Indocyanine Green Angiography of Well-Defined Plaque Choroidal Neovascularization in Age-Related Macular Degeneration

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Objective: To determine the natural course of well-defined plaque choroidal neovascularization (CNV) using indocyanine green angiography.

Methods: Two ophthalmologists, experts in macular diseases and indocyanine green angiography, examined 40 eyes with exudative age-related macular degeneration and a well-defined plaque CNV using complete ophthalmoscopic evaluation, fluorescein angiography, and indocyanine green angiography. The increase in the size of the plaques was analyzed using multivariate analysis, in relation to the worsening of visual acuity, with adjustment for age, sex, and length of follow-up.

Results: Mean follow-up was 13.5 months (median, 11 months). Initial and final mean visual acuity were 20/46 (median, 20/50) and 20/65 (median, 20/100), respectively. The mean initial size of the plaque was 6.62 mm² (median, 6.20 mm²), and the mean final size was 10.40 mm² (median, 9.76 mm²). The enlargement was statistically significant (P<.001).

Conclusions: We found that plaque CNV tends to become larger with time, the enlargement reaching about 40% in 1 year of follow-up. The resulting loss of visual acuity, however, is not significant, and is slightly correlated with the extension of the lesion; it also does not appear to be directly related to sex.

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The exudative form of age-related macular degeneration (ARMD) is marked by occult choroidal neovascularization (O-CNV), not clearly detectable by fluorescein angiography (FA) in 87% of cases.¹ Indocyanine green angiography (ICGA) identifies 90% of O-CNV, dividing it largely between focal CNV (29%) and plaque CNV (61%); the remaining 10% are ill defined. Plaque CNV can be further divided according to ICGA appearance of being well defined (27% of all CNV) and poorly defined (34% of all CNV).² Little is known about the natural history of these plaques, which some reports describe as slowly developing, not very aggressive CNV, with fairly good visual acuity (VA),³ and others describe as quickly developing, with a poor natural history.²

Our aim was to analyze the natural course of well-defined plaque CNV in relation to their enlargement, VA, and length of follow-up.

The correlation coefficients between the plaque measurements taken by both observers were 0.91 (P<.001) at baseline and 0.95 (P<.001) at the final examination. Mean follow-up was 13.5±8.5 months (range, 6-36 months; median, 11 months). Initial and final mean VA were 20/46±20/95 (median, 20/50) and 20/65±20/83 (median, 20/100), respectively, with a mean change of 20/166±20/105 (median, 20/200), which was statistically significant (P<.001).

The mean initial size of the plaque was 6.62±3.71 mm² (median, 6.20 mm²), and the mean final size was 10.40±6.40 mm² (median, 9.76 mm²), with a mean change of 3.78±4.80 mm² (median, 2.65 mm²). The enlargement was statistically significant (P<.001).

When the effect of the increase in the plaque size on the worsening of VA was investigated using multivariate analysis with adjustment for age, sex, and follow-up time, the increase was slightly, but not significantly, correlated with VA loss (partial R²=0.06; P=.09). Age (partial R²=0.12; P=.03) and length of follow-up (partial R²=0.11; P=.02) were the variables most closely correlated with the VA changes, being greater at higher VA change. Women had less...
MATERIALS AND METHODS

We examined 383 eyes of 355 consecutive patients with exudative ARMD and occult new vessels on FA; 117 were men and 238 were women. The mean age was 73.4 years (range, 55-92 years). Indocyanine green angiography failed to identify CNV in 122 eyes (32%); 132 eyes (34%) had focal CNV; and 129 eyes (34%) showed plaque CNV, ill-defined in 74 (57%) of the 129 eyes and well-defined in 55 (43%). Therefore, in our prospective study, we examined 55 eyes of 52 patients, 22 men and 30 women. At the end of follow-up, 12 patients (15 eyes) were excluded; 2 of them (3 eyes) died, 5 (6 eyes) had evident subfoveal CNV (and an ill-defined plaque CNV, not evaluable by the 2 observers), and 5 (6 eyes) did not return for visits. We therefore considered 40 eyes of 40 patients, 17 men and 23 women (mean±SD age, 72 ± 5.7 years) with exudative ARMD, with O-CNV on FA and well-defined plaque CNV on ICGA. There was no FA evidence of pigment epithelial detachment. All patients underwent a complete clinical ophthalmologic examination, including best corrected VA (recorded on standard Snellen charts), color retinography, FA, and ICGA. Fluorescein angiography and ICGA were performed no more than 3 days apart, and frequently on the same day. Informed consent was obtained. The angiographic examinations were performed using a complete high-resolution digital system (Topcon IMAGEnet 1024 System; Topcon Corporation, Tokyo, Japan) with a fundus camera (TRC-50IA; Topcon Corporation). For ICGA, 25 mg of indocyanine green (Infracyanine) diluted in 10 mL of aqueous solvent was injected into the antecubital vein; early (from choroidal filling to the retinal venous phase, up to 5 minutes), middle (10-15 minutes), and late phases (30-40 minutes) were recorded for each patient.

Inclusion criteria were ages 55 years or older, recent onset of symptoms (decrease of VA and/or metamorphopsia no more than 3 months before entry), ARMD without a well-defined CNV on FA, a clearly outlined area of ICGA hyperfluorescence (larger than 1 disc area) presumed to be a well-defined plaque CNV, initial VA of greater than 20/200, and minimum follow-up of 6 months. Exclusion criteria were presence of fibrous proliferation, previous macular laser treatment or surgery, no clear ocular media, and other disease affecting the posterior pole.

Well-defined plaque is characterized by a hyperfluorescent lesion on ICGA larger than 1 disc area, with sharp borders, well detectable in the middle and late angiographic phases.

Two ophthalmologists, both experts in angiography and macular pathology (A.P. and U.I.), independently outlined the plaque in the late phase of ICGA with the use of the area measurement device of a complete high-resolution digital system (Topcon IMAGEnet 1024 System, Topcon Corporation) (Figure 1). Neither knew the patients' names or the examination dates.

As the variables were not normally distributed (Shapiro-Wilk statistic), nonparametric tests were used. Agreement between observers was assessed using the Spearman coefficient to correlate measures taken by both independent observers. The signed rank test was used to investigate whether VA and the size of the plaques changed after follow-up. To investigate the independent effects of increasing severity of plaques, age, sex, and follow-up on the worsening of VA, multiple stepwise regression was performed after rank transformation of the dependent-variable VA change. Partial $R^2$ expressed the contribution of each variable. Classes of plaque increase were set up on the basis of quartiles of distribution, and the Kruskal-Wallis test was used to compare variables for the different classes of plaque increase. Analyses were performed using the SAS System. Unless otherwise specified, data are given as mean±SD.
loss of VA, but the difference was not significant (partial $R^2=0.09$; $P=.07$).

The Table presents patient data by quartiles of change in plaque size.

**COMMENT**

Freund et al reported that approximately 13% of the CNV lesions they studied were well defined by FA, with the remaining 87% considered occult. Indocyanine green angiography is a new technique that enhances imaging of the choroid and has been shown to be useful in better delineating O-CNV. The characteristics of the dye (fluorescent in the near infrared range and almost completely protein bound) have permitted better investigation of the choroidal abnormalities through the pigmented epithelium, hemorrhages, and turbid fluids. Indocyanine green angiography identifies the O-CNV better. It delineates focal, plaque, or mixed (focal and plaque) CNV. Focal CNV (29% of cases) is a bright, well-defined, hyperfluorescent lesion smaller than 1 disc area. Plaque is a large area of hyperfluorescence bigger than 1 disc area that may be well defined (27% of patients) or poorly defined (34% of patients). Well-defined plaques are moderately hyperfluorescent lesions with sharp borders, and they usually appear in the late phase of the ICGA, without any dye staining. Poorly defined plaques show irregular, unclear edges and often leak dye during the late phase of the examination. Plaque CNV are not usually eligible for laser treatment because of their size and frequent subfoveal location. However, ICGA has not yet permitted an evaluation of the natural course of the different types of CNV. Furthermore, new forms of presumed CNV (polypoidal CNV) are being evaluated.
Evidence that plaque corresponds to CNV was provided by Chang et al and Lauer et al. These histological studies showed that plaque consists of thick fibrovascular tissue within the Bruch membrane. However, clinicopathological data on these lesions is scant, and questions remain about their histological characteristics.

Poor natural evolution of CNV in ARMD is well known. Occult CNV also has a bad prognosis. We found no contributions of the natural history of focal CNV detected by ICGA, because most investigators considered ICGA-guided laser treatment effective. The natural course of hyperfluorescent plaque lesions is better known, because they are not usually treated, although results are far from uniform. In 1992, Yannuzzi et al first showed plaque lesions, by means of ICGA, as a vascularized retinal pigment epithelium (RPE) often associated with good VA and very slow progression; Guyer et al, however, found the natural history of plaques discouraging, with an increase of the plaque correlated with decreased VA and increased exudation.

Our study confirmed that plaques tend to get bigger (Figure 2 and Figure 3). We noted an increase of about 40% during a median follow-up of 11 months. There was significant VA loss during this period, but the enlargement of the plaque could explain only 6% of the variability of this loss, and multivariate analysis found the relationship was not statistically significant, probably because of the small sample size. No correlation was found between VA decline and other associated alterations such as subretinal hemorrhages and elevation of the neovascularization. There was, however, a significant correlation between patients’ age and VA loss, ie, the older the patient, the worse the VA. We can explain this by the more diffuse alteration of RPE and choroid in older patients, which may affect VA. Also, greater loss of VA was seen with longer follow-up. The worsening of VA, weakly correlated to the plaque increase, was progressive; at the onset, plaque CNV was located subretinally, and retinal changes were usually slight. As the plaque became larger, however, it caused chronic damage to the RPE and neurosensorial retina.

CONCLUSIONS

Well-defined plaques tend to enlarge in time, growing by about 40% during 1 year of follow-up. The loss of VA is slightly, but not significantly, correlated to plaque enlargement. Plaque lesions, therefore, appear to be a less aggressive, slower developing form of CNV, with a relatively good prognosis, although the natural tendency is to worsen. Further follow-up will be necessary to establish their course, considering those that develop into well-defined, classic CNV and those that proceed to natural involution.

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REFERENCES


ARCHIVES Web Quiz Winner

Congratulations to our March Web quiz winner, Alan G. Kabat, OD, FAAO, of Nova Southeastern University, Fort Lauderdale, Fla. The answer to the March quiz was retinal pigment epithelium tear and central serous chorioretinopathy. For a complete discussion of this case, see the Case Report and Small Case Series section in the April ARCHIVES (Kwok AKH, Cheng LL, Bhende P, et al. Tear of the retinal pigment epithelium and serous retinal detachment in a case of IgA nephropathy after renal transplantation. Arch Ophthalmol. 2000;118:382-383).

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