

Drusen classification in bilateral drusen and fellow eye of exudative age-related macular degeneration

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CLINICAL STUDY

Abstract

Aim To assess the value of the modified international classification system in screening high-risk patients with bilateral age-related maculopathy (ARM) from those with lower risk characteristics.

Methods In total, 164 digital images of 106 patients with either bilateral ARM (group A) or the fellow eyes of unilateral exudative age-related macular degeneration (AMD) (Group B) were included. Patients with no signs of ARM in both eyes or those with bilateral late AMD were excluded. The images were randomised and then graded by two masked ophthalmologists based on the modified International Classification of ARM.

Results The interobserver consistency between the two graders was high with a Kappa value of 0.82 (SE 0.34, $P < 0.0001$). There were no significant differences in the distribution of the stages of ARM between the two subgroups. Stage 3 was the most common stage in each group for both graders followed by stage 2a in the bilateral drusen group. Stages 1a, 2a and 2b were equally the next common stage in the fellow eye of choidal neovascularisation group.

Conclusion A screening system based on clinical characteristics would be of value in risk prediction in a clinical setting. Type of Drusen alone, as identified by the modified International grading system, may not be reliably predictive in screening for patients who are at high risk of developing choroidal neovascularisation.

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Introduction

Choroidal neovascularisation (CNV) is the leading cause of blindness in the developed world. For persons aged 75 years or older, age-related macular degeneration (AMD) is the major cause of the increased prevalence of blindness.^{1,2} The overall 2-year cumulative incidence of AMD in Rotterdam study was 0.2%, increasing to 1.8% in subjects of 85 years or older. This is lower than the incidence rate in the United States.¹ The prevalence in UK was about 1.64% of population (Melton Mowbray study).³ In one of the recent studies, it is estimated that in Britain there are 172 000 and 245 000 cases with geographical and neovascular AMD, respectively.⁴ The relative risk in AMD as a function of early-age related maculopathy (ARM) fundus signs has been described in various studies.^{5–9} The International ARM Epidemiological Study Group has described an international classification and grading system for ARM and AMD.¹⁰ This was followed by the Rotterdam study, a population-based prospective cohort study, which described stepwise progression of ARM.^{11,12}

The reliability of the current method of the modified international classification of ARM in screening for patients at high risk of developing CNV is still unclear. In this study, we compared the staging of disease in patients with bilateral ARM against the staging of ARM in the fellow eye of patients with unilateral exudative AMD. The aim was to identify if the modified international grading system could be used to differentiate between patients with a relatively low risk of visual loss (bilateral drusen subgroup) and those with a much higher risk of visual loss (fellow eye subgroup).

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Methods

Colour fundus images (Topcon TRC 50IX retinal camera) of consecutive patients referred to the Retinal Research Unit at King’s College Hospital, London, between December 2002 and December 2003 were reviewed. All images were centred on the macula and were of good quality (50° field). The inclusion criteria consisted of patients with bilateral ARM (drusen in both eyes) and fellow eye of patients with unilateral exudative AMD. We excluded all patients with no signs of ARM in both eyes and those with bilateral neovascular disease or advanced atrophy. Patients with ocular comorbidity from diseases other than AMD such as diabetes were also excluded. The selected images were randomised by an independent investigator and then graded by two ophthalmologists, independent of each other, using the modified International Classification of ARM (Figure 1).^{10–12} Graders were masked to the patient diagnosis. Discrepancies between the two graders were resolved by a third expert grader. The distribution of each stage of ARM within the two study subgroups was calculated as percentages. χ^2 linear correlation testing was used to identify the significance of the distribution of the disease stages between the two patient subgroups. The interobserver variability of the graders was assessed using the Kappa statistical method.

Results

After excluding images of poor quality, a total of 164 images, of 106 patients, were considered

suitable for inclusion. These were divided into two groups:

Group A = bilateral ARM (drusen/drusen) group, which included 133 images.

Group B = fellow eye of exudative AMD (drusen/CNV) group which involved 31 images.

The interobserver consistency between the two graders was high with a Kappa value of 0.82 (SE 0.34, $P < 0.0001$). The distribution of stages within each group is illustrated in (Table 1). There were no significant differences in the distribution of the stages of ARM between the two subgroups (Table 2), linear by linear association 0.052; $P = 0.82$. Advanced ARM (Stage 3) was the predominant stage in both groups: 45.86% for the drusen only group and 41.94% for the fellow eye group. *Post hoc* analysis was conducted to assess whether combining the stages of ARM 0a to 2b would improve the power of the sample in identifying a difference between the two subgroups. No significant difference in the distribution was found after

Table 1 Classification of mutually exclusive stages of ARM¹²

Stage	Description
0a	No signs of ARM at all
0b	Hard drusen (<63 μm) only
1a	Soft distinct drusen ($\geq 63 \mu\text{m}$) only
1b	Pigmentary abnormalities only, no soft drusen ($\geq 63 \mu\text{m}$)
2a	Soft indistinct drusen ($\geq 125 \mu\text{m}$) or reticular drusen only
2b	Soft distinct drusen ($\geq 63 \mu\text{m}$) with pigmentary abnormalities
3	Soft indistinct ($\geq 125 \mu\text{m}$) or reticular drusen with pigmentary abnormalities
4	Atrophic or neovascular AMD

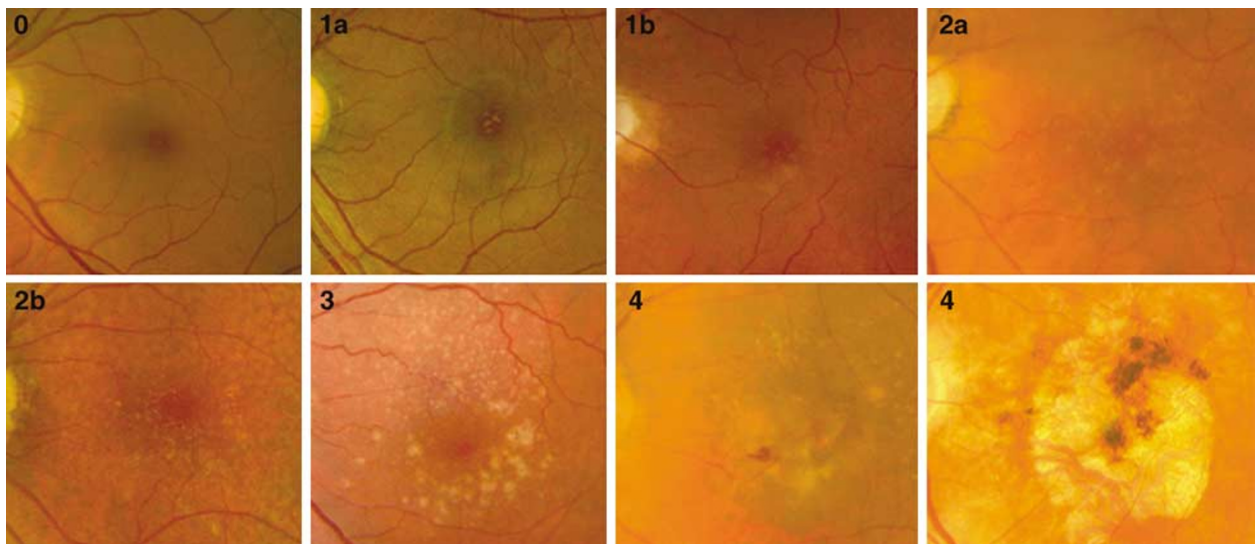


Figure 1 The modified international grading system for ARM.

Table 2 Distribution of stages in group A (bilateral drusen) and group B (fellow eye of exudative AMD)

Stage	Group A	Percentage	Group B	Percentage
Oa	1	0.75	0	0
Ob	13	9.77	3	9.60
1a	14	10.52	5	16.13
1b	3	2.26	0	0
2a	24	18.05	5	16.13
2b	17	12.78	5	16.13
3	61	45.86	13	41.94
Sum	133		31	

combined analysis (linear by linear association 0.182; $P = 0.7$).

Discussion

People with unilateral ARM are three times as likely to have early ARM in their second eye when compared with people with no ARM in both eyes.¹³ It is known that the fellow eye of exudative AMD is more likely to develop CNV. Retrospective studies showed that approximately 4–12% of patients with a CNV in one eye will have a CNV develop in their fellow eye within 1 year.^{14–17} A prospective study reported a 6% annual rate.¹⁸ AMD was shown to be bilateral in 57% of AMD cases.¹⁹

The absolute risk of AMD can be stratified by stage of early ARM as found in a large population based study.¹² For subjects with ARM stage 0, the overall risk of AMD within a 5-year period was virtually absent, irrespective of age. For subjects with ARM stage 1, the risk was 0.9%. Subjects with ARM stage 2 had an overall risk of 7.8%, which increased to 28% for those with ARM stage 3.¹² It could be expected that a subgroup of patients at high risk of developing CNV would have predominantly stage 3 ARM. This would make identification of drusen type a useful screening tool. In the Rotterdam study the concept that neovascular AMD develops from stage 2 or 3 has not reached statistical significance.¹²

Our retrospective analysis of patients presenting to a tertiary referral centre suggests that the modified international classification system did not identify any features that could be used as a basis for screening high-risk patients (fellow eye subgroup) from a more heterogeneous group of patients (bilateral drusen subgroup). Our study found that advanced ARM (stage 3) is equally prevalent in both patient subgroups studied. One possibility is that patients with mild ARM are less likely to be referred to a tertiary centre and may not be represented in our sample of patients with bilateral drusen. Our study is also limited by the relatively small

number of patients in the fellow eye subgroup. Data concerning long-term visual and disease outcome is required to clarify the significance of the distribution of ARM stage in our cohort of patients.

There is increasing evidence that the spatial distribution of drusen is also significant when assessing risk of visual loss in ARM. Holz *et al*²⁰ found that the degree of confluence of drusen within 1600 μm of the centre of the fovea and focal extrafoveal areas of atrophy of the retinal pigment epithelium were significant risk factors.

In a prospective series of 3684 patients followed up over a 10-year period in the Beaver Dam, Wisconsin study, larger drusen found in the inner circle of the Wisconsin template were more likely to have geographic atrophy. Large drusen found in the outer circle was more likely to be associated with persons who did not have advanced AMD.²¹

In summary, there is growing interest in the development of prophylactic intervention for early ARM aiming to prevent CNV formation. A method of identifying high-risk patients from those at lower risk of severe visual loss from CNV in a population of patients commonly found in a tertiary referral hospital is desirable for this purpose. Type of drusen, as identified by the modified International grading system, may not be reliably predictive in screening for patients who are at high risk of developing CNV.

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