

Scoring of dual fluorescein and ICG inflammatory angiographic signs for the grading of posterior segment inflammation (dual fluorescein and ICG angiographic scoring system for uveitis)

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Abstract *Purpose* To propose a semiquantitative dual fluorescein angiography (FA) and indocyanine green angiography (ICGA) scoring system for uveitis

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that would assist in the follow-up of disease progression and monitoring response to treatment. *Methods* The scoring system was based on the FA scoring systems, the standardized ICGA protocol, and schematic interpretation of ICGA findings in posterior uveitis that have been previously published. We assigned scores to the fluorescein and ICG angiographic signs that represent ongoing inflammatory process in the posterior segment. We rated each angiographic sign according to the impact it has on our appreciation of active intraocular inflammation. In order to permit direct comparison between FA and ICGA, we multiplied the total ICGA score by a coefficient of 2 to adjust to the total score of FA. *Results* A total maximum score of 40 was assigned to the FA signs, including optic disc hyperfluorescence, macular edema, retinal vascular staining and/or leakage, capillary leakage, retinal capillary nonperfusion, neovascularization of the optic disc, neovascularization elsewhere, pinpoint leaks, and retinal staining and/or subretinal pooling. A total maximum score of 20 was assigned to the ICGA signs, including early stromal vessel hyperfluorescence, choroidal vasculitis, dark dots or areas (excluding atrophy), and optic disc hyperfluorescence. *Conclusion* The combined fluorescein and ICG angiographic scoring system proposed herein may help estimate the magnitude of retinal versus choroidal inflammation, monitor disease progression and response to treatment, and provide comparable data for clinical studies. The applicability of the proposed system needs to be tested in clinical

settings, and intra- and interobserver variations need to be determined.

Keywords Uveitis · Intraocular inflammation · Fluorescein angiography · Indocyanine green · Angiography · Angiographic scoring

Introduction

Angiographic imaging of the posterior segment is essential in the appraisal of intraocular inflammation. Fluorescein angiography (FA) and indocyanine green angiography (ICGA) are well-established techniques that are widely used in the clinic and in studies of various intraocular inflammatory diseases. They are useful in assessing the activity of the inflammatory process, in identifying the primary focus of inflammation, extent, and complications of inflammation, in elucidating the cause(s) of visual loss, and in monitoring response to treatment. Furthermore, characteristic angiographic patterns may assist in diagnosis of some conditions [1–3].

Fluorescein angiography is especially useful in evaluating retinal inflammation, which is prominent in diseases such as Behçet's disease, idiopathic retinal vasculitis, birdshot retinochoroidopathy, and

intermediate uveitis where the retinal vessels are primarily inflamed. The hallmark of retinal disease activity is breakdown of the inner blood-retinal

Table 1 Fluorescein angiographic scoring system

Angiographic sign	Score
<i>Optic disc hyperfluorescence at 5–10 min</i>	
Normal staining of the scleral rim	0
Staining of the disc with distinct margins	
Partial	1
Diffuse	2
Leakage at the optic disc with blurring of margins and papillary vasculature	3
<i>Macular edema at 10 min</i>	
Faint hyperfluorescence	1
Incomplete ring of leakage	2
Complete ring of leakage	3
Pooling of dye in cystic spaces	4
<i>Retinal vascular staining and/or leakage at 5–10 min</i>	
Posterior pole arcades	
Focal	1
More extended or multifocal but limited area	2
Diffuse	3
For each quadrant	1
<i>Capillary leakage at 5–10 min</i>	
Posterior pole (excluding perifoveal ring of leakage)	
Limited	1
Diffuse	2
For each quadrant	
Foci of leakage limited in area or intensity	1
Diffuse leakage	2
<i>Retinal capillary nonperfusion</i>	
Macular ischemia (enlargement of foveal avascular zone)	1
Posterior pole (excluding macular ischemia)	1
For each quadrant	1
<i>Neovascularization of the optic disc (NVD)</i>	
<i>Neovascularization elsewhere (NVE)</i>	
At one focus	1
Multiple	2
<i>Pinpoint leaks</i>	
Limited area or at one focus (≤ 3 DD)	1
Extensive (>3 DD)	2
<i>Retinal staining and/or subretinal pooling at 5–10 min</i>	
Limited or at one focus (≤ 3 DD)	1
Extensive (>3 DD)	4

DD, disc diameter

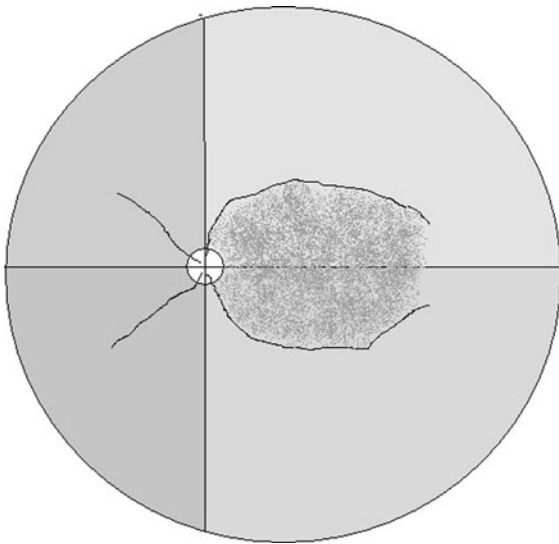
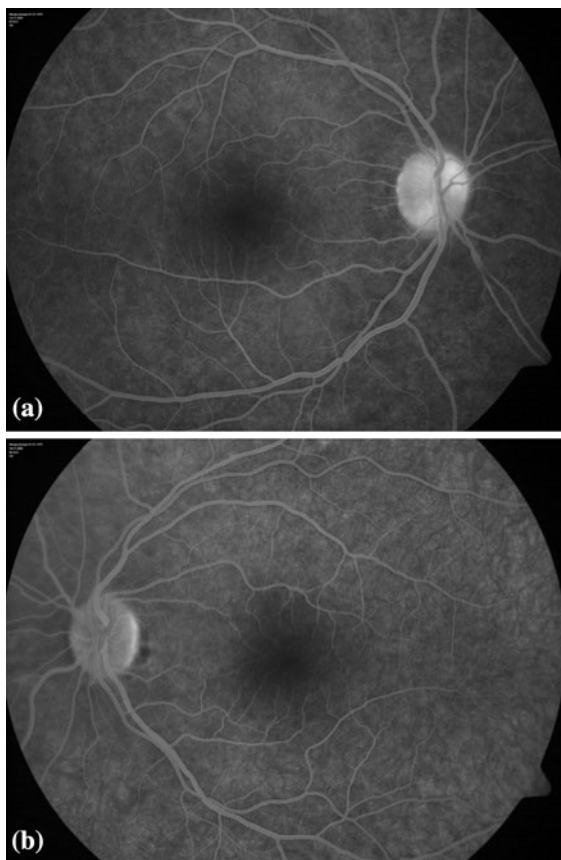


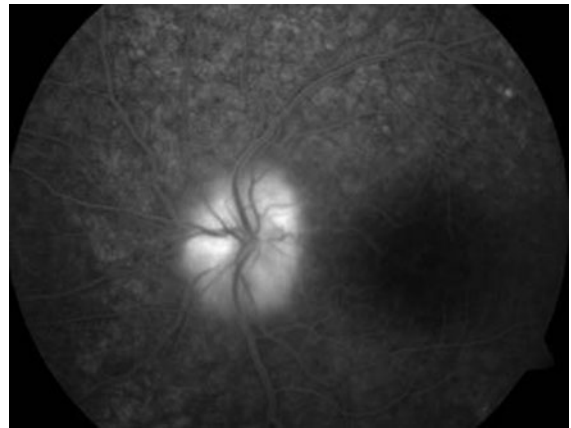
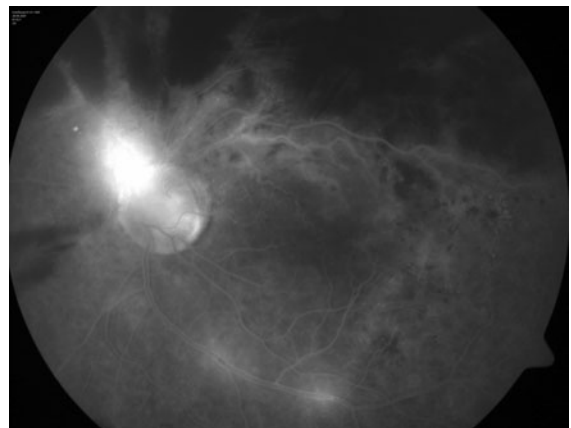
Fig. 1 Fundus diagram showing how the fundus is divided into four quadrants by a horizontal and a vertical line passing through the optic disc. The shaded area between the temporal vascular arcades is defined as the posterior pole

Table 2 Total maximum score for fluorescein angiography

Angiographic sign	Maximum score
Optic disc hyperfluorescence	3
Macular edema	4
Retinal vascular staining/leakage	7
Capillary leakage	10
Retinal capillary nonperfusion	6
Neovascularization of the optic disc (NVD)	2
Neovascularization elsewhere (NVE)	2
Pinpoint leaks	2
Retinal staining/pooling	4
Total	40

**Fig. 2** Fluorescein angiogram of patient with Behçet's disease showing staining of the optic disc in the right eye (a) (score = 1), and normal staining of the scleral rim in the left eye (b)

barrier demonstrated by leakage of dye from retinal vessels and capillaries. Fluorescein angiography is essential in the recognition of primary retinal

**Fig. 3** Fluorescein angiography shows leakage at the optic disc with blurring of margins (score = 3)**Fig. 4** Fluorescein angiography of a patient with severe occlusive retinal vasculitis showing hyperfluorescence of neovascularization at the superior nasal margin of the optic disc in late frame. Note that there is no blurring of the remaining margins of the disc (staining of disc score = 1 + NVD score = 2, giving a total score of 3 for the optic disc)

inflammatory signs or secondary retinal involvement caused by uveitis, including retinal vascular leakage, retinal vascular occlusions, retinal ischemia, neovascularizations, cystoid macular edema, macular ischemia, and serous retinal detachment [1–3]. Fluorescein angiography is especially useful in the evaluation of optic disc involvement in uveitis.

Because of the limitations of FA in imaging the choroidal circulation and associated pathologies, ICGA has become a more useful tool in studying choroidal inflammatory disorders. Several reports have shown that ICGA revealed choroidal lesions that were not detected by ophthalmoscopy or FA in patients

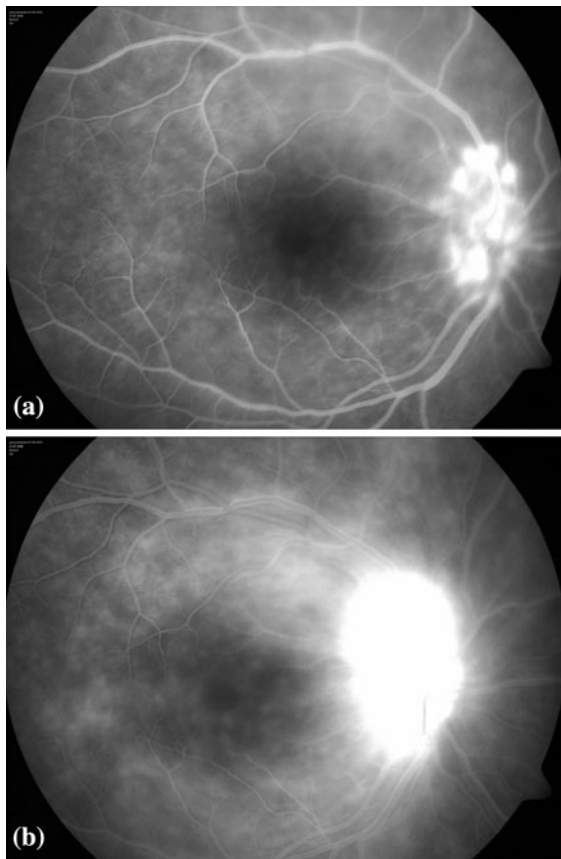


Fig. 5 Fluorescein angiogram of a patient with Behçet's disease showing neovascularization of the optic disc (a), and staining of vessel walls, diffuse capillary leakage, and marked hyperfluorescence at the optic disc with blurring of margins in late frame (b) (disc score = 3 + NVD score = 2 + vascular staining = 3 + capillary leakage at posterior pole = 2 + macular edema score = 1, giving a total score for this frame of 11)

with a variety of chorioretinal inflammatory disorders, including ocular sarcoidosis [4, 5], ocular tuberculosis [6], ocular syphilis [7], ocular toxoplasmosis [8–10], sympathetic ophthalmia [11], Vogt–Koyanagi–Harada (VKH) disease [12], multifocal choroiditis [13–15], acute posterior multifocal placoid pigment epitheliopathy (APMPPE) [13, 16], multiple evanescent white dot syndrome (MEWDS) [13, 17, 18], serpiginous choroiditis [19, 20], the choroidal involvement in birdshot chorioretinopathy [21], and lupus choroidopathy [22–24]. The use of ICGA has also made it possible to better understand the pathogenesis of several choroidal inflammatory disorders and to classify these entities based on either predominant inflammation of the choriocapillaris or predominant

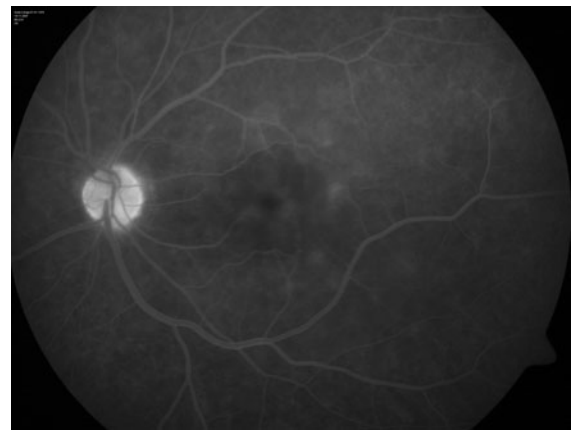


Fig. 6 Late-phase fluorescein angiographic frame showing disc staining, faint hyperfluorescence at the macula, and foci of capillary leakage at the posterior pole (disc score = 1 + macular edema score = 1 + capillary leakage score = 1, giving a total score for this frame of 3)

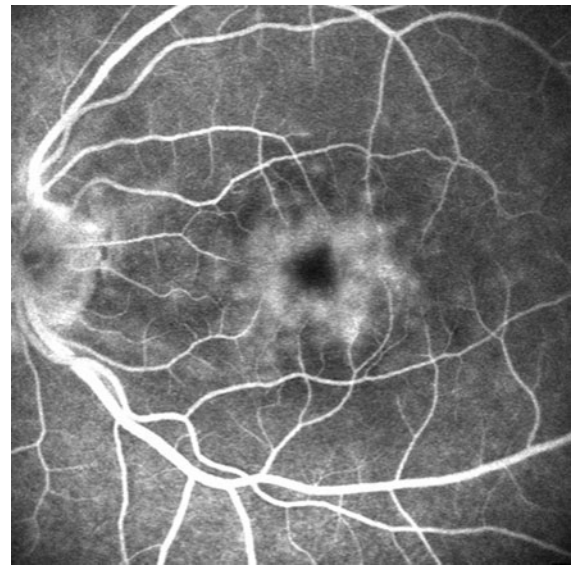


Fig. 7 Late-phase fluorescein angiographic frame showing a complete ring of leakage around the fovea (score = 3)

inflammation of the stromal choroidal vessels with or without secondary choriocapillaritis [25].

Standard angiographic protocols have been developed for both FA and ICGA [1, 2, 26]. In clinical practice, interpretation of angiographic findings is mainly subjective and descriptive. Lack of level I evidence that supports the use of FA or ICGA in the management of uveitis may be partly due to the inherent limitations in the use of angiographic data. Most of the studies in the literature describe

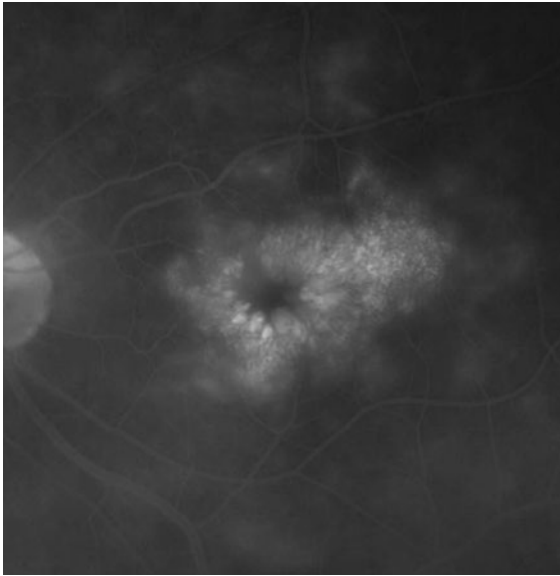


Fig. 8 Fluorescein angiography showing pooling of dye in cystic spaces at the macula and foci of capillary leakage at the posterior pole (macular edema score = 4 + foci of capillary leakage score = 1, giving a total score of 5)

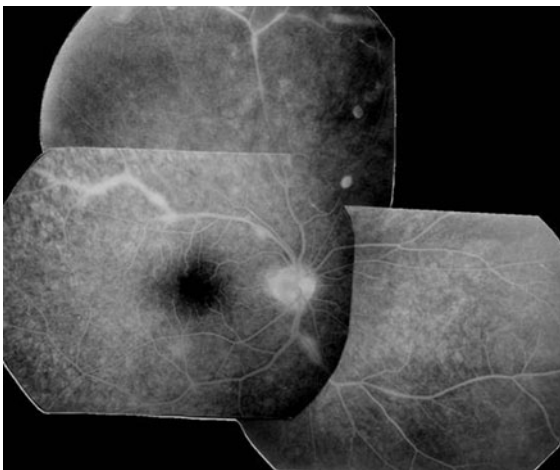


Fig. 9 Fluorescein angiography shows staining/leakage of posterior pole arcade and peripheral retinal vessel [score = 2 (posterior pole) + 1 (periphery) = total score for vascular staining/leakage in this frame = 3]

angiographic findings in series of patients with certain uveitic conditions [4–10, 12–15, 17, 19–22, 25–31]. Although there are also nonrandomized clinical trials that have used angiography to monitor therapeutic intervention, angiographic data were presented in a qualitative manner [12, 15, 20, 21, 32]. We are not aware of any ICGA scoring system

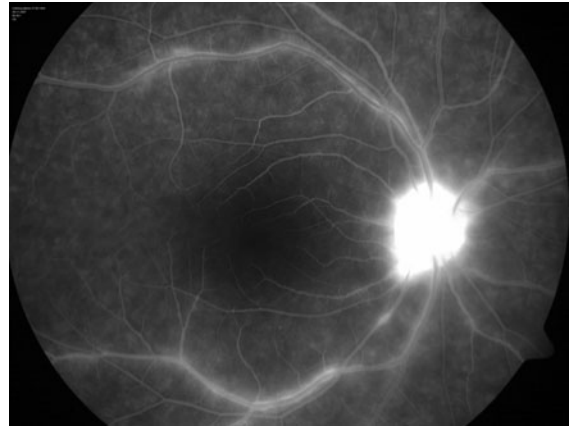


Fig. 10 Fluorescein angiography showing diffuse staining and leakage of both arcades (vascular staining = 3 + disc score = 2, giving a total score for this frame of 5)

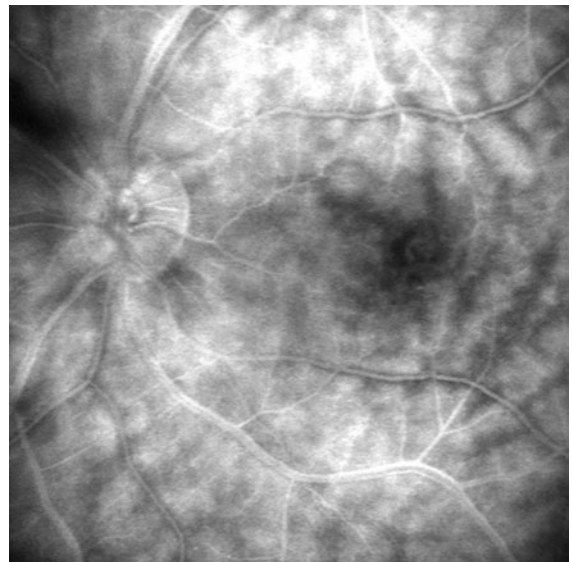


Fig. 11 Fluorescein angiography showing diffuse capillary leakage at the posterior pole (capillary leakage score = 2 for posterior pole)

that has been used in uveitis patients. A FA scoring system for uveitis was published in 1991 [33]. However, different FA scoring systems have been used in subsequent clinical studies [34–36]. Common use of a standard system would enhance comparability of reported data. For this purpose, the Standardization of Uveitis Nomenclature (SUN) Working Group held an international workshop and published standard methods for clinical grading of intraocular inflammation [37]. However, angiographic

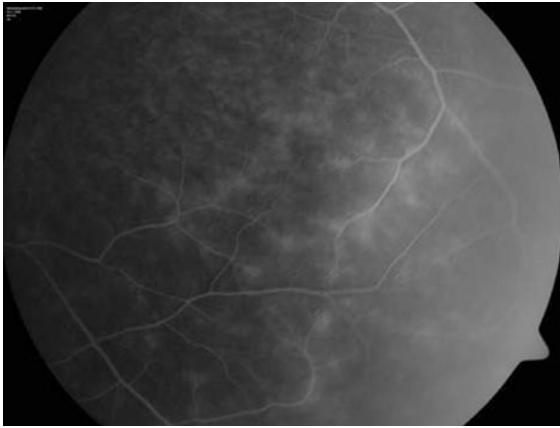


Fig. 12 Fluorescein angiography showing foci of capillary leakage in the peripheral retina (score for this quadrant = 1)

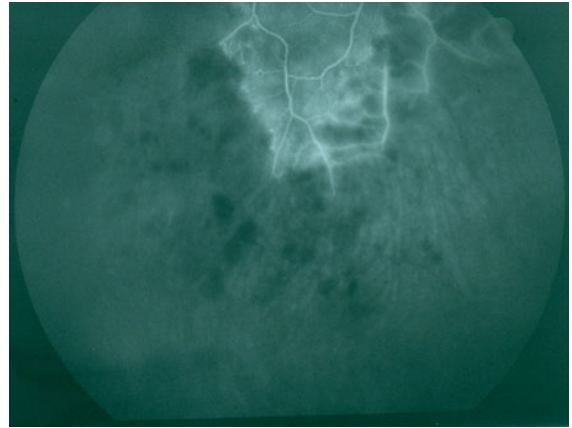


Fig. 14 Fluorescein angiography showing peripheral retinal capillary nonperfusion

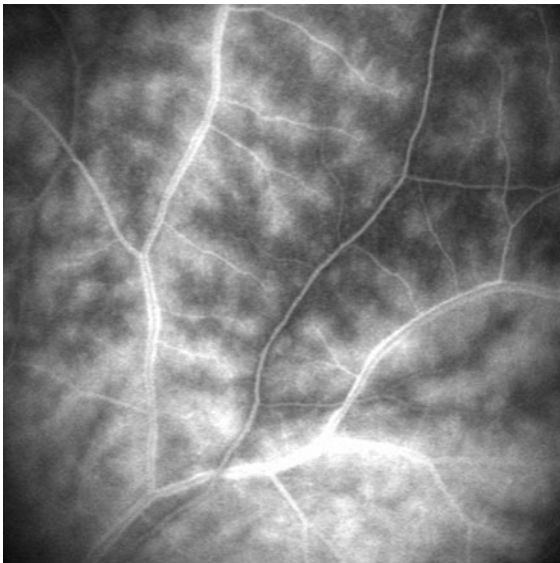


Fig. 13 Fluorescein angiography showing diffuse capillary leakage and staining of vessel walls (capillary leakage score = 2 + vascular staining score = 1, giving a total score for this quadrant of 3)

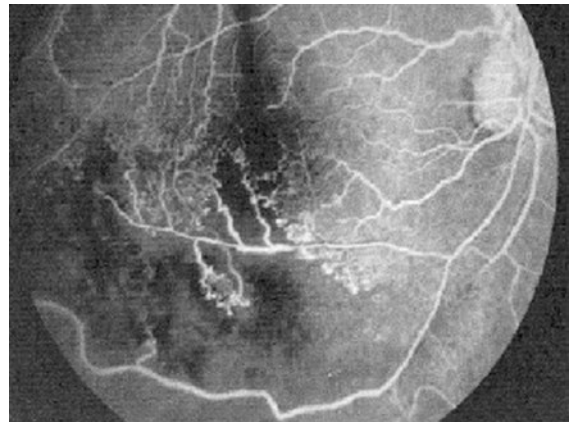


Fig. 15 Fluorescein angiography showing enlargement of foveal avascular zone and retinal capillary nonperfusion at the posterior pole (nonperfusion score = 2)

grading in uveitis was not included in that workshop.

The purpose of the present report is to propose a dual fluorescein and ICG angiographic scoring system for uveitis. We believe that a combined grading system is required in order to estimate the magnitude of retinal versus choroidal inflammation. A semi-quantitative grading system would assist in the follow-up of disease progression and monitoring response to treatment. It would also enhance the use

of quantitative and comparable data for clinical research. The scoring system was primarily developed for angiographic systems using traditional fundus cameras coupled to a digitizing system.

Methods

The design of the system was based on the FA scoring systems, the standardized ICGA protocol, and schematic interpretation of ICGA findings in posterior uveitis that have been previously published [26, 33, 34]. It was considered a prerequisite for interpretation and scoring of FA or ICGA findings that the assessor is provided with the ophthalmoscopic

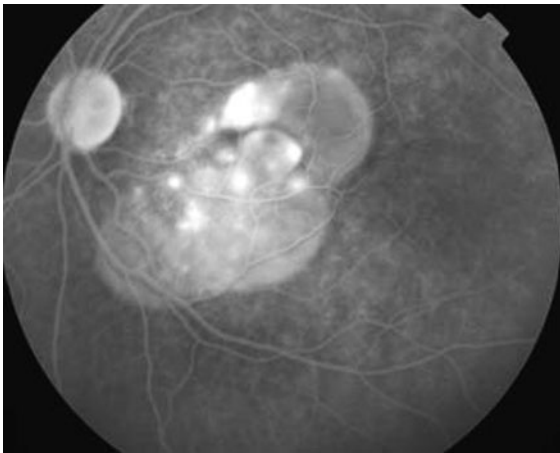


Fig. 16 Fluorescein angiography showing pinpoint leakage and subretinal pooling of dye at the posterior pole in an eye with posterior scleritis (pinpoint leakage score = 1)

findings, i.e., color fundus photographs, and all angiographic frames obtained throughout the procedure; for example, hyperfluorescence on FA can be attributed to a window defect by comparing the intensity of hyperfluorescence in early and late frames as well as making correlations with the color fundus photographs. Similarly, dark dots on ICGA can be attributed to atrophy only by direct comparison to the color fundus photographs. In classical teaching of FA, staining refers to the deposition of fluorescein into involved tissues [38]. Increased visibility of scleral staining due to severe chorioretinal atrophy or staining of fibrotic scars can be distinguished from staining of inflamed retina by direct comparison with the fundus photographs and evaluation of early and late frames. Retinal staining is defined as the deposition of dye in the retina in late frames of FA. The angiographic systems used to establish this scoring system were systems using a traditional fundus camera coupled to a digitizing system, including instruments such as the Topcon 50 IA fundus camera (Tokyo, Japan) coupled to a Topcon Imagenet digitizing system.

We first outlined the fluorescein and ICG angiographic signs that represent ongoing inflammatory process in the posterior segment. Angiographic findings related to structural damage such as window defects on FA were excluded. Then, we rated each angiographic sign according to the impact it has on our appreciation of active intraocular inflammation; for example, capillary leakage on FA was considered

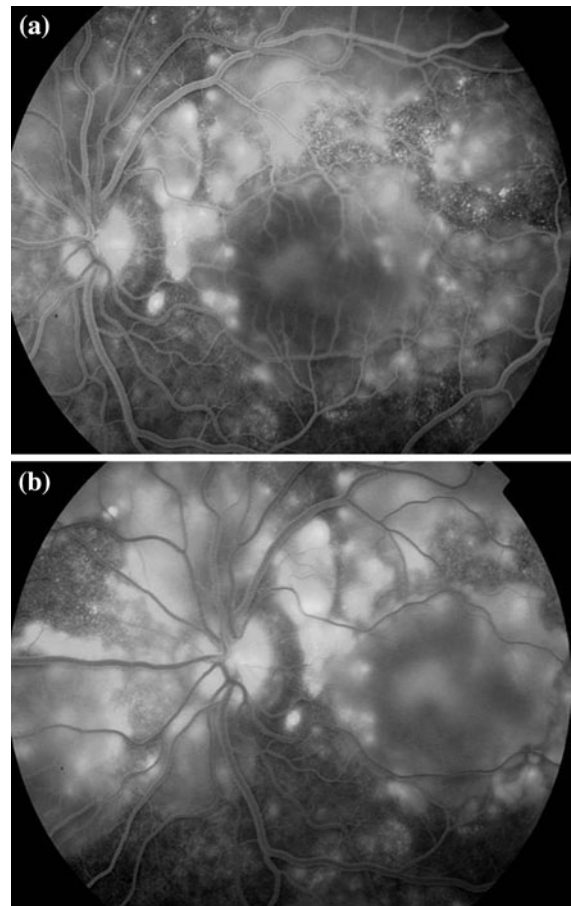


Fig. 17 Fluorescein angiography showing extensive pinpoints (a) (pinpoint leakage score = 2) and subretinal pooling of dye (b) in the left eye of a patient with acute Vogt-Koyanagi-Harada disease (subretinal pooling score = 4)

to have the highest significance for active inflammation, and thus was given the highest score. After determining a maximum score for each sign, we graded the severity and/or extent of that particular sign. Grading of optic disc hyperfluorescence and macular edema were based on severity. To determine the extent of other signs such as capillary leakage we divided the fundus into four quadrants by a horizontal and a vertical line passing through the optic disc. The area between the temporal vascular arcades was defined as the posterior pole, and angiographic signs in the posterior pole were graded separately (Fig. 1).

In order to be able to score the whole fundus properly dual angiography should be performed according to a standardized protocol published previously, including in particular panorama pictures at

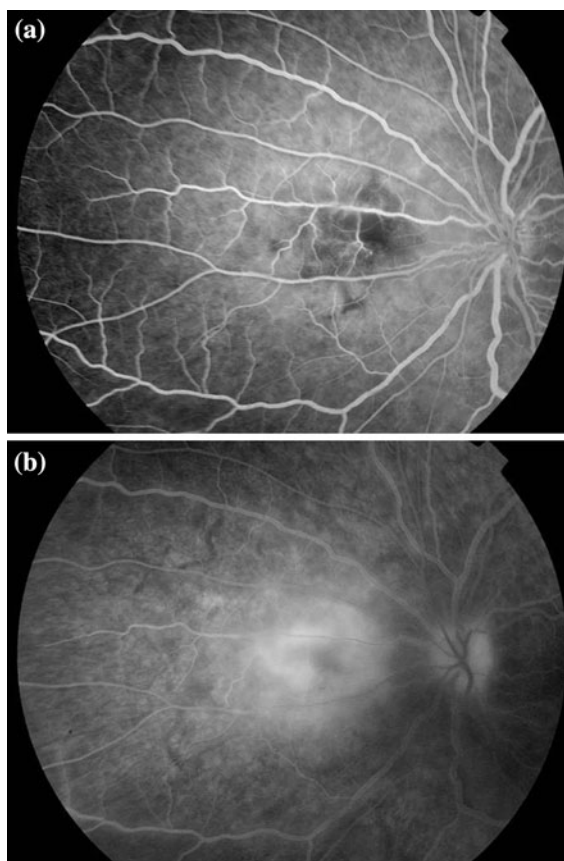


Fig. 18 Fluorescein angiography showing early focal hypofluorescence (a) and late retinal staining (b) in an eye with toxoplasmic retinochoroiditis (retinal staining score = 1)

5–8 min for FA and panoramas for ICGA performed between 8 and 12 min and between 28 and 35 min.

In order to permit direct comparison between FA and ICGA, we multiplied the total ICGA score by a coefficient of 2 to adjust to the total score of FA. In this way the score is able to indicate whether the inflammation is predominantly choroidal or retinal.

Results

The proposed scoring system for FA and the total maximum score for each angiographic sign are shown in Tables 1 and 2, respectively. Optic disc hyperfluorescence was graded from 1 to 3, with partial staining of the disc receiving the lowest score (Fig. 2) and leakage at the disc with blurring of margins receiving the highest score (Fig. 3). Neovascularization of the disc (NVD) was given an

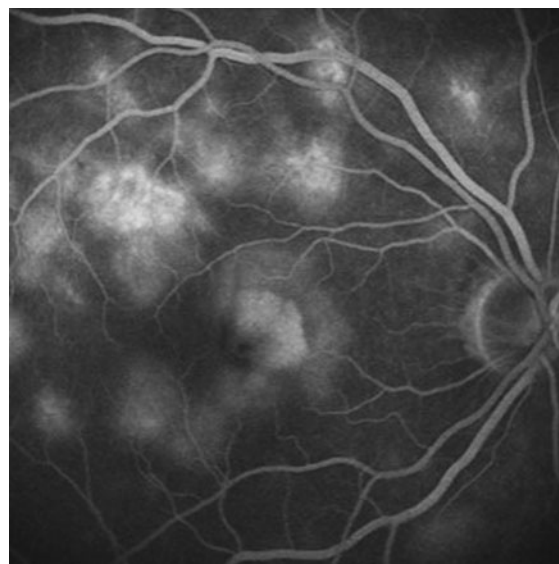


Fig. 19 Late phase fluorescein angiographic frame showing staining of several active lesions in the right eye of a patient with acute posterior multifocal placoid pigment epitheliopathy (retinal staining/pooling score = 4)

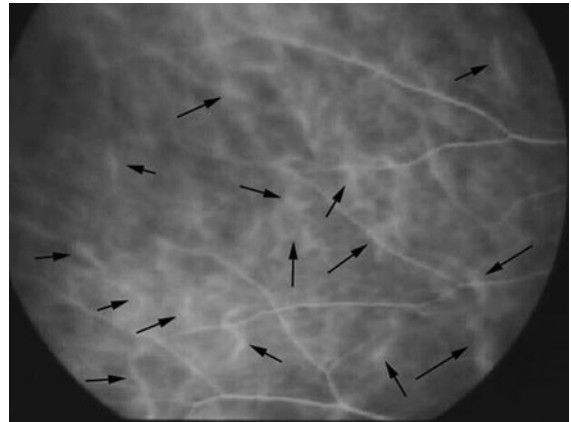
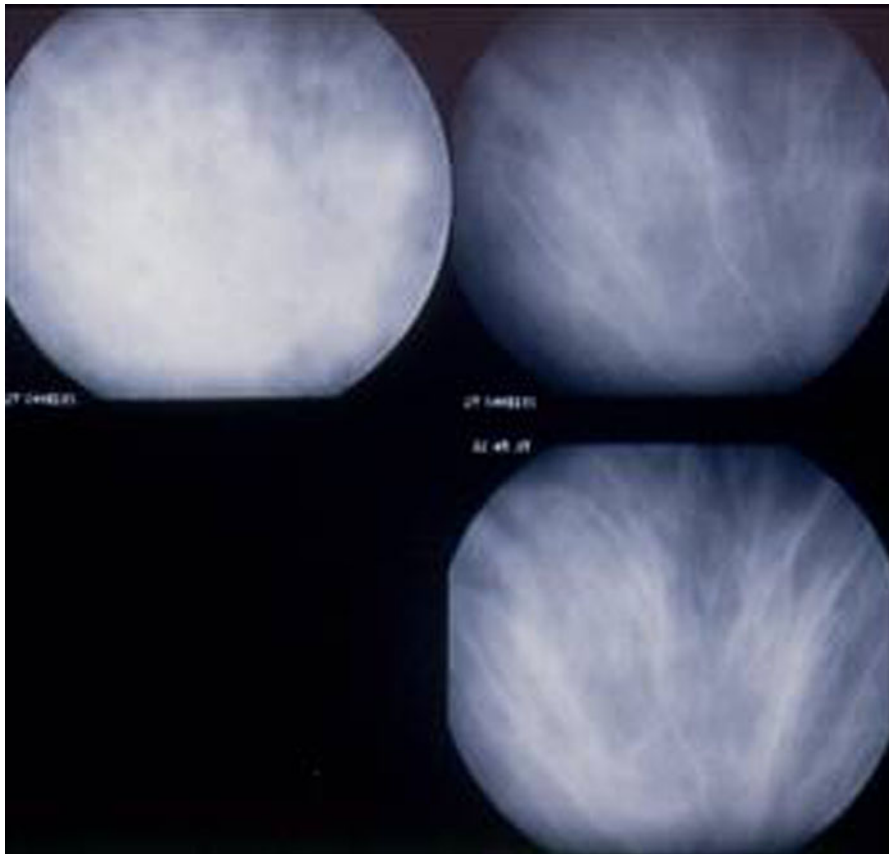
Table 3 Indocyanine green angiographic scoring system

Angiographic sign	Score
<i>Early stromal vessel hyperfluorescence at 0–5 min</i>	
Posterior pole	1
1–2 Quadrants	1
More than 2 quadrants	2
<i>Choroidal vasculitis at 10–20 min (fuzzy vessels)</i>	
Faint: fuzzy vessels, course recognizable (focal/diffuse)	1
Moderate: vessels more blurred but course can be guessed	
Localized/limited area (≤ 2 quadrants)	2
Diffuse (>2 quadrants)	3
Or fuzzy vessels without any recognizable course	
Localized/limited area (≤ 2 quadrants)	4
Diffuse (>2 quadrants)	6
<i>Dark dots or areas (excluding atrophy) (indicating choroidal stromal foci or choriocapillaris nonperfusion)</i>	
Posterior pole	
Sparse and/or faint	1
Numerous and/or pronounced	2
For each quadrant	
Sparse and/or faint	1
Numerous and/or pronounced	1.5
<i>Optic disc hyperfluorescence (>15 min)</i>	
Perceptible	1
Pronounced	3

Table 4 Total maximum score for ICG angiography

Angiographic sign	Maximum score
Early stromal vessel hyperfluorescence	3
Choroidal vasculitis (fuzzy vessels)	6
Dark dots	8
Optic disc hyperfluorescence	3
Total	20

additional score of 2 whether it was secondary to extensive retinal ischemia (Fig. 4) or severe intra-ocular inflammation (Fig. 5). Macular edema was graded from 1 to 4, with pooling of dye in cystic spaces at the macula receiving the highest score (Figs. 6–8). Staining of retinal vessel walls or

**Fig. 20** Indocyanine green angiography showing early stromal vessel hyperfluorescence in the posterior pole and in the quadrant shown (early hyperfluorescent vessel score = $1 + 1 = 2$)**Fig. 21** Indocyanine green angiography in a case of VKH disease showing fuzzy choroidal vessels, the course of which is no more recognizable in the top left picture (score = 6, as this picture was seen all over the fundus). After 3 days of intravenous methyl prednisolone the vessels remain fuzzy but

their course could be guessed in the top-right picture (score = 3, as this picture was diffuse). After several weeks of corticosteroid therapy fuzziness is faint and course of vessels is recognizable in the bottom picture (score = 1)

leakage of vessels may be focal/multifocal (Fig. 9) or may be diffuse along the course of vessels. We made this distinction only for posterior pole arcades (Fig. 10). Involvement of other parts of the retinal vascular tree was graded as only absent or present, with a score of 1 for each quadrant where this finding was seen to any extent. On the other hand, capillary leakage was considered a more important measure of inflammation and we tried to grade this finding instead of recording it as absent or present (Figs. 11–13). We did not consider retinal capillary nonperfusion (Fig. 14) as a direct measurement of inflammation. Therefore, extent of retinal capillary nonperfusion was graded according to the number of quadrants where it was present rather than the total area of nonperfused retina. Any area of capillary nonperfusion in the posterior pole was given an additional score of 1 with or without enlargement of the foveal avascular zone (Fig. 15). Pinpoint leakage and subretinal pooling of dye may be localized (Fig. 16) or extensive (Fig. 17); for example, late staining associated with a focus of toxoplasmic retinochoroiditis would get a score of 1 (Fig. 18), whereas acute posterior multifocal placoid pigment epitheliopathy with extensive involvement of the fundus would get a score of 4 (Fig. 19).

The proposed scoring system for ICGA and the total maximum score for each ICG angiographic sign are shown in Tables 3 and 4, respectively. Early stromal vessel hyperfluorescence is best appreciated in the posterior pole, but also in other parts of the fundus (Fig. 20). Ill-defined choroidal vessels are the hallmark of active choroidal vascular inflammation detected on ICGA. Although massive disruption of choroidal vessel walls results in diffuse choroidal hyperfluorescence it is difficult to quantify this finding. Therefore, grading was limited to the definition of course of choroidal vessels (Fig. 21). Dark dots on ICGA may be due to atrophy, choriocapillaris nonperfusion (Fig. 22), or impaired choroidal diffusion of ICG dye because of inflammatory choroidal lesions (choroidal foci) (Fig. 23). Atrophy must be excluded for this finding to be considered as a sign of active choroidal inflammation. In order to be able to monitor choroidal inflammation based on this finding we tried to grade the distribution, number, and prominence of dark dots (Fig. 24). Optic disc hyperfluorescence evaluated in the intermediate or late angiographic phase (>15 min) on ICGA is given a

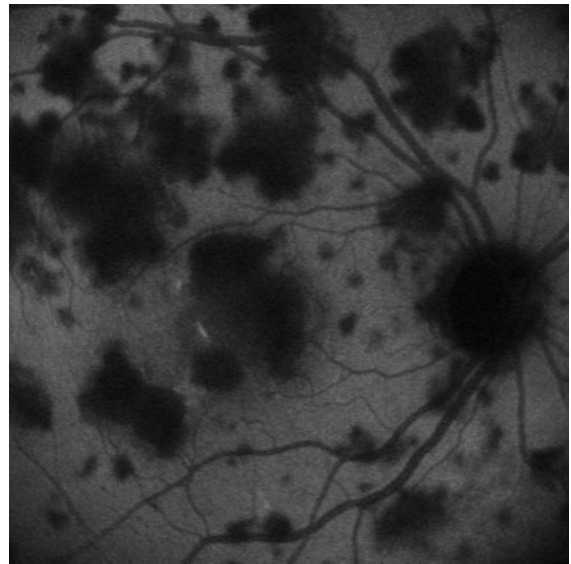


Fig. 22 Same eye as in Fig. 19, indocyanine green angiography showing dark dots corresponding to the active lesions seen on fluorescein angiography (score = 2 for this frame)

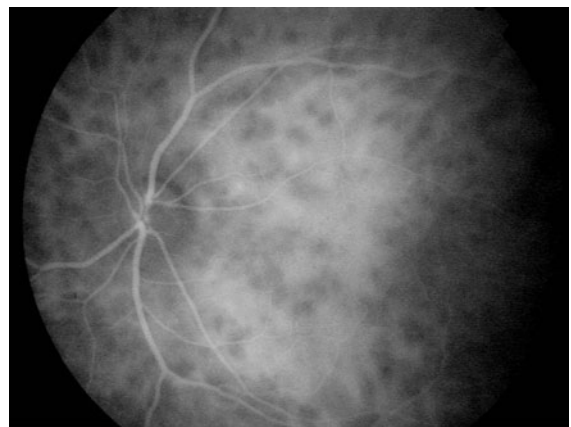


Fig. 23 Indocyanine green angiography showing numerous dark dots in the posterior pole of the left eye of a patient with Vogt-Koyanagi-Harada disease. Similar dots were seen in the periphery in all quadrants (dark dot score = 10)

score of 1 when perceptible (Fig. 25) and a score of 3 when pronounced (Fig. 26).

The total maximum score of FA is 40 and that of ICGA is 20 in the proposed system. When the ICGA score is multiplied by a coefficient of 2, it is possible to compare the score of the two angiographic studies and determine whether inflammation is preponderantly affecting the retina or the choroid.

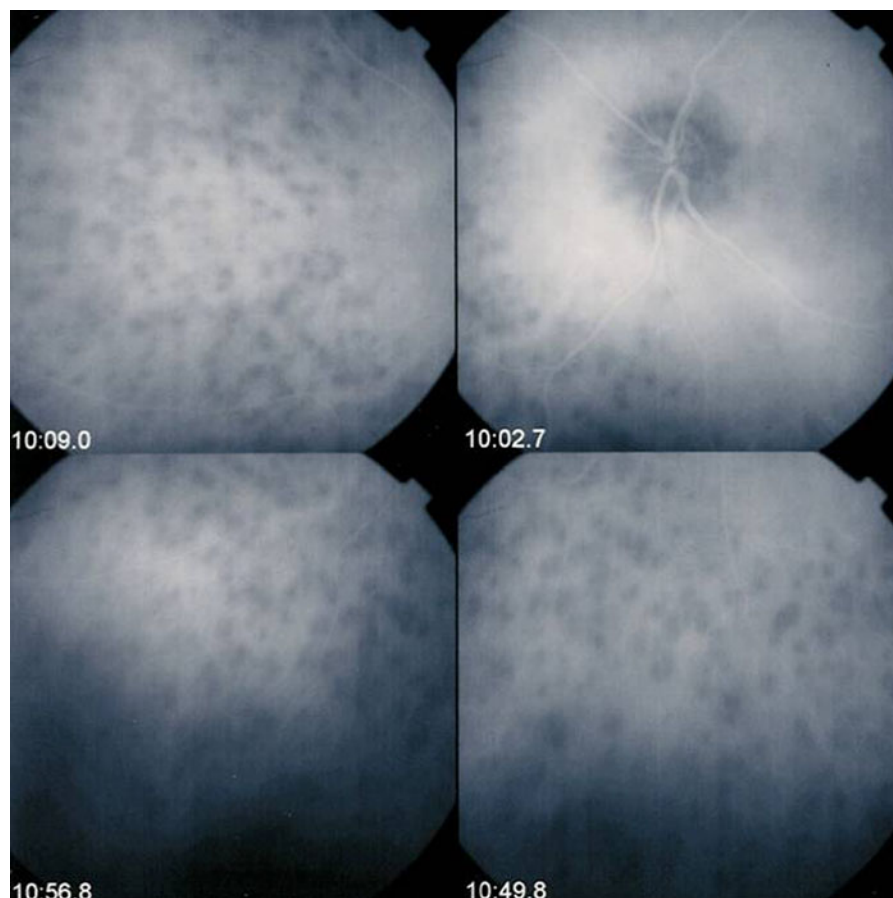


Fig. 24 Indocyanine green angiography showing numerous dark dots, faint or scarce in the posterior pole and pronounced in the peripheral quadrants of the fundus (score = 7)

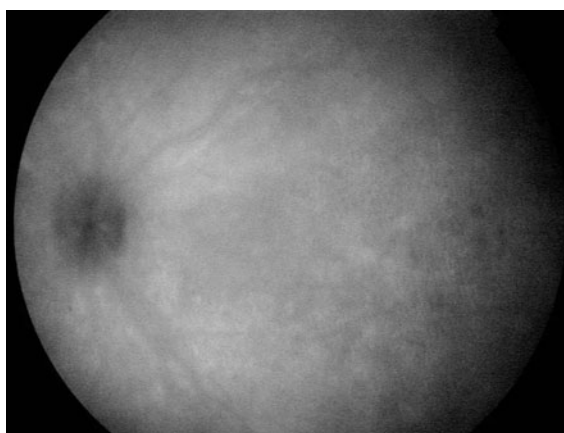


Fig. 25 Indocyanine green angiography showing perceptible optic disc hyperfluorescence (score = 1)

Discussion

Combined use of FA and ICGA in patients with uveitis may provide a thorough evaluation of posterior segment inflammation; it thus may help in discerning the predominant site of inflammation, and the relative extent and severity of inflammation in the retina versus the choroid can be appreciated by simultaneous angiographic imaging of both structures.

Present technology does not permit quantitative comparison of fluorescein or ICG angiograms or between the two studies. Other objective imaging methods such as optical coherence tomography yield quantifiable data, yet angiography remains the mainstay of our evaluation of posterior segment inflammation. At this stage of knowledge and experience with the use of

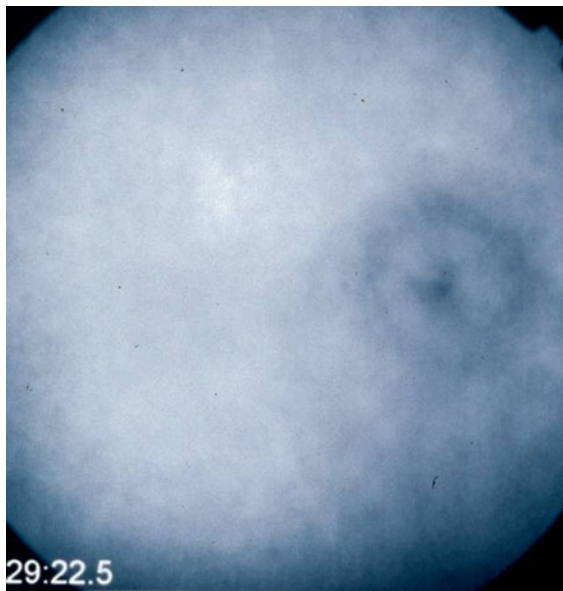


Fig. 26 Indocyanine green angiography showing pronounced optic disc hyperfluorescence (score = 3)

FA and ICGA, analysis of angiograms should not remain only descriptive. Until the technology develops, the use of a scoring system may help in patient follow-up and clinical research. The combined fluorescein and ICG angiographic scoring system proposed here is semiquantitative. Recording of angiographic findings as present or absent could have produced a simpler scoring system. However, a simple scoring system would be easy to use but inefficient in evaluating the amount of inflammation. Therefore, we tried to score both the extent (area of fundus involved) and the magnitude (severity) of the most important parameters that were thought to correlate most with the degree of intraocular inflammation; for example, macular edema is scored as present or absent in the system proposed by BenEzra et al. [33]. However, various grading systems have been used in studies where the amount of angiographic macular edema was the primary outcome measure. In these studies, grading of macular edema was based on the percentage of macular area with late leakage [39, 40] or on the circumference of perifoveal ring of leakage and/or the area of hyperfluorescence measured by disc diameters [41–44]. Although macular edema is the most frequent vision-threatening complication of uveitis, it is not always a direct measure of active intraocular inflammation because it may persist after acute signs of inflammation subside. Therefore, we propose a grading system that is simpler than that used in other

studies but still quantifies the amount of macular edema. On the other hand, we considered retinal capillary leakage as the most important measure of intraocular inflammation and tried to grade the extent of this angiographic finding. In previously published fluorescein angiographic scoring systems, retinal capillary leakage was not scored separately [33] or was only grossly scored [34].

The applicability of the system proposed here needs to be tested in clinical settings. Intra- and interobserver variations need to be determined. Even if it proves to be useful in only some of the uveitic conditions, it will be a major advance in standardizing data obtained by an essential method that we all use in our patient care. The compatibility of the scoring system with other imaging systems such as systems using scanning laser ophthalmoscopy should also be tested, at least for some of the angiographic findings, and is presently underway to verify whether the scoring parameters can also be used with these angiographic systems.

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