EXTENDED REPORT

Types of choroidal neovascularisation in newly diagnosed exudative age-related macular degeneration

S Y Cohen, C Creuzot-Garcher, J Darmon, T Desmettre, J F Korobelnik, F Levrat, G Quentel, S Paliès, A Sanchez, A Solesse de Gendre, H Schluep, M Weber, C Delcourt

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Aim: To describe the types and location of choroidal neovascularisation (CNV) in exudative age-related macular degeneration (AMD), including vascularised pigment epithelial detachments (PED), and most recently described subtypes, such as retinal choroidal anastomosis, also termed “retinal angiomatous proliferation” (RAP).

Methods: Prospective multicentre consecutive descriptive case series. A total of 207 consecutive cases of newly diagnosed exudative AMD undergoing fluorescein angiography (FA) were recruited by 7 French referral hospital-based or private centres. Indocyanine green angiography (ICG) also was performed, when judged necessary by investigators. Types and location of CNV were classified by two independent experts and adjudicated by a third when discordant.

Results: All patients had FA, while ICG was performed in 50% of subjects. A total of 17.6% had classic CNV only, 5.4% and 8.3% had predominantly and minimally classic CNV, respectively. Occult CNV could be classified in occult CNV without PED (32.7%) and occult CNV with PED, ie, vascularised PED (23.9%). RAP was observed in 15.1% of cases, and accounted for 30% of vascularised PED. In 5.8% of the cases there was haemorrhagic AMD and 4.8% had fibrovascular scars. Lesions were mainly subfoveal (80%). Agreement between the centre’s ophthalmologist and the final validated expert classification was moderate ($\kappa=0.52$ for location and 0.59 for type of lesion).

Conclusion: This study confirms that newly diagnosed cases of exudative AMD are mainly occult and subfoveal. RAP appeared as a common lesion in patients with newly diagnosed exudative AMD.

See end of article for authors’ affiliations

Correspondence to: Salomon Y Cohen, Centre Ophtalmologique d’Imagerie et de Laser, 11 Rue Antoine Bourdelle, 75015 Paris, France; sycohen@club-internet.fr

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Age-related macular degeneration (AMD) is the leading cause of blindness in industrialised countries, representing 50% of all blindness cases.¹ It is currently the third most common cause of blindness worldwide, behind cataract and glaucoma.¹ More than 80% of severe visual loss in AMD is due to choroidal neovascularisation (CNV) and its consequences: exudation, bleeding and disciform scarring.² At the time of completion of the present study, the only approved treatments for exudative AMD in France were laser photocoagulation and verteporfin photodynamic therapy (PDT). The choice of treatment with these laser-based therapies depended on the location, composition and size of the lesion. Fluorescein angiography has been used to define lesion size and composition. It allows distinction between well demarcated classic CNV, and ill-defined occult CNV. This angiographic distinction is of major importance for the choice of treatment; laser photocoagulation being preferred in cases of extrafoveal or juxtafoveal classic CNV, while PDT was preferred in cases of subfoveal predominantly classic and occult only CNV.^{3–5} The location and exact boundaries of occult CNV often are difficult to determine precisely on fluorescein angiography due to obscuration of the neovascular membrane by overlying turbid exudates, blood and/or pigment, and rapid fluorescein pooling beneath a serous PED. As the vast majority of CNV at diagnosis are of the occult type,^{6–7} the lack of precise definition of the lesion is a limitation for the application of treatment with laser based therapies, and probably also for its outcome.

Indocyanine green (ICG) angiography has been shown to be valuable in detecting and improving delineation of occult CNV.^{8–9} ICG angiography is of particular help for the identification of vascularised PED (serous PED with occult CNV)^{9–11} and retinal choroidal anastomoses, also called retinal angiomatous proliferation (RAP).^{12–14} Both of these features appear to be

associated with poor prognosis, both in the natural history of neovascular AMD, and in treatment outcome.¹⁵ Use of ICG angiography could be helpful to guide treatment.

While many studies have assessed treatment outcome or natural history on selected groups of patients, there are few studies that have aimed at assessing the frequency of the different types of lesions and locations.^{6–7, 17} However, such studies are necessary in order to assess the proportion of patients that could benefit from the currently approved treatment modalities, the proportion of patients for which no therapy is available who might be candidates for antivascular endothelial growth factor (VEGF) therapies, and finally for medico-economic studies. Three previous studies estimated the frequency of the different types of lesions, but did not use ICG at all.^{6–7, 17}

The objectives of the present study were to perform a prospective review of newly diagnosed patients with exudative AMD in seven French referral centres in their routine practice to determine the frequency of the different types and location of lesions, including vascularised PED and RAP, and to assess the inter-grader agreement for the classification of the type and location of lesions.

PATIENTS AND METHODS

The study was performed in four private and three hospital-based referral centres all over France. Each centre recruited 40 consecutive patients with newly diagnosed exudative AMD in at least one eye undergoing fluorescein angiography in the

Abbreviations: AMD, age-related macular degeneration; CNV, choroidal neovascularisation; FA, fluorescein angiography; ICG, indocyanine green angiography; PED, pigment epithelial detachments; RAP, retinal angiomatous proliferation; VEGF, vascular endothelial growth factor

centre. Patients with myopic CNV or with CNV of origin other than AMD and patients with idiopathic polypoidal choroidal vasculopathy were not included. Eyes having already received treatment for CNV were also excluded. The study began on 14 March 2005 and was completed after 3 months even if the target number of 40 patients had not been recruited. Fluorescein and ICG angiography were carried out in accordance with the routine practice at each centre. Fundus camera and/or scanning laser ophthalmoscope were used according to the routine practice of the different centres. Because management of patients did not differ from the routine practice and collected data were completely anonymous, approval of the study by an institutional review board/ethical committee was not necessary, according to French legislation.

For each patient, the centre provided one red-free photograph and at least three images of fluorescein angiography: one early phase (<45 s), one mid-phase (between 45 s and 3 min) and one late-phase (>5 min). In cases of suspicion of occult CNV or RAP, ICG angiography was performed in accordance with routine practice in the centres. When performed for ICG angiography, at least two images had to be provided: one early-phase (<2 min) and one late-phase (>20 min).

In addition to the photographs, a short questionnaire was completed for each subject in the study. The centre's ophthalmologist indicated (for each included eye) the size of the lesion as obtained by comparison to the disc diameter of the studied eye, the location of CNV (extrafoveal, juxtafoveal, subfoveal), and the classification of CNV types (classic only, predominantly classic, minimally classic, occult without PED (with or without RAP) and vascularised PED (with or without RAP). The prescribed treatment after the visit was also recorded. The selected images and questionnaires were then reviewed by two independent experts who were blinded to the centre and the identity of the subject. All lesions were classified by both experts and the results compared after completion of the evaluation. Any disagreement was resolved by a third, independent expert. At completion of the study, there were two diagnoses for each included subject for the size of the lesion, the location, and the classification of CNV: a local diagnosis delivered by the centre's ophthalmologist and a validated expert diagnosis.

All data were entered into a database and analysed with SAS statistical software V.8.2. The κ coefficient was used to compare the local and validated diagnoses for location and type of CNV.

RESULTS

A total of 207 patients with newly diagnosed exudative AMD in at least one eye were recruited. There were no significant differences among centres with regard to age and gender of the patients or in types, location and size of the lesions (data not shown). Overall, two third of the patients were women and mean age was 79 years (67.2% of women, mean age 79.1 ± 7.3 ; table 1). ICG angiography was performed in 102 subjects (50%).

Table 2 presents the final classification of lesions, according to type and location.

Of the 207 eyes, 2 were judged impossible to grade and were therefore subsequently excluded from this table. The size of the lesion was on average 2.1 optic disc diameters (standard deviation 1.19), ranging from 0.20 to 7. Of the 205 subjects with gradable photographs, only 16 (7.8%) and 23 (11.2%) were extra- and juxtafoveal, respectively. Moreover, of these 39 cases, only a third (14 cases) was of the classic or predominantly classic types. The remaining cases of extra- or juxtafoveal lesions were occult without PED (14 cases) and vascularised PED (9 cases) associated with RAP in more than two thirds of cases.

Most of the cases of newly diagnosed exudative AMD were subfoveal (166 cases, 81.0%). Of these, 33 (19.9%) were classic only or predominantly classic, 15 (9.0%) were minimally classic, 53 (31.9%) were occult without PED (of which 5 cases had associated RAP), and 40 (24.1%) were vascularised PED (of which 10 cases had associated RAP).

Overall, RAP was diagnosed in 31 (15.1%) out of 205 eyes.

Finally, 12 newly diagnosed cases already had haemorrhaging representing more than 50% of the lesion, and 10 had disciform scarring.

When comparing the local and centralised (final) classification, κ was 0.52 for location of the lesions and 0.59 for type of the lesion, showing moderate agreement. Local ophthalmologists tended to classify more lesions into classic only (48 cases against 36 for the final classification) and more cases as extrafoveal (24 cases against 16 for the final classification).

With respect to treatment, at the end of the visit, the centres' ophthalmologists prescribed PDT in almost half of the cases (99 cases), laser treatment in 32 cases (15.5%), intravitreal injection of triamcinolone in 9 cases (4.3%), associations of these treatments in 31 cases (15.0%), and other therapies in 5 cases. In 31 cases (15.0%), no treatment was prescribed.

DISCUSSION

The present study describes the frequency of the different types and locations of exudative AMD, in a series of 207 consecutive newly diagnosed cases recruited in 7 referral centres in France. There have been few previous studies of large numbers of subjects giving the distribution of the type of lesions according to their locations. In particular, to our knowledge no prospective study used ICG angiography in addition to fluorescein angiography. Therefore, some features of exudative AMD (in particular RAP) might not have been precisely described in these studies.

In concordance with previous studies, in our data, 81% of newly diagnosed cases were subfoveal.^{6,7} Our study is also consistent with previous studies showing that lesions with classic CNV represented only a minority of cases with exudative AMD: predominantly classic (including classic only) CNV represented about 20% of the cases with exudative AMD, both in the present and in previous studies,^{6,7} except in a study by

Table 1 Characteristics of the subjects

	Location	Subjects (n)	Male (%)	Mean age (SD)
Private centre	Paris	40	35.0	79.6 (8.0)
Private centre	Paris	40	27.5	80.5 (7.0)
Private centre	Lambersart	40	22.5	78.0 (6.8)
Private centre	Nice	40	42.5	79.3 (7.8)
Public centre	Dijon	10	40.0	78.8 (3.8)
Public centre	Bordeaux	25	32.0	78.0 (8.0)
Public centre	Nantes	12	41.7	77.8 (6.7)
Total		207	32.8	79.1 (7.3)

Table 2 Final classification of lesions, by type and location (determined by experts)

	Extrafoveal, n (%)	Juxtafoveal, n (%)	Subfoveal, n (%)	Total, n (%)
Classic only CNV	3 (1.46)	10 (4.88)	23 (11.22)	36 (17.56)
Predominantly classic CNV	1 (0.49)	0 (0.00)	10 (4.88)	11 (5.37)
Minimally classic CNV	0 (0.00)	2 (0.98)	15 (7.32)	17 (8.29)
Occult CNV without PED				
Without RAP	1 (0.49)	4 (1.95)	48 (23.41)	53 (25.85)
With RAP	5 (2.44)	4 (1.95)	5 (2.44)	14 (6.83)
Vascularised PED				
Without RAP	0 (0.00)	2 (0.98)	30 (14.63)	32 (15.61)
With RAP	6 (2.93)	1 (0.49)	10 (4.88)	17 (8.29)
Haemorrhage >50%	0 (0.00)	0 (0.00)	12 (5.85)	12 (5.85)
Disciform scars	0 (0.00)	0 (0.00)	10 (4.88)	10 (4.88)
Other forms	0 (0.00)	0 (0.00)	3 (1.46)	3 (1.46)
Total	16 (7.80)	23 (11.22)	166 (80.98)	205 (100.00)

CNV, choroidal neovascularisation; PED, pigment epithelium detachment; RAP, retinal angiomatous proliferation.

Moisseiev *et al* who found 37% of classic CNV.¹⁷ Most of classic CNV were subfoveal (64% in the present study). Overall, most of the newly diagnosed cases were subfoveal occult CNV. Our study also confirmed that minimally classic CNV represents a small group of patients, observed in 8% in the present study, and in 6–19% in other studies.^{6–7} In all three studies, the vast majority of minimally classic lesions were subfoveal.

In the present study, ICG angiography was performed in case of occult CNV according to the practice of all centres. However, it was not performed in all included cases. As shown by previous studies, when only fluorescein angiography is used, occult CNV in serous PED often cannot be detected at all, thereby underestimating the frequency of vascularised PED.^{9–11} In the present study, vascularised PED was present in a considerable number of patients (49 of 205 cases, 24%), and about half of all occult lesions (49 of 116 cases with occult CNV). This is consistent with previous studies of occult lesions, using ICG. In a study by Slakter *et al*, among 150 prospective cases with occult CNV, 82 (55%) had vascularised PED, while among 79 retrospective cases with occult CNV, 35 (44%) had vascularised PED.¹³ In a study by Guyer *et al*, among 657 cases of occult CNV, 235 (35%) had vascularised PED.⁸

The present study allowed us to show RAP as a frequent lesion in neovascular AMD, observed in 15.1% of cases. In association with vascularised PED, they accounted for about 30% of vascularised PED. In the study by Slakter *et al*, 22 of 82 (27%) cases with vascularised PED had RAP, while 9 of 68 (13%) cases with occult without serous PED had RAP.¹³ In a study by Kuhn *et al*, 50 of 186 cases (27%) with vascularised PED had RAP.¹² In a series of 205 newly diagnosed cases with occult CNV, 49 of 154 eyes with PED (32%), and in 8 of 51 eyes without PED (16%) had RAP.¹⁴ Recently, in a retrospective study of 126 consecutive newly diagnosed patients with neovascular AMD, 17 (13.5%) had RAP.¹⁸

The need for therapies that are efficient for all types of CNV appears real, as that classification of CNV according to location and type by the ophthalmologists shows only moderate to good inter-grader agreement both in our work and previous studies,^{6–19–20} which is an important limitation for type- and location-based therapy choices.

In conclusion, our study showed that newly diagnosed exudative AMD cases were mainly subfoveal and occult CNV. Cases of RAP appeared to be frequent in newly diagnosed CNV. The moderate agreement between the treating French ophthalmologist and experts for the determination of lesion location and subtype from diagnostic angiograms ($k = 0.52$ and 0.59 , respectively) is similar to that demonstrated in previously published reports.^{19–20} In these French referral centres in 2005, therapeutic modalities were chosen on the basis of the type and location of the lesions, according to recommendations.

However, with the availability of newer anti-VEGF treatments, such assessments to determine treatment eligibility might no longer be necessary.

Authors' affiliations

S Y Cohen, G Quentel, Centre Ophtalmologique d'Imagerie et de Laser, Paris, France

C Creuzot-Garcher, Centre Hospitalier Universitaire, Dijon, France

J Darmon, Centre d'Imagerie et de Laser, Nice, France

T Desmettre, Centre d'Imagerie et de Laser, Lambertsart, France

J F Korobelnik, Centre Hospitalier Universitaire, Bordeaux, France

F Levrat, S Paliès, A Solesse de Gendre, H Schluep, Pfizer, Paris, France

A Sanchez, Biostatem Company, Nîmes, France

M Weber, Centre Hospitalier Universitaire, Nantes, France

C Delcourt, Inserm U593, Bordeaux, France; Université Victor Segalen, Bordeaux, France

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SYC, CC-G, JD, CD, TD, JFK, GQ, MW and AS are consultants for Pfizer, France. HS, SP, ASdeG and FL are employees of Pfizer, France.

REFERENCES

- 1 **Resnikoff S**, Pascolini D, Etya'ale D, *et al*. Global data on visual impairment in the year 2002. *Bull World Health Organ* 2004;**82**:844–51.
- 2 **Ferris FL 3rd**, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984;**102**:1640–1642.
- 3 **Bressler NM**. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials—tap report 2. *Arch Ophthalmol* 2001;**119**:198–207.
- 4 **Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization—verteporfin in photodynamic therapy report 2. Am J Ophthalmol 2001;**131**:541–60.**
- 5 **Macular Photocoagulation Study Group**. Occult choroidal neovascularization. Influence on visual outcome in patients with age-related macular degeneration. *Arch Ophthalmol* 1996;**114**:400–12.
- 6 **Olsen TW**, Feng X, Kasper TJ, *et al*. Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. *Ophthalmology* 2004;**111**:250–5.
- 7 **Zawinka C**, Ergun E, Stur M. Prevalence of patients presenting with neovascular age-related macular degeneration in an urban population. *Retina* 2005;**25**:324–31.
- 8 **Guyer DR**, Yannuzzi LA, Slakter JS, *et al*. Digital indocyanine-green videoangiography of occult choroidal neovascularization. *Ophthalmology* 1994;**101**:1727–35.
- 9 **Watzke RC**, Klein ML, Hiner CJ, *et al*. A comparison of stereoscopic fluorescein angiography with indocyanine green videoangiography in age-related macular degeneration. *Ophthalmology* 2000;**107**:1601–6.
- 10 **Yannuzzi LA**, Hope-Ross M, Slakter JS, *et al*. Analysis of vascularized pigment epithelial detachments using indocyanine green videoangiography. *Retina* 1994;**14**:99–113.
- 11 **Baumal CR**, Reichel E, Duker JS, *et al*. Indocyanine green hyperfluorescence associated with serous retinal pigment epithelial detachment in age-related macular degeneration. *Ophthalmology* 1997;**104**:761–9.
- 12 **Kuhn D**, Meunier I, Soubrane G, *et al*. Imaging of chorioretinal anastomoses in vascularized retinal pigment epithelium detachments. *Arch Ophthalmol* 1995;**113**:1392–8.

- 13 **Slakter JS**, Yannuzzi LA, Schneider U, et al. Retinal choroidal anastomoses and occult choroidal neovascularization in age-related macular degeneration. *Ophthalmology* 2000;**107**:742–53.
- 14 **Axer-Siegel R**, Bourla D, Priel E, et al. Angiographic and flow patterns of retinal choroidal anastomoses in age-related macular degeneration with occult choroidal neovascularization. *Ophthalmology* 2002;**109**:1726–36.
- 15 **Axer Siegel R**, Ehrlich R, Rosenblatt I, et al. Photodynamic therapy for occult choroidal neovascularization with pigment epithelium detachment in age-related macular degeneration. *Arch Ophthalmol* 2004;**122**:453–9.
- 16 **Arevalo JF**, Mendoza AJ, Fernandez CF. Indocyanine green-mediated photothrombosis with and without intravitreal triamcinolone acetonide for subfoveal choroidal neovascularization in age-related macular degeneration: a pilot study. *Retina* 2005;**25**:719–26.
- 17 **Moisseiev J**, Alhalel A, Masuri R, et al. The impact of the macular photocoagulation study results on the treatment of exudative age-related macular degeneration. *Arch Ophthalmol* 1995;**113**:185–9.
- 18 **Donati MC**, Carifi G, Virgili G, et al. Retinal angiomatous proliferation: association with clinical and angiographic features. *Ophthalmologica* 2006;**220**:31–6.
- 19 **Friedman SM**, Margo CE. Choroidal neovascular membranes: reproducibility of angiographic interpretation. *Am J Ophthalmol* 2000;**130**:839–41.
- 20 **Holz FG**, Jorzik J, Schutt F, et al. Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). *Ophthalmology* 2003;**110**:400–5.

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