescent lesions, and IICGV seems to operate through a mechanism of retroillumination due to the retinochoroidal fluorescence. These defects were present in 55.3% of the eyes we examined, the pupillary border being involved most.

The hyperfluorescent lesions seen with IICGV are the angiographic expression of clinical findings due to degeneration of the iris pigment epithelium, such as depigmentation of the pupillary margin, pigment dispersion during mydriasis, and increased iris transillumination. Some ultrastructural studies have described the extensive alterations of the iris pigment epitehlium in PXS beautifully (23, 24). We did not notice any relationship between iris pigment epithelium defects and hypoperfusion, or the other microvascular abnormalities.

The coexistence of cerebrovascular diseases with abnormal iris transluminance, together with the high prevalence of PXS, may support the hypothesis that hypoxia contributes to the development of PXS (20) and disturbances in the ciliary circulation are a possible cause of these changes (21). In these circumstances, PXS should always show iris hypoperfusion, whereas IICGV indicated normal iris perfusion in 8 eyes (14.2% of cases). Considering that the presence of exfoliation material is not a feature in any of the other ocular diseases associated with iris hypoperfusion, presumably this finding does not contribute to the development of PXS (5).

We did not notice any relationship between iris hypoperfusion and microneovascularisation, or anastomotic vessels. Thus, in contrast to other studies (5), iris hypoperfusion did seen to play a contributory role in the development of iris microvascular changes.

In essence, IICGV can be considered a useful tool for assessing the iris vascular pattern in PXS, especially in eyes with a heavily pigmented iris. IICGV shows up iris hypoperfusion and anastomotic vessels, whereas IFA shows microneovascularisation.

Clearly, further studies are still needed to clarify the clinical significance of microvascular changes in PXS and how the angiographic aspects are related to the different stages of the disease.

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