

Age-related Macular Degeneration: What's New

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Abstract

Introduction: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed western world, accounting for approximately 50% of all cases of registered blindness. The rising prevalence of this disease in Asia seems to parallel the same trend in the developed world. Because of the socio-economic impact of this disorder, much attention has been paid to elucidating the underlying pathogenic mechanisms, as well as seeking alternative forms of treatment. This review discusses the latest advances in AMD diagnosis, treatment and prophylaxis. **Methods:** Medline search with emphasis on randomised controlled clinical trials and large case-control series. Only articles cited on the Index Medicus were included in this review. **Results:** Recent advances in the diagnosis and treatment of AMD include conventional argon laser photocoagulation, photodynamic therapy (PDT), radiation therapy, surgical options and gene therapy. **Conclusions:** There have been numerous advances in the management of AMD and exciting new research applications have emerged. The introduction of exciting new modalities, such as PDT, has revolutionised the approach to treating CNVM and their effects on central vision. However, there has been no breakthrough in achieving satisfactory outcomes with the available techniques for treating occult neovascular lesions. As results of large prospective randomised clinical trials evaluating new treatment alternatives become available, a treatment algorithm for neovascular AMD will emerge that best minimises visual loss and may even result in visual improvement.

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Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed western world, accounting for approximately 50% of all cases of registered blindness. The prevalence of AMD seems to be increasing at a rate not commensurate with the increasing age of the population, although this observation cannot be fully explained. It is widely accepted that AMD is much less common in persons with Asian racial backgrounds, than Caucasian whites. Nevertheless, the rising prevalence of this disease in Asia seems to parallel the same trend in the developed world. For example, the disorder has become more common in the last 2 decades in urban Japanese communities; the rate of hospital referrals for AMD has doubled over the last 3 years.¹ Publications from Taiwan and anecdotal accounts from Singapore and Hong Kong imply that a similar increase in prevalence may be occurring in these communities.²

Visual loss in AMD results from 3 main processes: choroidal neovascularisation, retinal pigment epithelial detachment and geographic atrophy. The first 2 sequelae of

AMD are commonly referred to as the exudative forms of AMD.

Because of the socio-economic impact of this disorder, much attention has been paid to elucidating the underlying pathogenic mechanisms, as well as seeking alternative forms of treatment. In this article, the authors shall review the latest advances in AMD diagnosis, treatment and prophylaxis.

Definitions

An international classification and grading system for age-related maculopathy (ARM) and AMD was developed by a panel of experts in 1995.³

ARM was defined as the presence of drusen, areas of hyperpigmentation in the outer retina or choroid, or areas of hypopigmentation of the retinal pigment epithelium (RPE). AMD refers to the late stages of ARM, and may be of either exudative or non-exudative forms. The former, also called "wet" AMD, is characterised by any of the following (Fig. 1):

- RPE detachments;

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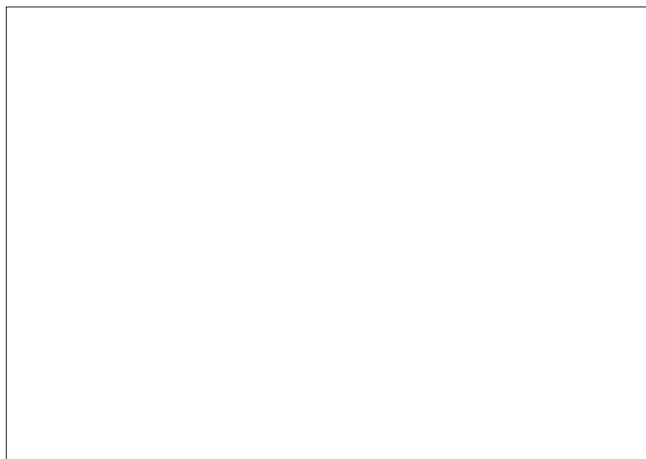


Fig. 1. Colour fundus photograph of the right eye showing a large central subfoveal choroidal neovascular membrane complex with surrounding subretinal haemorrhage, with overlying neurosensory retinal detachment. Multiple soft drusen deposits, another hallmark of age-related macular degeneration, are seen just beyond the vascular arcades.

- Subretinal or sub-RPE neovascular membranes;
- Subretinal haemorrhages;
- Hard exudates (lipids) within the macular area, not related to other retinal vascular disease;
- Epiretinal, intraretinal, subretinal or sub-RPE glial/scar tissue.

The non-exudative form of AMD (also known as “dry” AMD) or geographic atrophy is characterised by:

- Any sharply delineated round or oval areas of hypopigmentation or absence of RPE in which choroidal vessels are more visible than in surrounding areas. The size of this area should exceed 175 μm in diameter.

Location of Choroidal Neovascular Membranes (CNVMs)

Extrafoveal: greater than 199 μm from the geometric centre of the foveal avascular zone (FAZ)

Juxtafoveal: 1 to 199 μm from the geometric centre of the FAZ

Subfoveal: beneath the geometric centre of the FAZ

Classic versus Occult CNVM

Classic CNVM: early, lacy hyperfluorescence with well-demarcated margins and late leakage on fluorescein angiography (Fig. 2)

Occult CNVM: areas of leakage in the late phase of the angiogram not corresponding to a classic CNVM discernible in the early phase of the angiogram.

Recent Advances in AMD

Diagnosis and Terminology

The introduction of indocyanine green angiography

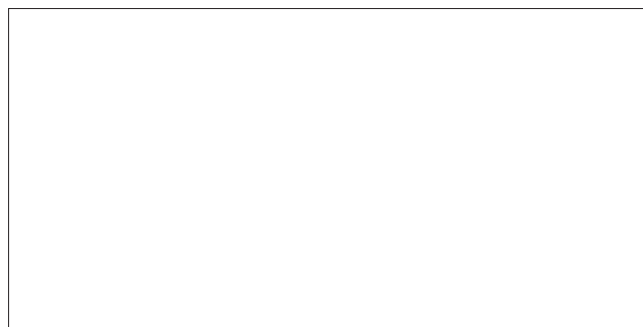


Fig. 2. Angiographic characteristics of polypoidal choroidal vasculopathy (PCV). (Left) Mid-phase fundus fluorescein angiogram (FFA) of the right eye showing a large subfoveal haemorrhagic pigment epithelial detachment (PED), with fluorescein pooling in the superior half of the lesion, with the inferior half showing blocked fluorescence due to the presence of subretinal blood. There is an area of focal hyperfluorescence in a notch on the nasal edge of the PED. (Right) Mid-phase indocyanine green angiogram showing a cluster of grape-like lesions corresponding to the notch seen in the FFA. These lesions are pathognomonic of polypoidal choroidal vasculopathy (PCV).

(ICGA) has increased our understanding of the origin and extent of choroidal neovascularisation. Based on fluorescein angiography (FFA), only 10% to 15% of all cases of exudative AMD are treatable. The majority of lesions on FFA are obscured by overlying blood, exudate or a pigment epithelial detachment (PED). ICGA is a new technique that allows enhanced imaging of poorly-defined or occult vessels.

Optical coherence tomography (OCT) allows a cross-sectional examination of the choroid, choriocapillaris-Bruch's membrane-RPE complex, inner retina and vitreous cavity. It also helps to distinguish between type I and type II CNVMs (these will be discussed in a following section).

Confocal scanning laser ophthalmoscopy (cSLO) is capable of taking high-resolution images of the retina and simultaneous FFA and ICGA recordings. In addition, the autofluorescent properties of intra and extracellular lipofuscin can be studied and quantified.

Polypoidal choroidal vasculopathy was first described in middle aged, obese black women presenting with recurrent haemorrhagic and exudative pigment epithelial detachments. Since this original description, there have been numerous reports of this entity occurring not only in the non-black population, but also in the elderly.⁴ In Japan, it is thought to represent a variant of AMD since patients are almost exclusively older than 50 years of age. The diagnosis is made clinically, where one or more orange-red nodules may be seen originating subretinally and protruding towards and elevating the overlying retina. These may be associated with a PED, with the polypoidal lesions often found at one edge of the detachment. They may also be found within the notch of some PEDs. In the past, these would have been ascribed to the presence of an occult CNVM within the PED notch. These polypoidal lesions

are best revealed on ICGA, which show grape-like clusters of early hypofluorescence at the terminal ends of an abnormal choroidal vascular network (Fig. 2). These lesions demonstrate late leakage, with washing out of dye from their core.

Laser Photocoagulation

Update of the Macular Photocoagulation Study (MPS)

The MPS Group, involving participating centres throughout the United States, conducted a series of multicentre, randomised clinical trials between 1979 and 1994 to determine whether prompt laser photocoagulation was preferable to observation in the management of patients with neovascular AMD and related non-AMD maculopathies, such as presumed ocular histoplasmosis, myopia and idiopathic causes. Under the eligibility criteria of the MPS, only 15% of enrolled eyes were eligible for laser treatment. Of this group, approximately half had CNVM involving the fovea. Of the remainder which did not initially involve the fovea, more than half subsequently developed subfoveal recurrent neovascularisation. In all these subfoveal lesions, laser photocoagulation led to a decrease in visual acuity following treatment. Because of the small proportion of patients with neovascular AMD who will ultimately benefit from laser therapy, as well as the disappointing results of treatment of subfoveal lesions, there has been strong impetus to search for treatment options that would result in a better visual outcome.

Treatment for extrafoveal CNVM: For extrafoveal CNVM, severe vision loss occurred in 64% of untreated eyes versus 46% of treated eyes after 5 years of follow-up.⁵ However, 54% of treated eyes developed recurrent CNVM, which tended to be typically subfoveal in position. In a subsequent trial, the MPS demonstrated benefit in treating these subfoveal recurrences.⁶ Another risk factor for recurrence after laser treatment was smoking. Fifty-one per cent of non-smokers compared to 85% of smokers developed recurrence.⁷ In general, eyes with subfoveal recurrences portended a much poorer visual prognosis.

Treatment for juxtafoveal CNVM: Severe vision loss after 5 years follow-up occurred in 65% untreated eyes and 55% treated eyes for lesions located between 1 and 199 μ m from the geometric centre of the FAZ.⁸ Hypertension was an important risk factor in this group such that, among hypertensive patients, treatment did not seem to alter visual prognosis; in non-hypertensive patients, 31% of treated eyes versus 64% of untreated eyes progressed to severe vision loss. Treatment benefit was greatest for eyes with only classic CNVM.⁹

Treatment for subfoveal CNVM: The most important risk factors for visual outcome were initial visual acuity, initial lesion size and whether the entire CNVM (classic or

occult) was completely covered by photocoagulation.⁵ Eyes which had a large lesion and moderate or good visual acuity had the worst visual outcome with treatment: visual acuity in treated eyes was substantially worse for the first 18 months and did not improve through 4 years of follow-up. All other groups of subfoveal CNVM benefited from treatment.⁶ For recurrent subfoveal CNVM, treated eyes had less severe vision loss than untreated eyes in all categories.¹⁰

ICG-guided laser photocoagulation of occult CNVM

Using ICGA, it is now possible to better delineate CNVM complexes, which are often obscured by blood, exudates or pigment epithelial detachments. Based on the location of hyperfluorescence on the ICGA, focal laser photocoagulation may be more accurately applied.¹¹ There is a selective uptake of long-wavelength laser energy by lesions primed with indocyanine green. As such, use of the diode laser for treating these lesions may be more effective than using green wavelength argon laser.

*Choroidal Neovascularisation Prevention Trial (CNVPT)*¹

The CNVPT was a prospective randomised clinical trial designed to study the effects of low-intensity laser treatment in eyes with drusen at risk of having CNV secondary to AMD. The treatment involved the placement of 20 laser burns, 100 microns in diameter in a pattern of 3 rows placed between the 12- and 6-o'clock positions beyond the temporal perimeter of the FAZ. The desired intensity was a grey-white burn. There was no significant reduction in the risk of developing CNVM in the treated eyes. On the contrary, there was an increased risk of developing CNVM in the short term. No observable difference in visual acuity between the 2 groups at 18 months follow-up was reported. Hence, unless longer-term results prove otherwise, there is no evidence to recommend prophylactic laser treatment for drusen at this time.

Photodynamic Therapy (PDT)

Most patients with subfoveal CNVM will not benefit from laser photocoagulation because the lesions are too large, they have relatively good visual acuity (better than 6/60), have poorly demarcated boundaries or are predominantly occult in nature. The principle of photodynamic therapy is as follows:

A photosensitiser, or light-activated drug, is first infused. Following infusion, the photosensitiser is activated focally by illumination with light from a laser source at a wavelength that corresponds to an absorption peak of the drug, but is not strong enough to create any thermal (photocoagulation) damage. It is believed that free radicals such as singlet oxygen and reactive oxygen intermediates are activated, which in turn cause sufficient endothelial cell damage in

CNVM to effect closure. One such photosensitiser is verteporfin (Visudyne; CIBA Vision Corp, Duluth, Ga). It is a benzoporphyrin derivative monoacid, with maximal absorption at 692 nm.

The Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) study was a multicentre, randomised clinical trial initiated in North America and Europe to investigate the clinical efficacy of verteporfin in AMD.¹² The 1-year, follow-up data have recently been published. Six hundred and nine patients with subfoveal CNVM caused by AMD measuring 5400 µm in greatest linear dimension, with evidence of classic CNVM and best-corrected visual acuity of 20/40 to 20/200 were recruited. They were randomly assigned (2:1 ratio) to verteporfin or placebo. The average number of verteporfin treatments per participant was 3.4 over the 1-year period. The primary outcome measure was the proportion of eyes with fewer than 15 letters lost (approximately <3 Snellen lines lost). At 1 year, 61% of verteporfin-treated eyes versus 46% of placebo-treated eyes had lost fewer than 15 letters of visual acuity from baseline. At 2-year follow-up, the rates of severe visual loss were 60% and 30%, respectively. The benefit was greatest in cases where the area of classic CNVM occupied greater than 50% of the entire lesion (i.e., predominantly classic CNVM), especially when there was no occult component to the lesion. For lesions in which the classic component constituted less than 50% of the entire lesion, there was no statistically significant difference between the 2 groups. The safety profile of verteporfin has been reported to be very high, with few ocular or systemic adverse events attributed to the drug. These included transient visual disturbances, injection site-related events and transient photosensitivity reaction.

Besides verteporfin, other currently available photosensitising agents are being tested. These include tin ethyl etiopurpurin (SnET2/Purlytin, Miravant), which is being evaluated in phase III trials, lutetium texaphyrin (Lutex/Optrin) (now in phase I/II) and mono-L-aspartyl chorine-6 (still undergoing preclinical studies).

At present, PDT is recommended only for predominantly classic AMD-related subfoveal CNVM.

Radiation Therapy

The rationale for radiation therapy is based on experimental and clinical evidence that proliferating endothelial cells are susceptible to ionising radiation. Benign intracerebral arteriovenous malformations and choroidal haemangiomas have been shown to regress using ionising beams.^{13,14} However, there has been conflicting evidence of the effectiveness of radiotherapy in the treatment of CNVM in AMD. The results of a large, multicentre, randomised trial studying the effects of radiation therapy

for subfoveal neovascular AMD (RAD study) in 205 patients were recently published. It was the first study to apply sham treatment.¹⁵ The treatment group received 8 fractions of 2 Gy external beam irradiation. At 1-year follow-up, there was no significant difference in loss of visual acuity between the 2 groups. Even when results of radiotherapy in classic and occult CNVM were separately analysed, no benefit was found. The authors of that study concluded that external beam radiation therapy at a dose of 16 Gy applied in 8 fractions provided no benefit as a treatment for subfoveal CNVM secondary to AMD at 1 year.

Surgical Advances

There has been increasing interest in the use of surgical techniques for the treatment of subfoveal CNVM: retinal rotation, limited macular translocation and surgical excision of CNVM.

Various approaches for retinal rotation have been advocated. The goal of surgery is to preserve foveal function by repositioning foveal photoreceptors over functional RPE/choriocapillaris. One such technique introduced by Machemer and Steinhorst involves inducing a total retinal detachment and performing a 360° retinotomy, before removal of the CNVM. The retina is then twisted around the optic nerve head and reattached. This manoeuvre achieves a 30° to 80° shift of the fovea, but may result in retinal detachment (20%), severe proliferative vitreoretinopathy (PVR), diplopia, cataracts and recurrence of CNVM. Visual outcome improved by at least 2 lines in 26%, remained stable in 61%, and worsened by 3 or more lines in the remaining 11%.¹⁶ A variation to this approach, introduced by Eckardt et al,¹⁶ includes simultaneous torsional extraocular muscle surgery on oblique with or without rectus surgery muscles. This is done to prevent torsional diplopia, which is a disabling postoperative complaint after extensive macular rotation surgery. Occasionally, muscle surgery has to be performed in the fellow eye as well, if the degree of cyclotorsion is excessive.

Limited macular translocation is a technique that uses scleral imbricating sutures to achieve a shift in the position of the fovea (albeit smaller shifts compared with retinal rotation).¹⁵ Only the temporal retina is surgically detached. Postoperative positioning of the patient is critical in achieving the desired shift and avoiding the formation of macular folds. The retina is allowed to reattach spontaneously. In 52 patients, visual outcome was encouraging: 33% of eyes managed to gain at least 2 lines of vision over the baseline at 6 months follow-up; 36% remained stable, while the remaining 30% experienced a loss of at least 2 lines of vision. More recently, de Juan and Vander¹⁷ successfully translocated the macula without

using scleral imbricating sutures. With refinements to this technique, limited macular translocation may be a promising option in the treatment of subfoveal CNVM, especially for cases that do not benefit from PDT.

Submacular surgery was first described by de Juan and Machemer in 1988.¹⁷ Since then, numerous retrospective reports have described improvements and stabilisation of vision by direct removal of CNVM. The technique involves placing a retinotomy about 3 mm from the foveal centre, creating a small retinal detachment at that site, and removal of CNVM with submacular forceps from the underlying tissue. Air-fluid exchange is then performed and the patient is placed prone for 48 hours. This technique is particularly useful for patients with type II CNVM,¹⁸ where the membrane lies above the plane of the RPE/Bruch's membrane complex. Unfortunately, this type of CNVM is usually not associated with AMD but occurs mainly in younger and middle-aged adults. In contrast, the more common form of CNVM in AMD is type I, which is characterised by new vessels that extend in the sub-RPE space. These new vessels establish a relatively firm adhesion to the overlying RPE. As such, surgical excision of type I CNVM invariably removes a significant portion of RPE, which is crucial to the survival of the overlying photoreceptors. To improve visual outcome in excision of type I membranes, several groups are investigating the possibility of transplanting RPE after surgical excision of CNVMs.^{18,19}

The on-going submacular surgery trial (SST) aims to determine the chance of improving or stabilising visual acuity by surgical removal of subfoveal CNVM. The current maximal size treatable is 9 disc areas.

Genetics of AMD and Gene Therapy

Once thought of as an acquired disease, there is mounting evidence that AMD patients may inherit the disease or may have a genetic predisposition for the disorder. Several genes causing diseases with phenotypes similar to AMD have been described. ABCR (ATP-binding cassette transporter), the gene known to cause about 40% of fundus flavimaculatus, has been implicated. It is present in about 16% of AMD patients.²⁰ Sorsby's fundus dystrophy is caused by a mutation in the TIMP-3 (inhibitor of tissue metalloproteinase) gene on chromosome 22. Other inherited retinal diseases which bear the hallmark drusen at the macula, with consequent visual loss from geographic atrophy or choroidal neovascularisation, include Doyne's honeycomb dystrophy and malattia leventinese. Both have been ascribed to the same locus on the EFEMP-1 gene on the short arm of chromosome 2.

If one or more causative genes are identified in AMD, they may be amenable to gene replacement or gene knockout

therapy. For example, the fibrovascular proliferation that is responsible for visual loss in AMD may respond to suicide gene therapy. Geographic atrophy, which is characterised by progressive degeneration of retinal elements, may respond to genes that retard biochemical degradation or inhibit apoptosis in affected retinal cells.

Conclusion

There have been numerous advances in the management of AMD, and exciting new research applications have emerged. It is difficult to exhaustively review all the clinical and basic science research that have taken place over the last decade, but there have been several breakthroughs that command our attention. The introduction of exciting new modalities, such as PDT and macular translocation surgery, has revolutionised the approach to treating CNVM and their effects on central vision. However, one key issue that has yet to be effectively addressed is the treatment of occult CNVM. There has been no breakthrough in achieving satisfactory outcomes with the available techniques for treating occult neovascular lesions. As results of large prospective randomised clinical trials evaluating new treatment alternatives become available, a treatment algorithm for neovascular AMD will emerge that best minimises visual loss and may even result in visual improvement.

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