

THE SIGNIFICANCE OF EARLY DETECTION OF AGE-RELATED MACULAR DEGENERATION

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Background: The main cause for visual loss in age-related macular degeneration (AMD) is the development of choroidal neovascularization (CNV), which has been shown to occur in 18% of patients over 5 years. Even though satisfactory treatments for CNV are available, in the majority of cases no improvement in visual acuity occurs and in those it does it is mostly limited. Early detection has the potential of significantly improving the final visual outcome of patients who develop subfoveal CNV.

Methods: This review is a summary of the importance of early detection in the management of AMD, in view of the current available treatment methods. It is a review of the results of early detection of AMD using the Preferential Hyperacuity Perimeter (PHP).

Results: Awareness for symptoms, use of the Amsler grid and monitoring by an ophthalmologist are not satisfactory means for early detection of AMD. The PHP has good sensitivity and specificity in detecting CNV patient early and differentiate them from intermediate AMD.

Conclusion: In an era of excellent treatments available for CNV treatment, early detection of CNV by novel technology modalities such as the PHP at a frequency that allows early detection (~4 times a year) is crucial in the armamentarium of AMD patient management.

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The main cause for visual loss in age-related macular degeneration (AMD) is the development of choroidal neovascularization (CNV), which has been shown to occur in 18% of patients over 5 years.^{1,2} Even though satisfactory treatments for CNV are available, they are not capable of reversing the injury

caused by subfoveal CNV nor do they improve vision in the majority of cases. As is the case in many medical settings, here, too, early detection is the key to preservation of functional vision. Recent publications have emphasized the benefits of treating AMD lesions while they are still relatively small.^{3–5} This, in essence, reflects the importance of identifying the presence of CNV before the onset of the inevitable and progressive significant visual loss associated with the condition.

The natural history of CNV is that it gradually increases in size by an average of 10–18 μm daily,^{6,7} that it grows closer to the foveal center in over half of

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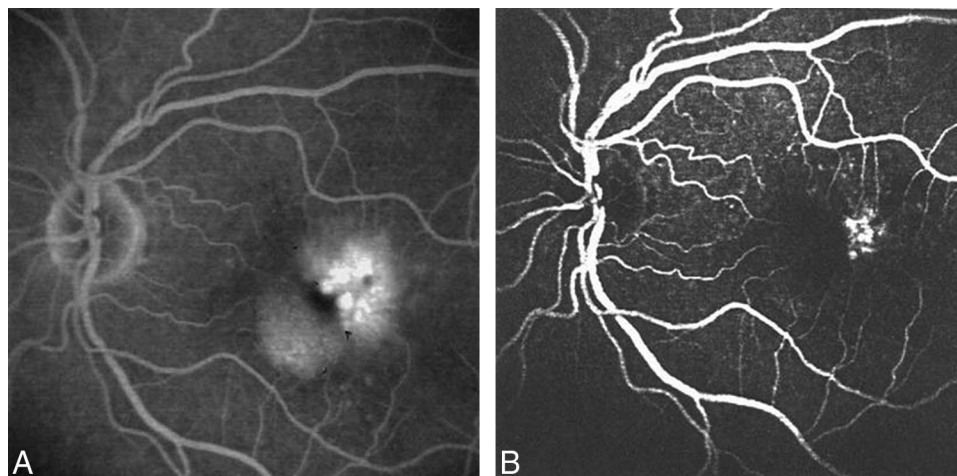


Fig. 1. **A**, Significant subfoveal hyperfluorescence indicating the existence of subfoveal choroidal neovascularization (CNV). **B**, Extrafoveal stippled hyperfluorescence in the same patient shown in **A** demonstrated on an angiogram taken 2 weeks earlier showing the existence of occult extrafoveal CNV.

the cases,⁷ and that it causes deterioration of visual acuity.⁸ Fig. 1A is a fluorescein angiogram demonstrating hyperfluorescence indicative of relatively extensive subfoveal CNV in a patient when she was seen by us in August 2001. Her visual acuity was 20/100. Although such findings are characteristic of typical CNV cases seen in many clinics, what makes this case special is that we had seen her 2 months earlier: not only was her lesion much smaller and extrafoveal, her visual acuity was 20/50 (Fig. 1B). We offered to treat her CNV by photodynamic therapy (PDT), but she declined treatment. This case report is a perfect example of a missed opportunity: the lesson to be learned is that each subfoveal lesion starts as a small one, often outside the fovea and in an eye with good vision, and that early detection and treatment might succeed in halting the progression to a devastating and irreparable loss of vision.

This review summarizes the importance of early detection in the management of AMD.

Treatment for AMD in the 21st Century

Antiangiogenic therapy has essentially replaced photodynamic therapy (PDT) as the treatment of choice for AMD. Evidence that earlier detection enhances treatment benefits is mostly indirect. According to the TAP and VIP report no. 1,² the larger the lesion at baseline, the smaller the treatment benefit in terms of the absolute level of visual acuity at 2 years after the initiation of treatment. In the Vision Trial with pegaptanib,³ it was clearly evident that the therapeutic benefit in the subgroup of early (smaller) lesions was much better than that for the total cohort. In their article on early retreatment with verteporfin,

Michels et al⁴ suggested that there was more loss of vision with increasing lesion size at baseline in both the early retreatment and in the standard retreatment group.

Ranibizumab (Lucentis) is a humanized anti-vascular endothelial growth factor (VEGF) antibody fragment that inhibits VEGF activity by competitively binding with VEGF. It is derived from bevacizumab (Avastin), a full-length humanized monoclonal antibody against VEGF. Ranibizumab is the first Food and Drug Administration–approved treatment for neovascular AMD that maintains or improves vision in at least 90% of patients and provides improvement in visual acuity within a range of 7.2 and 11.3 letters (MARINA¹⁰ and ANCHOR¹¹ studies, respectively) for the entire spectrum of CNV subtypes. Ranibizumab was associated with a less than 1.7% rate of major serious ocular adverse events, such as endophthalmitis and uveitis, in two pivotal Phase III trials.^{9–11} Even with ranibizumab, however, improvement was achieved in only 40% of patients with predominantly classic AMD (ANCHOR trial¹¹), and in only 34% of patients with minimally classic and occult AMD and presumed recent disease progression (MARINA trial¹⁰). Furthermore, a recent subgroup analysis of the MARINA study showed that treatment benefit was greater with higher baseline visual acuity and smaller lesion.¹² This means that to preserve our patients' visual acuity, we need to detect their lesions when the visual acuity is still good.

Why Early Detection?

For the first time in ophthalmologic history, treatment for CNV has resulted in an average improvement

in visual acuity. With an improvement of approximately nine letters on the Early Treatment Diabetic Retinopathy Study chart (averaged results cited in the ANCHOR and MARINA studies^{10,11}), the impact of early detection on visual acuity can be considerable. This can be demonstrated very simply: if we compare two patients arriving to the clinic with CNV, one with visual acuity of 20/50 and the other with visual acuity of 20/100, the first patient will end up with visual acuity of 20/32, which is sufficient for performing daily activities, such as driving and reading, while the other patient will end up with visual acuity of 20/64, which is insufficient for performing these basic daily functions. Consequently, for an average patient, earlier detection means a significant gain of vision, which may be equivalent to or better than the gain we achieve with most CNV treatments. The bottom line is that the impact of earlier detection on vision is enormous.

The economic impact of early detection can also be very significant. Recently, Javitt showed that the yearly Medicare-only related costs for a patient with severe visual impairment is more than \$4,000 USD.¹³ Assuming that there are approximately 50,000 patients affected in their second eye every year and that there is a 10-year life expectancy postdiagnosis, the annual savings for Medicare from early detection can be estimated to be at least \$2.25 billion USD. This figure is actually much higher when non-Medicare costs are included. Apart from the economic significance, we should not forget that the development of CNV with its resultant visual loss causes significant deterioration in the patient's quality of life,¹⁴ which may be improved significantly by even the preservation of a minimal visual acuity in the poorer eye.¹⁵

What, then, is required to detect a developing lesion while it is still small and visual acuity is still preserved? First, we inarguably need a sensitive and specific monitoring tool. Second, we need to increase the frequency by which we see aging patients since our chances of detecting CNV at an early stage are statistically low even with the best of tools. Third, there is a pressing need to heighten patient awareness. Many individuals are not aware that they have AMD, as was demonstrated by Attebo et al.¹⁶ Those authors conducted a population-based study of common eye diseases in an urban population aged 49 years or older in Australia and showed that while awareness of cataract and glaucoma were high (98% and 93%, respectively), awareness of AMD was low (20%), even though AMD is the leading cause of blindness. The authors' conclusion was that screening of people at risk may allow timely diagnosis and more effective therapy before advanced visual loss has occurred. Moreover, there is a significant delay in the presenta-

tion time to an ophthalmologist even among patients who already have symptoms. Haddad et al.¹⁷ reported that only one-third of patients with AMD seek ophthalmologic examination within the first month after the onset of symptoms. Their study included 1,598 patients with neovascular AMD, and the proportions of patients examined within 1 month, between 1 and 3 months, between 3 and 6 months, between 6 and 12 months, and after 12 months after onset of symptoms was 33%, 32.5%, 18.5%, 12%, and 4%, respectively. Such delay in presentation no doubt causes significant delay in diagnosis and treatment, resulting in avoidable visual loss. Finally, it is essential to increase the level of the care providers' awareness of the importance of early detection and the prompt need for patient referral.

Contemporary AMD Detection Modalities

Clinical evaluation involves instructing the patients to report symptoms such as distorted lines, blurriness, reduced vision, and dark areas in their visual field or use of the Amsler grid. Many investigators have pointed out that the patients who notice these symptoms or changes in the Amsler grid are detected relatively late in the stage of the disease when a large scotoma is already present.^{19–21} The reasons for AMD patients' failure to notice their macular pathology and for their poor performance of the Amsler grid are similar. First, the recognition of an existing scotoma is impeded by the cortical phenomenon of completion (the "filling-in phenomenon")²² and crowding.²³ In addition, patients are usually unable to properly maintain fixation during peripheral visual field testing, and so they scan the world with their fovea and ignore retinal defects until the defects are fairly close to the fovea itself or have become relatively large. Specifically, the noninteractive nature of the Amsler grid renders it unsuitable for monitoring patients because certain factors such as quality of examination performance and reliability measures cannot be assessed.

Another possible approach would be to examine aging patients regularly to look for the development of CNV. While yearly or even biyearly follow-up examinations would be helpful, it is unlikely that the timing of a visit would coincide with transformation of intermediate AMD (namely the existence of ≥ 5 drusen $\geq 63 \mu\text{m}$ in size) to CNV.² Moreover, even if the conversion had occurred recently, this feature is often difficult to diagnose with biomicroscopy alone.

There are a number of tools that could be used to monitor a patient at high risk for developing CNV. Hypothetically, we could do fluorescein angiography at each visit, but angiography is expensive, has side

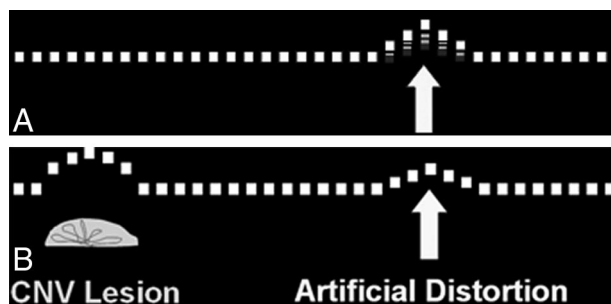


Fig. 2. The preferential hyperacuity perimeter. **A**, The patient is shown a dotted line with some of the dots deviating from the line ("artificial distortion"). The artificial elevation is made progressively smaller. **B**, When there is a choroidal neovascularization (CNV) lesion, competition occurs in the patient's brain between the artificial distortion and the pathologic distortion. When the CNV lesion causes a larger elevation than the artificial one, the patient will pick the spot of true distortion. Shown are the patient's horizontal and vertical lines covering the central 14 degrees of the visual field at a resolution of 0.75 degrees and the generation of a visual field map.

effects, and is time consuming. Biomicroscopy's clinical utility is variable and depends to a great extent upon the expertise of the examiner. A nonmydriatic digital camera provides limited stereopsis and the photographs are frequently nongradable, especially in the presence of small nonpharmacologically dilated pupils and/or media opacities.^{24,25} Optical coherence tomography (OCT) has recently emerged as an important means of detecting and monitoring patients with AMD by showing specific patterns in high-risk characteristics of non-neovascular AMD²⁶ that are capable of assisting in the decision-making of whether to retreat CNV.^{27,28} The reproducibility of OCT findings and their application to clinical practice, however, have yet to be demonstrated.

The Preferential Hyperacuity Perimeter

Our group recently demonstrated that the preferential hyperacuity perimeter (PHP, NotalVision) has much potential for assisting in the early detection of CNV in AMD.^{29–31} The technology is based on the phenomenon of hyperacuity, the human ability to perceive minute differences in the relative spatial localization of two objects in space. The brain is exceptionally sensitive to such deviation. The technology has been described in detail elsewhere.^{29–31} Briefly, the patient is presented with a pattern of dotted lines projected for 160 msec to the central 14 degrees of the visual field. Each line contains an artificial distortion at a different magnitude (Fig. 2A) and the distortion serves as a competitive stimulus to any pathologic distortion (hyperacuity defect) that might appear on the presented pattern. When there is a CNV lesion, attention competition between the artificial distortion

and the pathologic distortion takes place in the patient's brain (Fig. 2B). In general, the brain ignores smaller stimuli when there is a larger one. This is true for everyday stimuli and this phenomenon is exploited in PHP testing to assess the magnitude of the pathologic distortion: varying sizes of artificial distortion are presented, allowing quantification of the pathologic distortion by analyzing the patient's responses. Based on these responses, a visual field map is constructed, analyzed, and compared to normative data, thereby determining the likelihood of this defect being CNV.

The first PHP study was conducted in 2002 and published in 2003.²⁹ It was aimed at evaluating whether the PHP is better than the Amsler grid under supervised conditions in the office. The results showed that the PHP was more sensitive than the Amsler grid in each category of AMD, and that it was twice as sensitive for detecting CNV.²⁹ To validate this study, which was performed in our facilities, we performed an international multicenter study, which confirmed the results of the previous study, but also included a significant rate of false positive responses³⁰ and so the algorithm was amended.³¹ The PHP was further developed to be able to differentiate between patients at risk for developing CNV, i.e., those with intermediate AMD, and patients with recent onset CNV, to evaluate whether the PHP can be used as a tool for monitoring patients at risk for developing CNV. This more recent investigation³¹ was an international multicenter study performed in the United States, Europe, and Asia, and it demonstrated that the PHP can detect recent onset CNV with high sensitivity (82%) and differentiate these patients from those with intermediate AMD with high specificity (88%). In the same work, we also investigated whether reviewing color stereo photographs (simulating biomicroscopy) was effective for monitoring patients with AMD. To this end, all color stereo photographs of the study patients were graded in a masked manner by the participating retina specialists. Analysis of the findings showed that grading was less sensitive than the PHP (sensitivity of 70% [95% CI: 58%–81%] compared to 82% for the PHP, $P = 0.09$, McNemar), and that the specificity was higher (specificity of 95% [95% CI: 85%–99%] compared to 88% for the PHP ($P = 0.05$, McNemar). These results reflect that CNV could easily be missed in real-life situations in which biomicroscopy is frequently performed by less skilled practitioners.

The PHP does have limitations: first, like any other diagnostic device, it is necessary to gain experience and expertise in its use and in interpreting the visual field results. Scheduling of examinations in the clinics

will need to be altered to integrate the PHP into the diagnostic protocol. Still, the PHP is a promising tool for the early detection of CNV in the era of new and promising treatments, such as ranibizumab and bevacizumab. Indeed, the results of the MARINA trial¹⁰ have shown that minimally classic and occult AMD ranibizumab-treated eyes had a treatment benefit of 18 letters, and those from the ANCHOR trial¹¹ have shown that predominantly classic treated eyes had a treatment benefit of more than 20 letters.

In conclusion, the newly emerging treatment options have made it incumbent upon eye care professionals to upgrade monitoring techniques for earliest possible detection of CNV. This is especially true in the era of ranibizumab, which has been shown to stop the deterioration of visual acuity in more than 90% of patients, and to improve visual acuity in approximately 40% of patients. The public must also be encouraged to be more vigilant to any changes in vision, however subtle, to halt the progression of AMD and preserve vision in our graying society. The use of PHP in the clinic will significantly enhance the rate of early detection of CNV development, leading to earlier and more effective treatment and better final visual acuity. Finally, similar to other medical disciplines such as cardiology where home monitoring has improved the management of heart attacks and cardiac arrhythmias,³² further development of PHP technology for use at home can improve even further the rate of early detection and consequently enhance visual outcome following treatment.

Key words: age-related macular degeneration (AMD), choroidal neovascularization (CNV), early detection, progressive, subfoveal.

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