Age-related Macular Degeneration

Synonyms: macular degeneration (the term senile macular degeneration is now obsolete)

Age-related macular degeneration (AMD, or AMRD) is the term applied to ageing changes without any other obvious precipitating cause that occur in the central area of the retina (macula) in people aged 55 years and older.[1]

AMD is a progressive chronic disease of the central retina and a leading cause of vision loss worldwide. Most visual loss occurs in the late stages of the disease[2];

Pathophysiology[3]

AMD is characterised by the appearance of drusen in the macula, accompanied by choroidal neovascularisation (wet AMD) or geographic atrophy (dry AMD). The two forms of AMD have differing pathophysiology and progression.

Dry AMD/geographic atrophy (GA)
The characteristic lesions of dry AMD are soft drusen and changes in pigmentation (hypopigmentation and/or hyperpigmentation) of the retinal pigment epithelium (RPE). Atrophy of the RPE becomes more extensive with time. The dry form can advance and cause vision loss without turning into the wet form. The end stage of the dry form involves the whole macula becoming affected as the GA evolves.

- Dry AMD is the most common form of AMD, occurring in 90% of cases.
- Progression to visual loss is usually gradual.
- Eventually there is an area of partial or complete atrophy of the RPE. This may or may not involve the fovea.
- Those with dry AMD have a 4-12% chance per year of developing choroidal neovascularisation (wet AMD). Patients with extremely large drusen have an higher (30%) chance that their AMD will convert to the wet form within five years[4].

Wet AMD/neovascular AMD/exudative AMD
In the wet type of AMD, new blood vessels grow in from the choriocapillaris under the retina. They spread under or above the RPE or both. They are fragile and easily leak. Blood vessels don’t initially grow under the macula - they start off to the side of the retina and grow towards the centre. For some, it can take only days to grow under the macula; for others it will take weeks. They can reoccur, sometimes many years later. The consequences of abnormal vessel growth are haemorrhage and scar formation (disciform scarring).

- Wet AMD accounts for 10% of all cases of AMD but about 60% of advanced cases. Wet AMD is by definition considered advanced at presentation.
- Progression varies from a few months to three years. Untreated, most will become severely visually impaired within approximately two years.
- The end point of this type of AMD is scar formation known as disciform macular degeneration.
- Approximately 50% of patients who have wet AMD in one eye will also develop this condition in their second eye within five years.

Classification of severity[1]
There are several classification schemes based on the presence and severity of the characteristic features of AMD, namely drusen, pigmentary irregularities, GA and neovascularisation. These classification systems are moderately good at predicting progression but are highly precise and detailed. The ‘Age-Related Eye Disease Study’ (AREDS) trial developed a simpler classification system which has proved more clinically useful[5, 6].

- No AMD: none or a few small drusen.
- Early AMD: multiple small or a few intermediate drusen +/- abnormalities of the RPE.
- Intermediate AMD: extensive intermediate or one or more large drusen +/- GA not involving the fovea.
- Advanced AMD: GA involving the fovea +/- any features of wet AMD.

Idiopathic polypoidal choroidopathy[1]
This is a variant of AMD, consisting of neovascularisation, primarily located within the choroid. It shares some features with AMD - it involves the macula, it is seen in the same age-group, it shares common non-genetic risk factors, such as smoking and hypertension, and it shares common genetic risk factors. However, in contrast to AMD, polypoidal choroidopathy is seen in a younger age group than AMD, it more often occurs in the nasal macula and the polypoidal neovascular complexes may leak and bleed but are less likely to invade the retina.
Epidemiology

- AMD is the most common cause of severe visual impairment in older adults in the developed world.
- AMD is responsible for two thirds of registrations of visual impairment in the UK.
- The estimated prevalence of AMD in the UK is 4.8% of those over 65 years of age and 12.2% of those aged 80 years or more.
- There are around 70,000 new diagnoses in the UK each year.
- About 90% of all cases have dry AMD.
- Wet AMD accounts for about 50% of advanced AMD.
- Prevalence is increasing in line with an ageing population.[7]
- AMD is more common in people of Caucasian ethnicity.
- Women are more likely than men to develop AMD.
- Worldwide, over 30 million people have AMD.

Risk factors[3, 7, 8]

AMD is a multi-factorial disease; both environmental and genetic components play a role in its development. Several risk factors have been linked to AMD:

- Increasing age (the main risk factor).
- Smoking is a risk factor both for new-onset AMD and for progression to advanced disease. Risk increases with the number of pack-years. Smoking has a synergistic effect with genetic factors. There also seems to be a relationship between genes and response to treatment.
- Family history: several genes are associated with a risk of developing dry AMD. Siblings of affected people have four times greater chance of developing the disease. Concordance for identical twins is 40-100%.
- Presence of AMD in one eye greatly increases the risk of it developing in the other: 25-35% will develop visual impairment in the second eye within four years.[9, 10]
- All cardiovascular risk factors are also associated with wet AMD.[8]
- Some studies suggest an association between AMD and cumulative eye damage from ultraviolet light. People with light-colored eyes are more likely to develop dry AMD.
- People with diets that are high in fat, cholesterol and high glycemic index foods, and low in antioxidants and green leafy vegetables, may be more likely to develop AMD.
- Obesity (BMI greater than 30) increases risk by about 2.5 times.
- Ethnicity affects risk. AMD is very uncommon in native Africans and native Australians. It is most common in Caucasians.
- There is growing evidence that a high cumulative lifetime exposure to sunlight also increases the risk of developing AMD.[7]

Presentation[1, 3]

Symptoms

AMD causes painless deterioration of central vision, typically in a person aged 55 or more. Patients may initially be asymptomatic and retinal signs may be detected incidentally during a routine eye test.

General symptoms

- Reduction in visual acuity, noticed particularly for near vision.
- Loss of (or decreased) contrast sensitivity (the ability to discern between different shades).
- Abnormal dark adaptation (difficulty adjusting from bright to dim lighting). There may be a central dark patch in the visual field noticed at night, which clears within a few minutes as the eyes adapt.
- Photopsia (a perception of flickering or flashing lights).
- Light glare.
- Visual hallucinations (Charles Bonnet syndrome). These can occur with severe visual loss of any cause. Visual hallucinations are often not reported unless specifically asked about.

Dry AMD symptoms

- Visual deterioration tends to be gradual. A common presentation is difficulty with reading, initially with the smallest sizes of print and then later with larger print.
- People may not notice visual deterioration when only one eye is affected, so that the visual loss only becomes apparent when the second eye becomes affected.
- When GA is bilateral and involves both foveae, patients may complain of deterioration of central vision.

Scotoma - the person may describe a black or grey patch affecting their central field of vision.
The most common symptoms typical of onset of exudative AMD are central visual blurring and distortion. Most patients will complain that straight lines appear crooked or wavy.

Visual deterioration may develop quickly. A person may suddenly become unable to read, drive, or see fine detail such as facial features and expressions.

Vision may suddenly deteriorate to profound central visual loss in the event of a bleed. This may be preceded or accompanied by a shower of floaters.

As for dry AMD, when exudative AMD occurs in the second eye, patients may suddenly become aware of their visual loss.
Examination

- Examination may reveal a normal or decreased visual acuity associated with distortion on the Amsler grid. See separate Examination of the Eye article.
- Fundus examination reveals drusen (discrete yellow deposits) in the macular area, which may become paler, larger and confluent in patients progressing to exudative AMD.
- Late in the disease, a macular scar may develop, resembling a thick yellow patch over the macular area.
- Areas of sharply demarcated hypopigmentation or hyperpigmentation of the peripheral retina are sometimes seen, representing GA of the RPE.
- Macular signs of wet AMD include well-demarcated red patches representing intraretinal, subretinal or sub-RPE haemorrhages or fluid. There may be patchy pigmentation.

Differential diagnosis\(^3\)

Painless loss of vision can be caused by:

- Refractive errors.
- Cataracts.
- Some corneal diseases - eg, Fuch's endothelial dystrophy.
- Posterior vitreous detachment or retinal detachment.
- Retinal artery occlusion or retinal vein occlusion.
- Central serous retinopathy.
- Cerebrovascular disease including amaurosis fugax, transient ischaemic attack and stroke.
- Some drugs or chemicals including methanol, chloroquine, hydroxychloroquine, isoniazid, thioridazine, isotretinoin, tetracycline or ethambutol.
- Pituitary tumour, central nervous system tumour and papilloedema.
- Macular hole.
- Primary open-angle glaucoma (central visual loss occurs late).
- Optic atrophy.

Conditions causing similar retinal signs to those observed in AMD include:

- Diabetic maculopathy.
- Macular degeneration associated with high myopia (greater than ~6 dioptres): atrophic or neovascular changes usually occur at a younger age than AMD and have a different natural history and response to treatment.
- Rare inflammatory syndromes causing choroidal neovascularisation (for example ocular histoplasmosis). There are usually signs of active or previous uveitis.
- Central serous retinopathy.
- Macular telangiectasia.
- Macular dystrophy usually inherited and often symmetrical.
- Type 2 membranoproliferative glomerulonephritis.
Investigations

Secondary care investigations are aimed at confirming the diagnosis, assessing the extent of the disease and the possibilities for intervention, and keeping a record in order to measure treatment effects and disease progression:

- **Slit-lamp biomicroscopy** to identify drusen and any pigmentary, exudative, haemorrhagic, or atrophic changes affecting the macula (looking for the characteristic area or areas of pallor with sharply defined and scalloped edges). This also helps to detect retinal thickening or elevation due to neovascular AMD.
- **Colour fundus photography** is used to record the appearance of the retina.
- **Fluorescein angiography** is used if neovascular AMD is suspected, in order to confirm the diagnosis and assess the lesions. Fluorescein dye is injected intravenously and photographs of the retina are taken serially to detect abnormal vasculature or leakage from capillaries.
- **Indocyanine green angiography** may be used to visualise the choroidal circulation, which provides additional information to fluorescein angiography.
- **Ocular coherence tomography** produces high-resolution cross-sectional and three-dimensional images of the retina. The guideline from The Royal College of Ophthalmologists states that this test is mandatory for diagnosis and that monitoring response to therapy can reveal areas of GA that may not be clinically visible on biomicroscopy.

Management of suspected age-related macular degeneration

If AMD is suspected, refer the person urgently for further assessment, ideally to be seen within one week of referral. Urgent referral is particularly important in people who present with distortion or with rapid-onset visual loss, as these suggest wet AMD.

Refer to one of the following, the choice depending on local referral pathways:

- A fast-track macular clinic or medical retina clinic treatment centre.
- A local district general hospital eye service.
- An optometrist: only an option if they can be seen within one week and the optometrist is able to refer directly to an ophthalmologist.

Advise the person that if there is either a delay of more than one week in being seen by an ophthalmologist or symptoms are worsening whilst they are waiting to be seen, they should attend Eye Casualty as soon as possible, or seek other immediate medical attention to expedite urgent specialist assessment.

Management of dry age-related macular degeneration

There is no treatment which prevents progression of dry AMD, although lifestyle adjustments may slow progression. Management consists mainly of counselling, smoking cessation, visual rehabilitation and nutritional supplements in those expected to benefit. Co-existing visual impairments such as cataract and refractory error should be appropriately managed (although a Cochrane review found that it is not possible to conclude from the available data whether cataract surgery is beneficial or harmful in people with AMD).

There is currently considerable interest in implantable lens systems for end-stage disease (see below).

Advice and support

People diagnosed with AMD will receive information about their condition from secondary care; however, consider offering information such as:

- If the person develops worsening symptoms, or develops symptoms in the second eye, they should either:
  - Present as soon as possible to Eye Casualty or a similar urgent walk-in hospital eye clinic; or
  - Present as soon as possible to the GP so that an urgent re-referral can be made to specialists.

- Information about secondary care treatments.
- What can be done to slow progression.
- Explain that many people with severe sight loss experience visual hallucinations.
- Consider registering as sight-impaired. Registration is voluntary but provides access to benefits and help.
- If appropriate, information on accessing low vision services (see below).
- Signposting to relevant organisations - for example:
  - The Macular Society provides support and comprehensive information about AMD and living with AMD, in print and audio format.
  - The Royal National Institute of Blind People provides information and support (including contact details for local support groups) for the visually impaired.
  - Citizens Advice can provide advice on available benefits.

- Driving: many people with AMD are able to drive, depending on the severity of the disease, if their vision fulfils the requirement by the DVLA. It is the person’s legal responsibility to check whether their eyesight is good enough to drive. Registration for sight impairment or severe sight impairment normally rules out holding a driving licence. If there is uncertainty about fitness to drive, advise the person to contact the DVLA.
Lifestyle advice[3, 5, 6]

- Advise smokers to stop smoking: this reduces the risk of AMD progression in people with existing disease.
- Encourage the person to eat a healthy, balanced diet rich in leafy green vegetables and fresh fruit: this is likely to improve concentrations of macular pigment in the fundus. There is no firm evidence that this helps to slow the progression of AMD but it is sensible and is unlikely to do any harm.
- Patients may be advised to take a dietary supplement by their consultant ophthalmologist. This would typically be for people with intermediate AMD in one or both eyes, or advanced AMD in one eye. The AREDS trial of 2001 and the follow-up work (AREDS2) concluded that specific dietary supplements may reduce the risk of progression by 25% in these patients. The supplements are widely sold as the AREDS2 formula and consist of:
  - 500 mg vitamin C
  - 400 IU vitamin E
  - 10 mg lutein
  - 2 mg zeaxanthin
  - 25 mg zinc
  - 2 mg copper

- There is no evidence to support the use of these supplements for people with less than intermediate AMD and there is no evidence that they are useful in primary prevention. They are not risk-free. Zinc supplementation causes a small increase in the risk of hospitalisation due to genitourinary conditions. There is possibly a small increased risk of heart failure associated with vitamin E supplementation in patients with diabetes mellitus.
- A number of studies have looked at using statins and ginkgo biloba extracts (these contain flavonoids and terpenoids which have antioxidant properties) to slow disease progression; however, studies have been inconclusive. These are not treatment options used in the UK.

Visual rehabilitation
This is the mainstay of management for most patients with dry AMD. It revolves around maximising any remaining visual function and assisting the person to maintain an independent life for as long as possible. It may involve:

- Refraction check to make sure that any remaining vision is the best it can be.
- Low visual aid clinic referral to help the person to make the most of their remaining sight. The services may include: provision and training on the use of optical aids (such as magnifiers) and advice on lighting, tactile aids, electronic aids and other non-optical aids. Low vision services may be provided by social services, community optometrists, eye departments, or the voluntary sector.
- A person does not need to be registered as sight impaired to access low vision services. In fact, access to low vision services before the person develops serious visual difficulties gives them the chance to adapt before they are severely affected.
- The service may also provide advice on benefits, concessions and support groups for people who are sight impaired. See separate Severe and Partial Sight Impairment article.

Management of wet age-related macular degeneration

Intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents are the current standard of care. Treatment is carried out by ophthalmologists with a special interest in retinal and macular problems. Interventional treatment takes place either in theatre or in a designated treatment 'clean room' under local anaesthetic.

Anti-VEGF inhibitors[1, 3, 13]

VEGF is a pro-angiogenic growth factor that also stimulates vascular permeability and has a major role in the pathology of neovascular AMD. Since anti-VEGF therapy has become available there has been a substantial improvement in the prognosis of people affected by neovascular AMD

- Anti-VEGF drugs include ranibizumab, bevacizumab and aflibercept.
- The anti-VEGF drugs are administered by intravitreal injection, usually given monthly for three months and then at variable times thereafter, depending on response. Treatment and follow-up may be for beyond two years.
- Most patients will maintain vision at their current level and about a third will gain some improvement in vision; however, about 10% will not respond to therapy.
- Patients should understand the risk associated with intravitreal injections and be instructed to report symptoms suggestive of endophthalmitis without delay.

Pegaptanib is not currently recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of neovascular AMD. Ranibizumab and aflibercept are recommended if the manufacturer provides it with the discount agreed in the patient access scheme and all of the following circumstances apply in the eye to be treated:

- Best-corrected visual acuity is between 6/12 and 6/96.
- No permanent structural damage to the central fovea.
- Lesion size is less than or equal to 12 disc areas in greatest linear dimension.
- There is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes).
- It is recommended that treatment with ranibizumab should be continued only in people who maintain adequate response to therapy.
Bevacizumab was developed for systemic treatment of colorectal cancer. It is cheaper, so whilst it is not currently licensed for intraocular use, it is widely used around the world on account of its price. Studies suggest that ranibizumab and bevacizumab have similar efficacy [7, 14].

Clinical Editor's Note
Nov 2017 - Dr Hayley Willacy draws your attention to the story of a threat of legal action to doctors in the North East by the makers of ranibizumab and aflibercept (Bayer and Novartis) [15]. This is because they have been offering patients with wet AMD the choice of a safe, effective but much cheaper drug - bevacizumab. This is not licensed for wet AMD, but several publicly funded trials have shown that it is as safe and effective as aflibercept and ranibizumab. Prescribing the cheaper drug could save the region’s NHS up to £13.5 m a year within the next five years, but Bayer and Novartis are threatening legal action, claiming it would breach a patient’s legal right to an approved drug. The counter-argument from the CCG is that pharmaceutical companies "should not dictate which drugs are available to NHS patients. The choice between three clinically effective drugs should be one for NHS clinicians and patients to make together.”

January 2018 update - NICE has recently produced new guidance on AMD [16]. They have judged that bevacizumab is as safe and effective as the licensed treatments and therefore the GMC has agreed that it will not raise concerns over fitness to practise in clinicians who prescribe it.

Older treatments
These have largely been superseded by anti-angiogenic therapies and are not usually recommended. However, they may have a role for selected people in whom anti-angiogenic drugs are not advisable. They include:

Laser photocoagulation[1]
Laser photocoagulation could only ever be considered for lesions well away from the fovea because of the risk of severe visual loss arising from a laser scar.

Photodynamic therapy (PDT) with verteporfin[17]
This involved laser treatment to lesions following intravenous injection of verteporfin, which is selectively taken up by proliferating vascular endothelial cells. The principle of treatment was to destroy the neovascular membrane without damaging the overlying neurosensory retina.

Macular translocation[18]
The macula is detached with only a small strand of tissue connecting it to the optic disc; the underlying abnormal neovascularisation is removed from the choroid and the macula is re-attached, rotated away from the diseased site. This results in a distorted image (as the macula is in a different position) which is corrected by a further operation to rotate the globe, such that the image is correctly positioned again. NICE has concluded that there is insufficient evidence to recommend this. A less invasive version involves lifting the macula from the underlying choroid and then folding the sclera so that a healthy piece of choroid is brought to lie under the macula.

Future possibilities
New lines of investigation are looking at neurotrophic growth factors and immunomodulatory drugs [7].

New therapies for end-stage age-related macular degeneration

Implanted lens systems[19]
This relatively new approach to end-stage disease may help patients with end-stage AMD of either type:

- A series of lenses (a 'miniature telescope') is used to deflect, focus and enlarge the central visual image on to a functional part of the retina peripheral to the macula. Implantation is usually performed under local anaesthesia. The brain appears able to adapt, using the healthy part of the retina to view central images. Patients usually require visual rehabilitation.
- A study of 217 patients reported that 67% and 68% of eyes with an implanted lens system improved by three or more lines of best-corrected distance and near visual acuity [20]. In a case series of 35 patients, best-corrected distance visual acuity improved in all patients after a mean of 20 months [21].
- Complications can be significant, including posterior capsule rupture and choroidal haemorrhage in 5% in one series. Later complications include condensation in the telescope, diplopia, increased intraocular pressure requiring treatment and corneal oedema.

NICE recommends that this treatment only be carried out in units where appropriate auditing mechanisms are in place [22]. It is currently not available on the NHS, and is expensive, as the lens systems are tailored to the individual patient.
Complications

- Serous retinal detachment (in exudative AMD only).
- Haemorrhage (in exudative AMD only).
- Complications of treatment include:[1] :
  - Hypersensitivity reaction to a drug.
  - Endophthalmitis.
  - Retinal detachment.
  - Severe uncontrolled uveitis.
  - Ongoing periculcular infections.
  - Thromboembolic phenomena.
  - Traumatic cataract.
  - Ongoing visual loss (20% of patients).

- The complications of visual impairment include:[3] :
  - Depression - this occurs in 24-33% of people with AMD and at twice the rate compared with elderly people without AMD.
  - Visual hallucinations (Charles Bonnet syndrome).
  - Falls and fractures.
  - Limitations in mobility, activities of daily living and physical performance.
  - Reduced quality of life.

Prognosis[3, 7]

- AMD is a progressive, irreversible disease affecting central vision only. The process tends to be a slow one in dry AMD, unless concurrent pathology develops in the same or fellow eye, when the decline becomes more apparent.
- In untreated wet AMD leads to significant visual losses (6/60 or worse) within three years.
- In dry AMD three lines of visual acuity are lost in 31% of people within two years of diagnosis and in 53% of people within four years.
- In untreated wet AMD: the prognosis is poor.
- The risk of neovascular AMD developing in the second eye is 12% at one year and 27% at four years.

Prevention

- The strongest risk factor is age, so currently the most important advice remains to focus on modifiable risk factors, such as control of hypertension, maintaining or achieving an ideal weight and smoking cessation.
- Studies have shown that increased intake of the macular carotenoids lutein and zeaxanthin and foods rich in these nutrients (eg, spinach and collard greens) is associated with a decreased risk of neovascular AMD[8].
- A risk assessment tool to look at the risk of AMD in an unaffected individual has been developed and is available online. It is intended for use by ophthalmologists[3, 7].

Further reading & references

- Miniature lens system implantation for advanced age-related macular degeneration; NICE Interventional Procedure Guidance, September 2016
- Age-Related Macular Degeneration: Guidelines for Management; Royal College of Ophthalmologists (2013)
- Macular degeneration - age-related; NICE CKS, March 2016 (UK access only)
- Assessing fitness to drive: guide for medical professionals; Driver and Vehicle Licensing Agency
- Pegaptanib and ranibizumab for the treatment of age-related macular degeneration; NICE Technology Appraisal Guidance, May 2012
- Age-related macular degeneration; NICE Guideline (Jan 2018)
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