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Screening for age-related macular degeneration using nonstereo digital fundus photographs

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Abstract

Age-related macular degeneration (AMD) is a disease with significant visual morbidity and accounts for the majority of blind registrations in the developed world including the UK. Certain forms of neovascular AMD are amenable to treatment but require expeditious referral to a retinal specialist.

Aim **To evaluate the possibility of using nonstereo fundus photographs as a low-cost screening tool for neovascular AMD.**

Design **Retrospective review of patients referred to the macular clinic of a teaching hospital in London.**

Methods **A total of 198 randomised digital fundus photographs, without any other clinical information, were presented to two independent ophthalmic interns who graded them into one of the three categories: normal, age-related maculopathy (ARM), or neovascular age-related macular degeneration (AMD) to determine the urgency of referral to clinic. The results were compared with the known diagnosis for each patient and sensitivities and specificities for each diagnostic category calculated.**

Results **The intraobserver Kappa statistic was 0.75 and 0.91 for grader 1 and 2, respectively. The interobserver Kappa was 0.54. The mean sensitivity and specificity for the identification of ARM was 60.5 and 76.3%, respectively The mean sensitivity and specificity for the identification of AMD was 85.7 and 78.8%, respectively.**

Conclusion **Nonstereo digital fundus photograph is a reasonable screening tool for CNV and may aid in decreasing the visual morbidity it causes by enabling timely referrals and treatment.**

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Introduction

Age-related macular degeneration (AMD) is the most common cause of blind registration in the majority of the developed world today including the United Kingdom.[1–3] According to current estimates there are around 172 000 people with geographic AMD in the UK and 245 000 with neovascular AMD.[4] It is thus a condition, which causes significant visual morbidity.

There is still considerable variability in terminology of age-related macular disease. Most medical retinal specialists segregate it into age-related maculopathy (ARM) and AMD. The former can be early with drusen and/or mild RPE abnormalities or late with features of geographic atrophy. AMD is usually neovascular in nature with features of choroidal neovascularisation (CNV), pigment epithelial detachment (PED) etc.[5]

Since vision loss usually accompanies the late complications of ARM, some still refer to this as AMD. Atrophic ARM leads to gradual loss of vision, which is usually not as severe as neovascular AMD that can cause extensive loss of central visual acuity relatively rapidly. Until recently there was no treatment for subfoveal CNV that did not produce immediate, severe loss of vision as a side effect.

However, with recent advances new techniques have emerged that can stabilise or retard the deterioration in vision in selected cases of neovascular AMD. The most effective treatment techniques include photodynamic therapy (PDT)[6–9] and transpupillary thermotherapy (TTT)[10–12] that use laser to ablate the neovascular membrane. However, they have

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a narrow window of opportunity to treat for maximum therapeutic benefit.

The rationale of screening for neovascular AMD is the assumption that facilitating access to treatment earlier in the disease could well-improve therapeutic outcomes. If eligible patients were identified before severe loss of vision, smaller and potentially less active lesions could be treated more frequently, resulting in more successful treatments as a whole.

Telescreening for AMD is still in its infancy compared to that for diabetic retinopathy probably because early signs like patchy atrophy and small drusens are more difficult to detect and grade than microaneurysms and haemorrhages.[13]

Previous studies have utilised 35 mm colour film photographs or digitised images thereof to screen the target population for choroidal neovascularisation.[14–16] However, to the best of our knowledge there have been no studies on the effectiveness of primary digitally captured images for AMD screening.

The aim of this study was to investigate the reliability of nonstereoscopic digital photographic screening for neovascular AMD.

Materials and methods

All digital images were selected from the photographic database of the medical retina department at King's College Hospital. This database resulted from the routine clinical care of patients seen in the department. The local ethical committee was consulted and approval obtained. Mydriasis was performed using 1% Tropicamide and 2.5% Phenylepherine. Digital colour fundus images were then captured using the Topcon TRC-50EX fundus camera (Topcon Corporation, Tokyo, Japan).

The subset of 198 images used in this study was selected by a medical retinal specialist (VC). This included macular images of the following: normals (66), ARM (57), as well as neovascular AMD (56). Another 19

images were duplicated and represented in random order with the other images in order to assess intraobserver agreement. Normal fundus images were drawn from fellow eyes of patients with uniocular disease including retinal vascular occlusions. Only one eye of each patient was selected to be included in the study.

The images were processed and presented to two independent ophthalmic interns (SJ and SH) in random order using the Imagenet system. No information regarding the age, sex, visual acuity, or clinical history of the patients in the study group was given to the graders. The images were viewed on a Dell computer monitor set at 32 bits true colour with a 1280×1024 pixel resolution.

The observers were instructed to grade the images into one of the three categories Normal, ARM (early or late) and AMD (including CNV and PED).

Normals had none or minimal changes of age-related disease at the macula. The ARM group included patients with drusens, hard exudates and retinal pigment epithelial (RPE) changes including geographic atrophy. The AMD group included patients with features of CNV, subretinal haemorrhage, PED, and subretinal fluid.

The two grader's interobserver and intraobserver agreement on the category the patient would be placed in was assessed using the kappa statistic. The results were compared with the known category for each patient decided by the medical retina specialist (VC) based on the clinical history, examination findings and investigations. The sensitivities and specificities for each diagnostic category were calculated.

All analyses were carried out using the Statistical Package for the Social Sciences SPSS 8.0.0. (SPSS Inc., Chicago, IL, USA).

Results

The agreement between the two graders and the true category classification is depicted in Tables 1 and 2. The

Table 1 True classification (TC) × grader 1 classification cross tabulation

			Grader 1			Total
			Normal	*ARM*	*AMD*	
True classification (TC)	Normal	Count	58	7	1	66
		% within TC	87.9	10.6	1.5	100.0
	ARM	Count	4	29	24	57
		% within TC	7.0	50.9	42.1	100.0
	AMD	Count	4	6	46	56
		% within TC	7.1	10.7	82.1	100.0
Total		Count	66	42	71	179
		% within TC	36.9	23.5	39.7	100.0

Table 2 True classification (TC) × grader 2 classification cross tabulation

			Grader 2			Total
			Normal	*ARM*	*AMD*	
True classification (TC)	Normal	Count	32	24	10	66
		% within TC	48.5	36.4	15.2	100.0
	ARM	Count		40	17	57
		% within TC		70.2	29.8	100.0
	AMD	Count		6	50	56
		% within TC		10.7	89.3	100.0
Total		Count	32	70	77	179
		% within TC	17.9	39.1	43.0	100.0

Table 3 Grader 1 × grader 2 classification crosstabulation (interobserver variability)

			Grader 2			Total
			Normal	*ARM*	*AMD*	
Grader 1	Normal	Count	31	21	14	66
		% within grader 1	47.0	31.8	21.2	100.0
	ARM	Count		36	6	42
		% within grader 1		85.7	14.3	100.0
	AMD	Count	1	13	57	71
		% within grader 1	1.4	18.3	80.3	100.0
Total		Count	32	70	77	179
		% within grader 1	17.9	39.1	43.0	100.0

Table 4 Subjective 1 × subjective 2 crosstabulation (grader 1) intraobserver variability

			Subjective 2			Total
			Normal	*ARM*	*AMD*	
Subjective 1(Subj1)	Normal	Count	5	2		7
		% within Subj1	71.4	28.6		100.0
	ARM	Count		2	1	3
		% within Subj1		66.7	33.3	100.0
	AMD	Count			9	9
		% within Subj1			100.0	100.0
Total		Count	5	4	10	19
		% within Subj1	26.3	21.1	52.6	100.0

agreement between the two graders (interobserver variability) is shown in Table 3. The interobserver Kappa was 0.54, primarily due to disagreement over 'normals'.

The cross tabulation and calculation of the intraobserver variability using the duplicated images (Tables 4 and 5) gave a Kappa statistic of 0.75 and 0.91 for grader 1 and 2, respectively.

The mean sensitivity and specificity for the identification of ARM was 60.5 and 76.3%, respectively.

The mean sensitivity and specificity for the identification of AMD was better at 85.7 and 78.8%, respectively (Table 6).

Discussion

Screening of retinal pathology using fundal photographs has been extensively used for conditions like diabetic

Table 5 Subjective 1 × subjective 2 crosstabulation (grader 2) intraobserver variability

			Subjective 2			Total
			Normal	ARM	AMD	
Subjective 1 (Subj1)	Normal	Count	2	1		3
		% within Subj1	66.7	33.3		100.0
	ARM	Count		5		5
		% within Subj1		100.0		100.0
	AMD	Count			11	11
		% within Subj1			100.0	100.0
Total		Count	2	6	11	19
		% within Subj1	10.5	31.6	57.9	100.0

Table 6 Sensitivity and specificity of detection of ARM and AMD

	Grader 1		Grader 2		Mean	
	ARM (%)	AMD (%)	ARM (%)	AMD (%)	ARM (%)	AMD (%)
Sensitivity	50.88	82.14	70.17	89.28	60.53	85.71
Specificity	89.34	79.67	63.30	78.0	76.32	78.84

retinopathy where the fundus photographs can be obtained by a trained technician at the GP surgery or designated centres and the images sent to the tertiary referral centre for grading.[17] The previous gold standard for retinal photographic screening techniques has been film-based fundus images. According to the Wisconsin ARM grading system these have to include the central 30–35 degrees centred on the fovea and are usually presented as stereoscopic colour transparencies to the graders.[18]

However, with improvement in technology there has been a recent surge in interest in the use of high-resolution digital imaging as a screening tool. Digital imaging has many inherent advantages over conventional film-based screening methods.[17] It enables the photographer to instantly judge the quality of image capture and repeat it if necessary. The time, cost and inconvenience of mounting the slides is reduced and it is possible to transmit the images in a compressed format over long distances via electronic mail.[18] Hence, experts at a referral centre can grade them easily and quickly without the need for patient contact and an appropriates clinic appointments can then be arranged. Digital imaging systems also allow for image magnification, contrast enhancement and use of various filters to facilitate grading. These reasons make it a viable and attractive option to film-based screening in the future.

In spite of its wide spread prevalence, screening for AMD in the past has not been a fruitful exercise due to lack of treatment options and inability to intervene in the disease progression. With advancement in laser

techniques and pharmacological adjuncts, it is now possible to delay or even halt the progression of the disease in certain cases.[6–12]

The most popular among these is photodynamic therapy (PDT), which utilises the dye verteporfin to sensitise the retinal cells to the effect of laser energy. The neovascular membrane is then obliterated with much lower energy levels than would otherwise be required.[6–9]

However, it is crucial that the patient be referred to the treating physician at the earliest for the maximum benefit. The constraints of resources and infrastructure may however, lead to a significant delay between initial presentation to an eye care provider and obtaining a retinal opinion. A recent study found that 16% of patients were seen by retinal specialists >6 months after onset of visual symptoms.[19]

Clearly there is a need for a tool that will reduce this delay to enable prompt treatment of the selective but sizeable proportion of patients eligible for PDT. Investigators have looked into the possibility of using a screening service for AMD with consistently favourable reports. These have used variously film-based fundal images, using both stereoscopic and nonstereoscopic methods.[13–15]

Scholl *et al* sought to establish the reliability of digital nonstereoscopic images for grading of ARM. They reported that there was close agreement between digitised nonstereoscopic images and stereoscopic colour slides.[15] However, we have not come across any study that has evaluated the ability of digital fundal photography to screen for ARM.

We chose ophthalmic interns as graders, equating their ability to that of a photographic screener. The calculations for sensitivity levels comparing the graders to the specialist were very good, so the graders correctly identified most cases with neovascular AMD. We have discovered a good correlation between observer grading and clinical outcome in our study. Most false negatives were those with small classic CNV which are difficult to identify using nonstereo images alone as there might be no secondary clues, for example, exudates and haemorrhage; however, the elevation is more likely to be seen with stereo images.

We feel nonstereo screening techniques, while not as good as stereo photograph, can be easily implemented in GP practices, and offer the potential benefit of setting up a direct telemedicine link to the local hospital.

Hence, we feel that a nonstereo digital fundus photograph is a reasonable screening tool for CNV and may aid in decreasing the visual morbidity it causes by enabling timely referrals and treatment.

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