disease with change of life style, suggesting that the most important factors have not yet been identified.

In non-Caucasians relatively little information is available on AMD. There is a need to determine whether or not there is genetic predisposition. The natural history of disease has not been documented. In addition, those structural changes predisposing to visual loss are unknown. They have not been documented in any detail clinically, and there is little histopathological documentation of ageing at the posterior pole. It is important that studies of AMD in Caucasian societies should now be repeated in Eastern Asia.

What benefits would there be from this new information? Defining the genetic influences would point to the relevant pathogenic mechanisms involved, and identify those at high risk of visual loss. If the environmental pressures conferring risk were known, public health measures could be taken. New therapeutic measures may come to light, and those most likely to benefit from such measures would be identified. The high prevalence of the disease in Caucasian communities, and the apparent rise in the prevalence in communities previously not considered to be at risk, highlight the urgency for an increasing level of research. Over the last 5 years there has been steadily increasing research activity investigating the pathogenesis of AMD, and the hope is that this continues.

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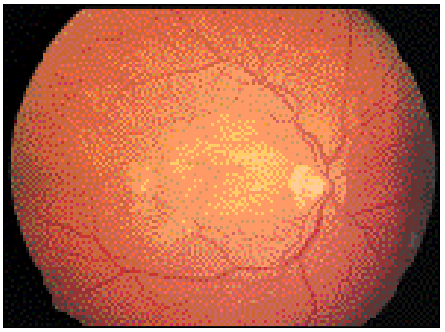


Early subretinal neovascular membrane in a Caucasian eye

Photo: Clare Gilbert

Age-Related Macular Disease: Intervention Possibilities

Usha Chakravarthy
MBBS FRCOphth PhD
Senior Lecturer/Consultant
Patricia Hart
MBBS FRCOphth
Consultant Community Ophthalmolologist
Queen's University of Belfast and Royal Victoria Hospitals
Belfast BT12 6BA, Northern Ireland

Introduction

Age-related maculopathy (ARM) is a degenerative disorder of the central retina typically with an age of onset after the fifth decade. It is characterised in the early stages by drusen, pigmentary changes and degeneration of the retinal pigment epithelium (RPE). In the later stages there is atrophy of the photoreceptors and RPE (geographic atrophy or dry form) and choroidal neovascularisation (CNV or wet form); the latter resulting in the typical disciform scar. Only the later stages of ARM (termed AMD) featuring geographic atrophy and/or CNV result in moderate or severe loss of vision.

Some of the hypotheses for the development of CNV are that

(a) tissue barriers to blood vessel growth are disrupted by degeneration
(b) inflammatory cells incite the neovascular response
(c) decreased choroidal perfusion and impaired oxygen transport result in ischaemia and neovascularisation

The only proven treatment for choroidal neovascularisation is focal laser photocoagulation.[1] Less than 20% of lesions are eligible for laser treatment at clinical presentation and even in these the benefit is modest. Thus, many different therapeutic approaches are being investigated which include preventive strategies and methods to manage established disease.

Preventive Strategies

CNV in the expanding elderly population brings a high level of visual disability and social cost. Thus, there is great interest in preventing the ingrowth of new vessels before there is severe loss of visual function, particularly since there is no treatment for the atrophic form and existing therapies are of minimal benefit for CNV. A number of preventive strategies are therefore under consideration.[2] As oxidative stress has been suggested as playing a role in macular tissue damage leading to ARM, dietary supplementation with antioxidants is being tested in a randomized controlled trial. The National Eye Institute, USA, is sponsoring the Age-Related Eye Disease Study (AREDS): a multicentre, clinical trial to evaluate the role of antioxidant vitamins (with or without zinc supplementation) in the prevention of age-related macular degeneration and cataract.[3] As the development of these degenerative disorders is often a long process, any beneficial effects in the treated group are unlikely to become apparent for at least another 5 years.

Within the past several years, there has also been significant interest in the role of low intensity laser treatment to eyes with large diffuse drusen in the prevention of CNV and loss of vision. Pilot studies have reported a decreased incidence of CNV and a lower rate of loss of vision among treated eyes. Initial results from a large randomized clinical trial (The Choroidal NeovascularizationPrevention Trial; CNVPT)[3] are now available. Essentially this study enrolled patients into one of two groups. The first group consists of patients with established neovascularisation in one eye with soft drusen in the fellow eye (Fellow Eye Study).[3] The second group consists of individuals with bilateral soft drusen (Bilateral Drusen Study). Prophylactic argon laser photocoagulation was performed in the fellow eye in the Fellow Eye Study and in one eye in the Bilateral Drusen Study. Interim analysis has demonstrated increased rates of CNV but decreased rates of vision loss in fellow eyes treated with laser in the Fellow Eye Study. Among patients with bilateral drusen, treated eyes and observed eyes had similar rates of CNV and loss of vision. Thus, there is a possibility that some interventions may succeed in reducing the rate of visual loss but all the indicators suggest that the effects, if any, will be modest.

Current Status of Clinical Trials for CNV of AMD

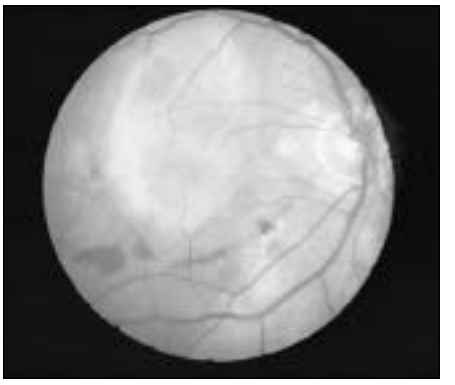
While prevention remains a primary goal, a significant proportion of the ageing population exhibits fully developed disease. Various new therapeutic approaches are under investigation in their management. These include the use of photodynamic

therapy (PDT),[4] radiotherapy and surgical excision. The TAP study (Treatment of AMD with PDT) involving 609 patients at 22 centres in the USA and Europe is a phase 3 clinical trial where patients with subfoveal CNV are randomized to visudyne or placebo. In this study a drug (a derivative of benzoporphyrin) was used to sensitize the neovascular tissue, following which the tissues were irradiated using a diode laser. The verteporfin in the Photodynamic Therapy Study (VIP study) uses a different photosensitizer but also includes many patients with subfoveal CNV who do not fit the criteria for the TAP study. The 12 month result of the TAP study has shown that patients treated with visudyne therapy were more likely to have stable vision or improved vision compared with those treated with placebo (<.0002). Analysis has revealed that 61.4% of patients treated with visudyne and 45.9% of patients treated with placebo had stable vision (CIBA Vision press release). Thus, while the treatment offers some hope for those already showing signs of advanced disease, the overall benefit is small.

Another treatmentcurrently under investigation is the possible role of radiotherapy in the prevention of severe visual loss in subfoveal CNV.[5] A number of phase 3 randomized controlled clinical trials are expected to announce their results within the next year. Of these the UK multicentre clinical trials (SFRADS) has enrolled 200 patients with subfoveal CNV, half of whom have been assigned to treatment with the other half assigned to observation only. Other trials include the German RAD study and the ROARMD study in Georgia, USA.

Experimental Strategies

A variety of other therapeutic approaches are under investigation at the experimental stage.[2] These include using techniques of photoreceptor rescue in animal models of macular degeneration, retroviral gene transfer, retinal pigment epithelial transplantation and studies of a variety of anti-angiogenic agents that prevent or suppress neovascularisation. In the long-term, studies are needed to identify the molecular pathways which result in the death of the photoreceptor, RPE cell and the choriocapillaris. In the medium term, the benefits of identifying modifiable risk factors are unlikely to affect the prevalence of AMD over the next few decades. However, significant research is continuing for the prevention and treatment of wet AMD and may result in improved treatment which could influence and prevent severe visual loss. Finally, research is needed to identify the optimal management strategies in those who have already developed AMD and address the value of visual rehabilitation and visual aids.



Age-related disciform macular disease
Photo: Clare Gilbert

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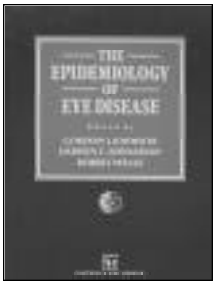
Book Review

The Epidemiology of Eye Disease

Edited by: Gordon J. Johnson, Darwin C Minassian and Robert Weale



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Review

This splendid and much needed book was written to answer the needs of postgraduate students on courses at the International Centre for Eye Health. It will be of great value to clinical and public health personnel involved in prevention of blindness and eye care programmes worldwide. The subjects covered are applicable in both developing and industrialised economies.

There are three sections to the book. The first section deals with epidemiological methodology, starting with basic principles and guidelines, through calculating sample sizes and planning an eye survey to data analysis and reporting.

The middle and largest section covers the epidemiology of specific diseases with a chapter on each one. The conditions are cataract, trachoma, glaucoma, vitamin A deficiency, onchocerciasis, leprosy, HIV/AIDS, diabetes and age-related macular degeneration. Other subjects which also have their own chapters are childhood blindness, eye injuries and conditions of the outer eye excluding those mentioned above.

Section three is a practical guide on how to get going on prevention of blindness programmes. The processes are detailed for planning, management and evaluation of eye-care services and each stage is illustrated with practical examples. The book is rounded off with the roles of both the WHO programme for prevention of blindness and the international non-governmental organisations. Finally the scene is set for intervention in industrialised countries.

Denise Mabey FRCOphth

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