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The diagnostic contribution of indocyanine green to fluorescein angiography in fellow drusen eyes of patients with wet age-related macular degeneration

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PURPOSE. *To assess the contribution of indocyanine green angiography (ICGA) to fluorescein angiography (FA) in evaluating fellow drusen eyes of patients with wet age-related macular degeneration (AMD) in the other eye.*
METHODS. *The records of paired FA and ICGA of patients with dry AMD in one eye and wet AMD in the other eye were retrospectively reviewed. Based on color fundus photographs, drusen were graded to low, moderate, or high grade of severity on FA. The FA and ICGA findings were compared.*
RESULTS. *Fifty-two pairs of eyes were included. Fluorescein angiography showed drusen of low severity in 11 (21.2%) eyes, of moderate severity in 31 (59.6%), and of high severity in 10 (19.2%). Leakage on both FA and ICGA was not demonstrated in any case of drusen of low or moderate severity. Only in 2 out of 10 eyes from the high severity group, 3.8% of the eyes of the whole study population, did ICGA reveal occult choroidal neovascularization (CNV) that was not observed on FA.*
CONCLUSIONS. *In selected eyes with drusen of high grade severity, ICGA may detect occult CNV, unrecognized clinically or by FA. ICGA had a small contribution to the diagnosis of occult CNV in fellow drusen eyes with any degree of severity. (Eur J Ophthalmol 2007; 17: 615-9)*

KEY WORDS. *Indocyanine green angiography, Fluorescein angiography, Wet age-related macular degeneration*

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INTRODUCTION

Digital indocyanine green angiography (ICGA) enhances imaging of the choroidal circulation (1). The benefit of using ICGA as an adjunctive technique to fluorescein angiography (FA) in the detection of choroidal neovascularization (CNV) has been established (1, 2). ICGA was particularly useful in identifying occult CNV (1-4). It was suggested that ICGA may be performed in eyes in which well-delineated neovascularization cannot be identified by fluorescein angiography (5).
Recently, new applications of ICGA have been reported for better diagnosis and treatment such as identification of feeder vessels, better visualization of retinal angiomatous proliferation, and evaluation of polypoidal choroidal vasculopathy (6-10).
Hanutsaha et al and Schneider et al found abnormal findings on ICGA in 11% and 9%, respectively, when they examined fellow eyes of patients with wet AMD in one eye and fluorescein angiographically nonsuspicious drusen in fellow eye (11, 12). However, to our knowledge, additional information regarding the contribution of ICGA to FA in high category risk drusen eyes for developing wet AMD is not available.

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The aim of this study was to further investigate the contribution of ICGA to FA in fellow drusen eyes of patients with unilateral wet AMD in our population.

MATERIALS AND METHODS

Selection of study population

Consecutive angiographic records of patients with unilateral wet AMD in one eye and drusen in fellow eye undergoing both FA and ICGA were retrospectively reviewed. Inclusion criteria were as follows: 1) 50 years or older, 2) wet AMD in one eye, 3) drusen without clinical and fluorescein angiographic evidence of CNV in the fellow eye, 4) clear ocular media, 5) no other retinal disease. Exclusion criteria were as follows: 1) fluorescein angiograms with findings suspicious for CNV due to AMD, 2) other retinal diseases and eyes with geographic atrophy.

Study design

Patients' demographic characteristics, data of initial visual acuity (VA), measured by Snellen chart, and of ophthalmic examination, including biomicroscopy, applanation tonometry, and contact lens funduscopy, were assessed. Color fundus photography, FA, and ICGA were analyzed by a retina specialist.

The drusen were classified into hard or soft drusen types according to the clinical color photographs and FA. Hard drusen were defined clinically as small (less than 63 μm) and round lesions with well-defined borders. On FA, hard drusen exhibited early hyperfluorescence. Soft drusen were larger than 125 μm with less well-defined margins. On FA, soft drusen became hyperfluorescent later and showed less intensive fluorescence compared to hard drusen.

Wisconsin AMD Grading System was used for determination of posterior pole subfields division and drusen characteristics (13). According to this Grading System, nine subfields were defined and four characteristics of drusen were classified. Parameters for drusen classification on color photographs or fluorescein angiography consisted of predominant drusen type, maximum drusen diameter, area size occupied by the drusen (number of subfields), degree of confluence, and pigmentation. Fading of dye in late FA exposures was also included.

Based on the above characteristics, the drusen were classified into three groups of severity: low, moderate, and high (Tab. I).

TABLE I - GRADING OF DRUSEN SEVERITY

	Grade of severity		
Clinical appearance	**Low**	**Moderate**	**High**
Type	Hard	Hard/soft	Soft
Maximal diameter, μm	<63	63–125	126–249
No. of subfields	1–2	3–4	5–9
Pigmentation	–	+/–	+
Confluence	–	+/–	+
FA fading of hyperfluorescence	+	+/–	–

FA = Fluorescein angiography

TABLE II - DISTRIBUTION OF ABNORMAL ICGA FINDINGS ACCORDING TO THE GRADE OF SEVERITY

	Grade of severity, no. of eyes (%)(n = 52)		
	Low, 11 (21.2)	**Moderate, 31 (59.6)**	**High, 10 (19.2)**
Abnormal ICGA leakage	0	0	2 (20)

ICGA = Indocyanine green angiography

An ICGA study was interpreted as normal if no abnormalities in dye filling of both choroidal and retinal vascular systems were noted. However, if there was evidence of abnormal hyperfluorescence, either as a focal spot (less than one disc area in size) or as a plaque (greater than one disk area in size), ICGA was defined as abnormal.

Outcome measures

The primary outcome measure was an abnormal hyperfluorescence on ICGA, which was not observed on FA of drusen eyes.

Statistical analysis

The chi-square test was used for statistical analysis.

RESULTS

Fifty-two pairs of eyes met inclusion criteria and were included into study. Twenty-four (46.2%) patients were men and 28 (53.8%) were women. The mean age of the patients was 76.9±8.2 years (range 63–92).

According to the drusen characteristics, 11 eyes (21.2%) were classified as low grade of severity, 31 (59.6%) of moderate severity, and 10 (19.2%) of high severity. There were no statistically significant differences in age or gender between the groups.

Initial VA of 20/50 or better was observed in 9 out of 11 (81.8%) eyes of low severity group, in 24 out of 31 (77.4%) eyes of moderate severity group, and in 7 out of 10 (70%) eyes in high severity group. A percentage of good initial VA was better in low severity group and worse in high severity group. The difference between the groups was not significant.

Fifty out of 52 eyes (96.1%) demonstrated no leakage on both FA and ICGA. Leakage on both FA and ICGA was not demonstrated in any case of drusen of low or moderate severity. In the high severity group, in 2 out of 10 (20%) eyes (3.8% eyes of the whole study population), ICGA revealed abnormal hyperfluorescence, which was not observed on FA. There was evidence of focal spot in both eyes. VA at the time of angiography was 20/30 and 20/200 in the drusen eyes.

Analysis of risk factors for abnormal ICGA findings revealed that abnormal findings on ICGA were observed in the high grade of severity 2/10 (20%) (Tab. II). Retinal pigment epithelial hyperpigmentation was also noted in those cases.

DISCUSSION

The findings of this study show that in two eyes with drusen of high severity, which comprise only 3.8% eyes from the whole study population, ICGA disclosed abnormal findings in fellow drusen eyes when there was no suspicion for CNV on clinical examination or on FA. This incidence is lower than found by Hanutsaha et al, who studied a series of 432 consecutive patients diagnosed with unilateral exudative AMD in whom the fellow eye had only drusen by clinical fundus examination and fluorescein angiography and found a higher incidence of 11% (46 eyes) abnormal findings on ICGA (11). Out of 46 eyes, 10 (21.7%) showed focal spots and 36 (78.3%) showed plaques (11). Schneider et al found an incidence of 9% (12). However, when we performed an analysis of the occurrence of abnormal ICGA in accordance with the grade of drusen severity, we found that all of the abnormal findings occurred in drusen eyes with high degree of severity included in each group. In this group it occurred in as high as 20%. The difference between our findings and Hanutsaha et al group may be explained by the difference in drusen grading of severity (11). The grade of severity may also explain the fact that in our study only focal spot was found as compared to the Hanutsaha et al study, which found focal spot and plaque (11). The difference in sample size may also contribute to different findings.

According to the classification used in Age-Related Eye Disease Study (AREDS), all study eyes were considered to be high risk drusen eyes for developing AMD, because of being fellow eyes of wet AMD. However, it should be emphasized that all eyes that showed ICGA abnormal findings were from high severity group. These eyes may be classified to 4a category, in view of the fact that large drusen were seen in these eyes (14).

We used the grading system suggested by Klein et al for bilateral drusen eyes and extrapolated it to the AREDS classification (13).

Thus, in view of the fact that abnormal findings demonstrated on ICGA showed signs of occult CNV, ICGA may be used in addition to FA to clarify the clinical picture in selected cases with high risk drusen and to identify occult CNV (15).

Although it is not necessary to perform ICGA according to

the Photodynamic Therapy Studies, identification of occult CNV may be important in the highlight of the results of photodynamic therapy with verteporfin that showed benefit of treatment in eyes with occult CNV (16). In these cases, ICGA may be a tool for early detection and follow-up of patients with high grade severity drusen eyes.

Hanutsaha et al, who also investigated whether ICGA can predict future development of wet AMD, found that eyes with abnormal findings on ICGA in spite of normal FA showed greater incidence (24%) of wet AMD development in comparison to eyes with no abnormal ICGA findings (10%) (11). Thus, ICGA may be considered a predictive value for the course of maculopathy in drusen eyes with high grade of severity.

An evidence-based update of Stanga et al showed that presumed occult CNVs can be identified much more clearly with ICGA (17). The ICGA may show hot spots and well-defined membranes confirming the presence of CNV. They concluded that, although the predictive value of the appearance of FA and ICGA in drusen has not been clearly established, there was evidence that drusen that show abnormal hyperfluorescence, either focal spots or plaques, more commonly proceed to exudative AMD.

In regard to other risk factors for wet AMD, it has been shown that a presence of large drusen was found to be an independent risk factor for the subsequent development of neovascularization in the fellow eye (relative risk, 2.4). Only 10% of eyes with no large drusen or any retinal pigment epithelial hyperpigmentation compared with 58% of eyes with both large drusen and retinal pigment epithelial hyperpigmentation developed neovascularization in the fellow eye within 5 years (18). In the present study, those two eyes with positive ICGA abnormal hyperfluorescence and negative FA had large drusen and also pigment hyperpigmentation.

ICGA appearance of drusen depends on type of drusen (15, 19). Hard drusen, either isolated hard drusen or hard cluster-derived drusen, are usually hyperfluorescent. When smaller hard drusen located more peripherally, it is difficult to distinguish from the background fluorescence, so they are isofluorescent during indocyanine green angiography. In contrast, all sizes of soft drusen derived from clusters of hard drusen were hypofluorescent that most marked in the early-mid phase ICG study and persisted into the late phase throughout the angiogram (15). The present findings are consistent with the described pattern of fluorescence among different types of drusen.

When we examined initial VA according to the groups of drusen severity, a tendency for better VA in low severity group and worse VA in high severity group has been observed. Investigators of the AREDS study used VA as one of the inclusion criteria, which was at least one eye with a VA of 20/32 or better, and found mean VA of about 20/25 in the better eye of participants (20, 21). Other investigators who studied patients with dry AMD did not include VA for characterizing dry AMD (15, 22, 23). We also did not use initial VA for grading or for inclusion criteria. However, a finding of worse initial VA in high severity group may be explained by the natural history of dry AMD, which is accompanied by marked VA loss (20).

Limitations of this study are its retrospective nature and small sample size. However, it provided some information about correlation between FA and ICGA in our population. The conclusion from the present findings is that in eyes with drusen of high grade severity, ICGA enhanced imaging of occult CNV, not observed by FA. In this selected group of eyes, ICGA may be considered in the treatment regime of occult CNV.

Proprietary interest: None.

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