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Fluorescein angiography and indocyanine green angiography for identifying occult choroidal neovascularization in age-related macular degeneration

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PURPOSE. *To assess whether fluorescein angiography (FA) alone without indocyanine green angiography (ICGA) can identify and localize occult choroidal neovascularization (CNV) in age-related macular degeneration (ARMD).*
METHODS. *Seventy-nine eyes of 77 consecutive patients with occult CNV were evaluated independently by two skilled physicians at first with FA alone and then with FA combined with ICGA by fundus camera.*
RESULTS. *The agreement between FA and ICGA was 73% and 68% for the two physicians (K=0.585 and 0.512, respectively). The first operator correctly identified 20/27 as plaque CNV; six had different sizes and locations. The second operator identified 25/30, with one mistaken for size and location. For focal CNV the first operator identified 34/39, and the second one 23/35.*
CONCLUSIONS. *Comparing the FA results with ICGA, CNV was correctly identified in about 60% of cases. Therefore, ICGA should be considered an indispensable diagnostic test to identify the presence, the type, and the location of occult CNV. (Eur J Ophthalmol 2005; 15: 759-63)*

KEY WORDS. *Age-related macular degeneration, Fluorescein angiography, Indocyanine green angiography, Occult CNV*

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INTRODUCTION

Fluorescein angiography (FA) can correctly identify choroidal neovascularization (CNV) in age-related macular degeneration (ARMD) in only 13% of the overall cases, the rest being considered occult CNVs (1).

Indocyanine green angiography (ICGA) allows the detection and delineation of CNVs, occult at FA, in 60 to 70% of the cases and is therefore considered complementary to FA in most instances (2).

The aim of this study was to assess whether it is possible to detect CNV using only FA, without ICGA, after 10 years of working with ICGA.

MATERIALS AND METHODS

Seventy-nine eyes of 77 consecutively recruited patients with ARMD complicated with occult CNV were evaluated by FA and ICGA. There were 32 men (41.5%) and 45 women (58.5%), mean age 71±6.3 years. All the patients complained of a decrease of visual acuity associated with mild or moderate metamorphopsia. All the eyes had FA typical of occult CNV. CNV is considered occult as a late leakage of an undetermined source and fibrovascular pigment epithelial detachment. Exclusion criteria were images of poor quality, previous treatments (such as laser photocoagu-

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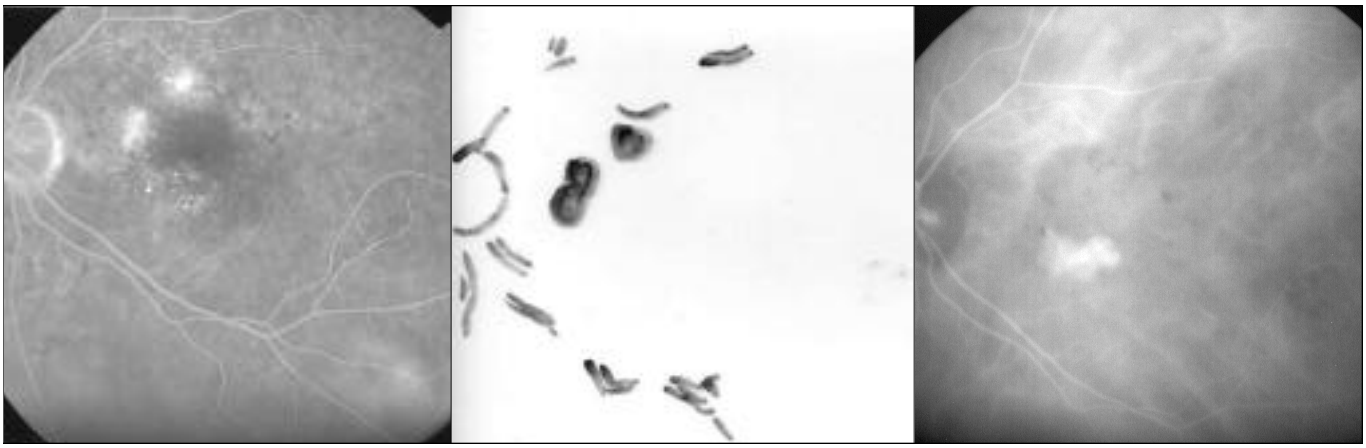

Fig. 1 - *In the middle is outlined the sites of the suspected choroidal neovascularization (CNV) on transparent paper overlying the digital fluores cein angiography (FA) image (left). The transparent sheet is superimposed on the corresponding indocyanine green angiography (ICGA) image (right). In this case the ICGA evidences a plaque CNV while two focal CNV have been drawn on the sheet.*

lation, photodynamic therapy, transpupillary thermotherapy), polypoidal lesions, or retinochoroidal anastomosis. Eyes with huge hemorrhages with blocked fluorescence also were excluded.

The eyes were studied by FA and ICGA using a Topcon Imagenet System (The Netherlands) after intravenous injection of 2 mL of 20% sodium fluorescein and, for ICGA, 25 mg of Infracyanine SERB (Laboratoires Pharmaceutiques, Paris, France) diluted in 10 mL of aqueous solvent. FA and ICGA were performed simultaneously. No stereo images were taken.

Images were recorded during the early (up to 2 to 3 minutes from the injection), middle (5 minutes), and late phases (10 minutes); later photographs were also taken at 10 minutes for FA and 30 minutes for ICGA.

The eyes were evaluated by two experienced physicians (A.P., G.V.) in two steps: the first with FA, and the second also with ICGA images. The two sets of images were complementary to one another. The two physicians performed their interpretation completely independently.

First phase

Each operator outlined the site of the suspected CNV, defining its dimensions, drawing the perimeter of the lesion margins on transparent paper overlying the digital FA image. They considered the following possibilities: absence of CNV, plaque CNV, focal CNV, multifocal CNV, mixed form, not evaluable. They were provided with the initial, middle, and late phases for each eye.

Second phase

Each transparent sheet was superimposed on the corresponding ICGA image at the same magnification as the FA and the two examinations were compared. On the basis of the ICGA images, the type, dimension, and site of the CNV were evaluated (Fig. 1). The CNV, according to published classifications, was defined as follows: focal CNV (area no more than 1 disc diameter); plaque CNV (area larger than 1 disc diameter), which may be well-defined or ill-defined; multifocal CNV (several focal CNV); mixed forms (focal and plaque CNV); no CNV; not evaluable. Statistical analysis was done using the chi-square test and the K statistic, which is a measure of the reliability of two categorical variables (FA and ICGA classification). K values lower than 0.4 have a low agreement; K between 0.4 and 0.75 agreement is fair to good; K values larger than 0.75 indicate close agreement. The ICGA evaluation given by each operator is taken as the reference for this calculation. FA alone is tested for agreement with the reference.

RESULTS

In the first phase, which considered the eye's classification by FA alone, 43/79 (54%) eyes were classified equally (K=0.291) by the two physicians (Tab. I).

In the second phase, which considered the ICGA classification of CNV, 57/79 (72%) eyes (K=0.621) were concordant for both physicians (Tab. II).

TABLE I - CHOROIDAL NEOVASCULARIZATION (CNV) CLASSIFICATION BY FLUORESCEIN ANGIOGRAPHY (FA) ALONE FOR EACH OPERATOR

	FA–I operator	FA–II operator	Agreement
Plaque CNV	26	40	18
Focal CNV	43	29	24
Multifocal CNV	5	4	1
Plaque+focal CNV	–	–	–
Total			43/79

TABLE II - CHOROIDAL NEOVASCULARIZATION (CNV) CLASSIFICATION BY INDOCYANINE GREEN ANGIOGRAPHY (ICGA) FOR EACH OPERATOR

	FA–I operator	FA–II operator	Agreement
Plaque CNV	27	30	23
Focal CNV	39	35	29
Multifocal CNV	7	5	4
Plaque+focal CNV	2	8	1
Total			57/79

Taking the ICGA findings as the reference, the agreement between the two physicians was low in relation to the expected K value (K>0.75).

As the reference could thus not be considered univocal, concordance was calculated on the basis of each single operator's reference. If we consider the classification according to FA and ICGA for each single operator, the agreement still showed low K-values for all types of CNV (Tab. III). The first physician correctly classified 58/79 (73%) eyes (K=0.585) and the second one 54/79 (68%) eyes (K=0.512). The first operator correctly classified 20/27 (74%) eyes as plaque CNV and the second operator 25/30 (83%). Focal CNV was correctly identified in 34/39 (87%) and 23/35 (66%) eyes, respectively.

For plaque CNV, concordance for the first opera-

TABLE III - DISTRIBUTION OF THE CLASSIFICATION BY FLUORESCEIN ANGIOGRAPHY (FA) ALONE AND INDOCYANINE GREEN ANGIOGRAPHY (ICGA) FOR EACH OPERATOR

FA		ICGA Plaque	Focal	Multifocal	Plaque+focal	No CNV	Not evaluable
Plaque	1*	20	3	1	–	–	2
	2†	25	12	–	3	–	–
Focal	1*	4	34	3	1	–	1
	2†	1	23	1	3	–	1
Multifocal	1*	2	–	3	–	–	–
	2†	–	–	4	–	–	–
Plaque+focal	1*	–	1	–	1	–	–
	2†	4	–	–	2	–	–
No CNV	1*	1	1	–	–	–	1
	2†	–	–	–	–	–	–
Not evaluable	1*	–	–	–	–	–	–
	2†	–	–	–	–	–	–

*First operator, †Second operator; CNV = Choroidal neovascularization

TABLE IV - AGREEMENT BETWEEN FLUORESCEIN ANGIOGRAPHY (FA) AND INDOCYANINE GREEN ANGIOGRAPHY (ICGA) FOR EACH OPERATOR IN ALL TYPES OF CHOROIDAL NEOVASCULARIZATION (CNV)

	Eyes concordant–I operator	K values–I operator	Eyes concordant–II operator	K values–II operator
Plaque	20	(k=0.631)	25	(k=0.495)
Focal	34	(k=0.569)	23	(k=0.475)
Plaque+focal	1	–	2	–
Multifocal	3	–	4	–
Not evaluable	–	–	–	–
No CNV	–	–	–	–
Total	58/79		54/79	

tor gave K=0.631 and K=0.495 for the second. For focal CNV agreement was respectively K=0.569 and K=0.475. Concordance for other types of CNV was not tested because of the small number of eyes in this sample (Tab. IV).

Thus, the first operator wrongly classified 21 out of 79 eyes (27%) when reading FA alone (misclassified); the second operator had 25/79 (32%) eyes differently classified. The two proportions are similar (p=0.62) but only 14 eyes were similarly misclassified by both physicians (14/21=45.2% for the first operator and 14/25=50% for the second). Agreement between the two operators was low even in misclassified eyes (K=0.163).

Even when the two operators correctly classified the eyes as regards the type of CNV, its dimension and/or location were not always properly identified. The first physician identified 20/27 eyes as plaque CNV in both evaluations, but only 14 were definitely equal; in fact six eyes were differently dimensioned. In total 14/27 eyes (52%) were correctly identified. Moreover, of the 34 focal CNV eyes (39 eyes identified by ICGA), four were mistaken, two because of their dimension and two because of their location (30/39; 77% correctly identified). One mixed form was mistaken for dimension and of the three multifocal CNV identified, only one was definitely equal. For the second physician one plaque CNV was mistaken on account of its dimension (24/30; 80%) and two eyes were classified as focal CNV (21/35; 60%); of the two mixed forms one was equal and two multifocal CNV were mistaken because of their dimension. In total the CNV correctly identified by FA in comparison with ICGA amounted to 46/79 (58%) for the first operator and 48/79 (60%) for the second.

If all these cases are omitted from the calculation of the kappa statistic, the new values are lower than those previously reported. In fact, for plaque CNV kappa is respectively 0.430 and 0.489 for the first and second operator and 0.569 and 0.475 for focal CNV.

DISCUSSION

ICGA was introduced into clinical practice in 1992, and has proved invaluable in many pathologies (3). It shows 60 to 70% of the CNVs in ARMD that were occult by FA. ICGA enables us to better see where CNV are located and sometimes helps us to correctly identify them on the basis of FA alone, which often shows focal alterations of the retinal pigment epithelium (RPE), with small hemorrhages corresponding to the site of the CNV. The delineation of CNV by ICGA is correct in most of the cases even if clinical experience indicates that sometimes the ICGA patterns are difficult to interpret. Moreover ICGA findings also depend on the imaging system used and we well know that confocal scanning laser, not used in this study, can better identify CNVs in the early phase frames.

Thus, after 10 years' experience using ICGA, how many of the CNV that are occult on FA can a skilled operator detect in the FA alone?

Comparing two physicians' interpretations of CNV, we found their opinions were comparable in 54% of cases using FA alone and in 72% when using ICGA alone.

These differences are due to the fact that even with good-quality images from the same instrument, interpretation is necessarily subjective, especially for some lesions that are not clearly defined, e.g., poorly defined plaque.

In addition, in cases with extensive, deep hemorrhages it can be hard to properly visualize the entire extent of CNV. We have already reported that in our experience — unlike Guyer et al (4) — about 30% of cases presented difficulties in ICGA interpretation, making precise classification impossible (5).

Taking the ICGA interpretation as the reference, agreement between FA and ICGA was 73% for the first operator and 68% for the second.

The first identified focal CNV better than the second (34/39 as opposed to 23/35), but the second operator identified plaque CNV better than the first (25/30 as opposed to 20/27). The explanation of these differences — apart from individual experience — lies in the difficulty of assessing ICGA findings. Even when the ICGA identification of CNV is correct, the size and locations of the lesions may appear different to different operators, and are therefore further factors potentially lowering the agreement between them.

In conclusion, this study found that operators with many years of experience with ICGA could correctly identify about 60% of occult CNV using FA alone.

We are convinced this proportion is too small for a reliable assessment of whether a patient has CNV and for FA-guided treatment for occult CNV.

Thus, ICGA is an indispensable diagnostic tool for assessing the presence, type, and location of these lesions (6). ICGA should also be used in study protocols and in major therapeutic trials for future investigations in ARMD.

The authors have no proprietary interest in any aspect of the article.

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