Age related macular degeneration

Amresh Chopdar, Usha Chakravarthy, Dinesh Verma

Age related macular degeneration is an increasing problem worldwide. Current treatment options can delay progression, and research continues into ways of reversing retinal damage

An epidemic of "ageing" is impending in the Western world. According to the latest predictions released by the United Nations, the number of people aged over 60 will triple from 606 million worldwide in 2000 to nearly 2 billion by 2050. The increase in the population aged over 80 is expected to be more than fivefold, from 69 million in 2000 to 379 million by 2050. People aged over 60 constitute about 20% of the population in more developed regions of the world; by 2050 they will probably account for 33%.[1] The United Kingdom is predicted to have about 16 million people over the age of 60 by 2040.[2] One major implication of this demographic change is the emergence of conditions that are directly related to ageing. Age related macular degeneration is already the leading cause of blindness in the Western world. Between 20 and 25 million people are affected worldwide, a figure that will triple with the increase in the ageing population in the next 30-40 years.[2] According to the World Health Organization, 8 million people have severe blindness due to age related macular degeneration, excluding the countries where data are scare.[3] In a recent systematic review Fletcher et al estimate that somewhere between 182 000 and 300 000 people in the United Kingdom are blind or partially sighted as a result of age related macular degeneration.[4]

Summary points

- The UN estimates the number of people with age related macular degeneration at 20-25 million worldwide; WHO's estimate is 8 million people with severe visual impairment
- The main symptom of non-exudative age related macular degeneration is a gradual increase in difficulty of fine discriminate tasks; the main symptoms of the exudative form are central blurring and distortion of sudden onset
- Retinal angiography is the key to identifying choroidal neovascularisation and planning appropriate treatment
- Dietary modification and nutritional supplementation may form important strategies in preventing progression of disease
- Manipulation of the molecular environment in the vicinity of the retina can prevent angiogenesis and is likely to form the basis for the future management of choroidal neovascularisation
- For people with severe loss of vision, progress in the field of artificial vision offers a distant yet promising therapeutic possibility

Sources and selection criteria

We searched Medline for macular degeneration (classification, complications, physiopathology, diagnosis, prevention and control, diet therapy, drug therapy, radiotherapy, epidemiology, etiology, therapy, genetics, metabolism). We also referred to textbooks on the subject.

Anatomy and pathophysiology

The macula is an area up to 5.5 mm in diameter with the fovea at its centre. The fovea is located 4 mm temporally from the centre of the optic disc and roughly 0.8 mm below the horizontal line (fig 1). The centre of the fovea is the thinnest part of the retina (fig A on bmj.com). This area is free from any blood vessels and is referred to as the capillary-free zone (fig B on bmj.com). The macula has a preponderance of cone cells and is responsible for detailed central vision.

Although histologically the retina is a complex multilayered structure, a simpler approach is to consider it functionally as two parts. One functional entity is the photosensitive layer of rods and cones and their neural connections that gather light and convert it to electrical nerve impulses, transmitted via the optic nerve. The other part is the underlying retinal pigment epithelium and its basal lamina called Bruch's membrane, which together maintain the integrity of the barrier between the choroid and the retina. The choroid, which is mainly a vascular tunica, is sandwiched between the retina and the sclera and forms the main source of blood supply to the outer half of the retina.

East Surrey Hospital, Redhill, Surrey RH1 5RH
Amresh Chopdar *consultant ophthalmologist*
Queen's University and Royal Victoria Hospital, Belfast
Usha Chakravarthy *professor, ophthalmology and vision science*
Doheny Retina Institute, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
Dinesh Verma *associate professor of clinical ophthalmology*
Correspondence to: A Chopdar vision@nearpoint.fsnet.co.uk

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Additional figures are on bmj.com

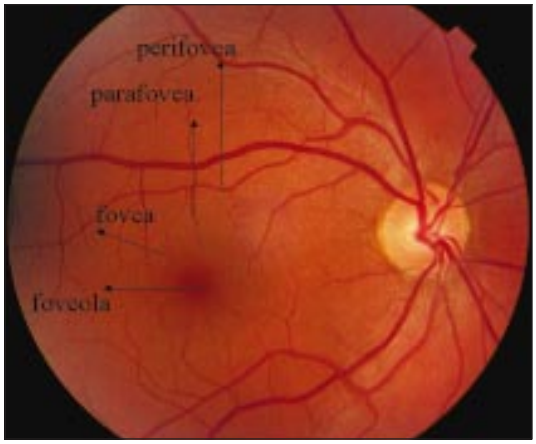

Fig 1 Colour photograph of a normal fundus showing the different zones of the macular area

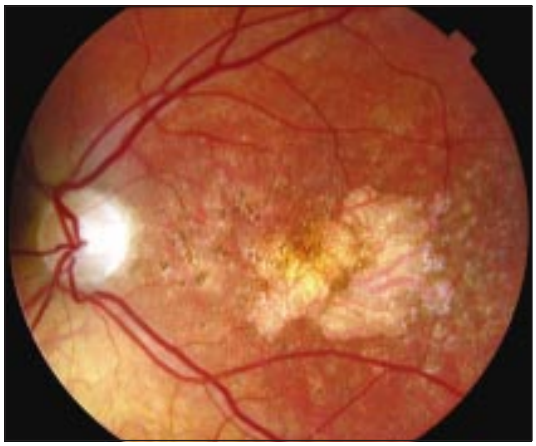

Fig 2 Colour photograph showing a typical case of the geographic pattern of retinal pigment epithelial atrophy in an age related macular degeneration

Causes of age related macular degeneration

Age related macular degeneration is a multifactorial disease, although its exact aetiology is unknown. Several risk factors are recognised, of which age is the strongest. Ocular risk factors include the presence of soft drusen, macular pigmentary change, and choroidal neovascularisation in the other eye.[5 6] Systemic risk factors include hypertension, smoking, and a positive family history.[7]

With advancing age, the cells of the retinal pigment epithelium become less efficient in performing their tasks for many reasons; the retina can no longer receive its proper nourishment and accumulates waste material, which leads to amorphous deposits termed drusen. The retinal pigment membrane cells slowly degenerate and atrophy, and central vision is lost. This form of disease is called the dry type of age related macular degeneration or geographic atrophy. Geographic atrophy progresses slowly over many years; the time to legal blindness (visual acuity ⩽3/60) varies between five and 10 years (fig 2).[8]

Alternatively, if the integrity of Bruch's membrane is broken, neovascular complexes from the choroid grow into the subpigment epithelial and subretinal spaces in a process called choroidal neovascularisation. The new blood vessels are leaky, leading to oedema (extravasation of blood and lipid materials), which progressively disrupts visual function. The end result is a dense fibrovascular scar that may involve the entire macular area. This form of disease is called exudative or the wet type of age related macular degeneration. Exudative age related macular degeneration is more sight threatening than the dry type and is responsible for 90% of cases of severe visual loss in elderly people (fig 3).

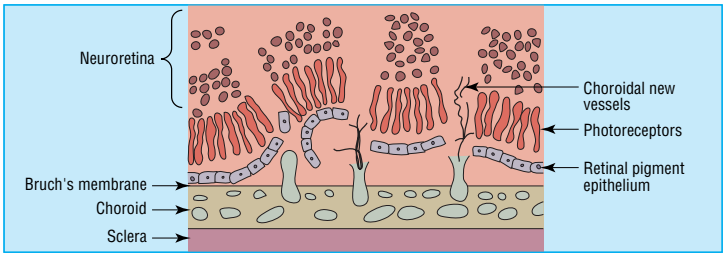

Fig 3 The concept of exudative age related macular degeneration. Note the choroidal new vessels growing through the breaks in the Bruch's membrane. (Modified from an idea of Bressler SB, et al. *Am J Ophthalmol* 1982;93:157-63)

Clinical features

The most common symptoms of age related macular degeneration are blurring of central vision, metamorphopsia, and reduced vision. This can ultimately lead to a central scotoma and severe loss of vision. If the patient is shown graph paper the squares may look distorted and the lines wavy. Ophthalmoscopic examination of the fundus shows patchy chorioretinal atrophy in the dry type and macular oedema in the wet variety, often associated with retinal haemorrhages and lipid exudate around the macula.

Diagnostic techniques

In addition to assessment of visual acuity and a full ophthalmological examination, exudative age related macular degeneration is usually investigated by retinal and choroidal angiography using fluorescein and indocyanine green dyes. Angiographic imaging is done by using specially designed fundus cameras fitted with appropriate filter combinations, and the detailed architecture of the retinal vascular tree can be displayed and recorded for analysis. In recent years digital angiography and tomographic techniques have allowed better delineation of choroidal neovascularisation for treatment and monitoring of progression of disease. Choroidal neovascularisation is recognised as areas of fluorescein leakage and may be described as classic or occult. Classic leakage is said to occur when the hyperfluorescence has distinct borders and occurs early in the transit phase of the angiogram, with subsequent obscuration of the boundaries towards the late phases. The main vessels feeding the choroidal neovascularisation can sometimes be located with indocyanine green angiography (fig 4). The occult variety is said to be present when the leakage from the choroidal neovascularisation is poorly defined; it appears late in the transit phase of the dye (fig C on bmj.com).[9] Eyes with choroidal neovascularisation may exhibit different proportions of classic and occult leakage.

Clinical advances

Laser photocoagulation using a thermal laser was the first effective treatment against exudative age related macular degeneration.[10 11] A decade after it had become widely used in clinical practice thermal laser photocoagulation was found to be applicable only to a small proportion of eyes with classic choroidal neovascularisation located outside the foveal avascular zone.[12] As most choroidal neovascularisation extends under the fovea, an alternative method using a non-thermal laser and a photosensitising drug has recently been shown to improve outcome in eyes with choroidal neovascularisation. This technique is called photodynamic therapy and uses verteporfin as the photosensitiser. Once infused into the circulation, verteporfin selectively binds to the low density lipoprotein protein receptor sites in newly formed choroidal neovascularisation. When a red laser transmitting at a wavelength of 689 nm is targeted at the site of the choroidal neovascularisation it activates the drug and releases free radicals in the endothelial cells, resulting in damage and selective closure of the abnormal vessels. The treatment of age related macular degeneration by photodynamic therapy study showed that a significantly lower proportion of treated eyes lost three or more lines of distance visual acuity than in the control group at both one and two years of follow up. This difference was more marked in eyes with classic or predominantly classic choroidal neovascularisation.[13 14]

Radiation treatment

Early clinical trials indicated that external beam radiation was ineffective in maintaining vision in choroidal neovascularisation.[15] However, a multicentre randomised trial of 12 Gy of fractionated radiotherapy, although it did not identify significant differences in distance acuity, found significant benefit in terms of maintained near acuity and contrast sensitivity in treated eyes.[16]

Prevention of age related macular degeneration

The age related eye disease study showed a significant reduction in the relative risk of developing neovascular age related macular degeneration in participants given long term supplementation with high dose zinc and antioxidant vitamins (A, C, and E).[17] A recent Cochrane review has urged caution in generalising these findings to other populations with different nutritional status, suggesting that some harm may be caused by long term micronutrient supplementation, particularly in smokers.[18] Another trial of supplementation with vitamin E showed no differences in the rate of progression to age related macular degeneration in treated and control groups.[19] By far the most biologically plausible micronutrients to have a potential protective role in age related macular degeneration are the carotenoids lutein and zeaxanthin, which are potent antioxidants found in high concentrations in the macular retina. The case for further trials aimed at testing the role of lutein and zeaxanthin in the prevention of age related macular degeneration is now compelling.

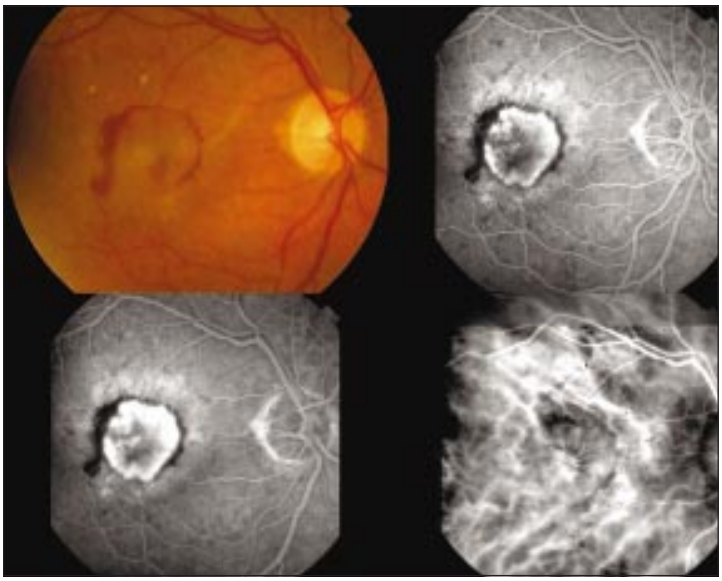

Fig 4 A case of classic choroidal neovascularisation. The colour photograph shows intraretinal haemorrhage and retinal oedema of the macular area. The next two frames show early and late phases of the fluorescein angiogram with leakage of dye. The final frame is a photograph from indocyanine green angiography, showing the detailed architecture of the choroidal vasculature

When should patients be referred for treatment?

Primary care physicians should promptly refer any person with central blurring or distortion of vision of sudden onset to the nearest centre with specialist retinal expertise. Timely treatment with thermal laser or verteporfin photodynamic therapy offers the best chance of restricting visual loss. Neither treatment is likely to restore vision that has already been lost. Most ophthalmologists are reluctant to prescribe prophylactic supplementation with high dose antioxidant vitamins and zinc for several reasons. Firstly, the evidence comes from a single clinical trial. Secondly, the value of the benefit is unclear as there was no difference in visual function between placebo and intervention groups. Thirdly, any treatment would have to be continued for as long as the patient lives. Fourthly, adverse effects are a potential problem. As the age related eye disease study showed maximum benefit in patients with unilateral advanced age related macular degeneration, we suggest that prophylaxis with zinc and other antioxidant vitamins should be restricted to such patients. Cessation of smoking and a diet rich in fresh fruit and vegetables should be recommended in patients who are found on routine testing to have bilateral age related macular changes with normal central vision,.

Future developments

Perhaps the most promising and exciting of all the therapeutic approaches is the manipulation of the molecular environment of the choroidal neovascularisation to induce its regression. Suppression of vascular endothelial growth factor secretion or blocking its interaction with its receptor offers one very exciting antiangiogenic therapeutic approach. Another molecule of interest is pigment epithelium derived growth

Additional educational resources

Fine SL, Berger J, Maguire MG, eds. *Age-related macular degeneration.* St Louis, MO: Mosby, 1998

Gass JDM. *Stereoscopic atlas of macular diseases.* St Louis, MO: 1999

Information for patients

Macular Disease Society, P O Box 16, Denbigh LL10 5ZA—www.maculardisease.org

Solomon Y, Solomon JD. *Overcoming macular degeneration: a guide to seeing beyond the clouds.* Avon Books, 2000

factor, which not only prevents angiogenesis but also improves the health of the retinal pigment epithelium through its trophic function and thus may be of value in restoring the integrity of the blood-retinal barrier.[20]

Other treatments being tested include a variety of antiangiogenic agents (anecortave acetate, triamcinolone acetonide), which are administered intravitreally or periocularly, along with feeder vessel photocoagulation and transpupillary thermotherapy using a newer type of laser. The results of most of these trials should be available within the next few years.

Currently, no treatment is available for patients with advanced disease and severe central vision loss. However, a major advance in semiconductor chip technology has made the manufacture of microphotodiode arrays possible. Pilot feasibility studies indicate that these minute chips can be implanted into the retina to interphase directly with the visual pathways with some prospect of neurotransmission to the brain. The Doheny Retina Institute of the University of Southern California is trying to develop a type of retinal prosthesis that would give a real hope of providing a visual stimulus to blind patients with severe retinal degeneration.[21 22]

Conclusion

Even though no current treatment will restore vision that has already been lost, immediate referral and fast tracking of people with symptoms of exudative age related macular degeneration to specialist retinal centres will offer individual patients access to the array of treatments that can help to minimise damage to the macula. With the impending epidemic of "ageing," age related macular degeneration is set to become a major public health problem, especially in the developed world. Continuing research in this field holds great promise for the future.

Competing interests: None declared.

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Corrections and clarifications

Socioeconomic position in childhood and adulthood and insulin resistance: cross sectional survey using data from British women's heart and health study

Tables 2 and 3 in the full version (see bmj.com) of this paper by Debbie A Lawlor and colleagues, contain the wrong regression coefficients in the final two columns (*BMJ* 2002;325:805-7). The magnitudes of the regression coefficients are about one tenth of the value that they should be, but the corrected values do not alter the conclusions of the paper. The corrected tables can be viewed at www.bmj.com/cgi/content/full/325/7368/805/DC1.

Doctors' use of electronic medical records systems in hospitals: cross sectional survey

During a recent exercise to update their material, the authors (Hallvard Lærum and colleagues) of this Information in Practice article that was published over a year ago, discovered that some of the information they had used was wrong (*BMJ* 2001;323:1344-8). The one DocuLive department in the investigation that had reported having the function "obtain results from clinical biochemical laboratory analyses" did not have it after all. Because of this, figure 2 should exclude the entry for clinical task No 10. The authors say that the error does not affect the principal findings or conclusion.