CHAPTER 2

AGE-RELATED MACULAR DEGENERATION

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Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. Despite recent advances in treatment, AMD causes considerable morbidity. For the non-ophthalmologist, a brief background on retinal structure is provided, followed by a description of the characteristic changes seen in AMD. Subsequently the typical clinical features of AMD are discussed with an outline of present management, followed by the current theories of AMD pathogenesis. The similarities between AMD and another neurodegenerative disease are then highlighted. Finally, we review the on-going clinical trials of potential treatments for the future. Since it is clear that multiple risk factors are involved in the pathogenesis of AMD, a multi-faceted approach will most likely be required in order to prevent further patients progressing to blindness as a result of this devastating condition.

INTRODUCTION

The retina is of neural origin and is considered an end-organ of the central nervous system. The centre of the retina, the macula, is particularly prone to age related degenerative changes, a process known as age-related macular degeneration (AMD). Unfortunately its effects can lead to impairment of central vision, which may be severe enough in some individuals to lead to legal blindness. Although some forms of AMD can be treated, the majority of patients sustain some loss of vision and there are as yet no definitive preventative measures known.

In this chapter a brief description of AMD including a summary of retinal anatomy is presented, followed by clinical features and current management. We then compare AMD with other neurodegenerative diseases and conclude with ongoing developments in research.

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EPIDEMIOLOGY

AMD is the leading cause of blindness in Europe, USA and Australia accounting for up to 50% of all cases.[1] It is a common disease—the prevalence in adults is around 3%.[2] The prevalence inevitably increases with age, as is the case with several other neurodegenerative diseases. Almost two-thirds of the population over 80 years old will have some signs of AMD.[3,4] The prevalence of visual impairment (defined by the World Health Organisation, as a visual acuity of less than 6/18 in the better eye) in the over 65s due to AMD is up to 3%.[5] AMD is more common in Caucasians than in other ethnic groups.[6] There is no obvious sex preponderance, although some studies suggest women may be more susceptible.[7]

NORMAL ANATOMY

The macula is defined as the centre of the retina. The retina forms the innermost of the three layers constituting the wall of the eyeball. The tough fibrous white sclera forms the outermost wall and the vascular choroid sits in between the two. The retina consists of two delicate, thin layers of tissue. The innermost layer is the neurosensory retina, which consists of sensory cells, neurons and their supporting cells. The outer layer is the retinal pigment epithelium (RPE).

The outer layer of the neurosensory retina consists of photoreceptor cells, which detect light from the external sources and convert this to neuronal signals. These are then relayed for processing via the optic nerve in the visual cortex. This is located in the posteriorly situated occipital cortex. There are two types of photoreceptor cells named after their histological shape. Cones are utilised for colour vision and fine detail in bright light conditions. Rods are utilised for night vision. Cones are distributed mainly within the macular region, whereas rods are distributed more peripherally. However, overall rods are more numerous (comprising 95% of all photoreceptors) and indeed the macula consists mostly of rods.[8]

Each photoreceptor cell consists of an outer and inner segment, nucleus (the "cell body") and axon. The outer segment is in close contact with the RPE and consists of discs containing photosensitive pigments. These discs are constantly renewed. The used discs are shed and phagocytosed by the RPE (see below). As a photoreceptor cell is exposed to light, a renewable chain of chemical reactions is triggered in the outer segment discs, (the "visual cycle"), leading to the creation of electrical neuronal impulses ("phototransduction"). The inner segment, attached to the outer segment by a connecting cilium, contains multiple mitochondria and other supporting organelles. The axon synapses with bipolar cells deeper in the neurosensory retinal structure. The bipolar cells in turn synapse with ganglion cells. The axons of the ganglion cells make up the innermost nerve fibre layer, which carry signals generated by the photoreceptor cells to the optic nerve. Other cells provide a supporting role (e.g., Horizontal, Amacrine and Muller cells).

The RPE layer, despite being only one cell thick, performs important supporting functions, including phagocytosis of discarded photoreceptor cell outer segments, absorption of excess heat from incoming light, regulation of transport to and from the retina, maintenance of the extracellular matrix and metabolism of retinol (a vitamin A derivative involved in the visual cycle). The inner surface of an RPE cell contains

microvilli, which are in contact with the outer segments of up to 45 photoreceptor cells. Approximately 1 million discs per year are phagocytosed by each RPE cell. These discs are engulfed in phagosomes within the RPE cells, which on fusion with lysosomes are exposed to lysosomal enzymes.[9] Each RPE cell contains numerous granules of the pigment melanin, called melanosomes.[10]

The optic disc is a pink-yellow circular structure, which acts as a landmark during retinal examination. It represents the beginning of the optic nerve and is the point at which neurons from the neurosensory retina converge and then leave the eye. Sandwiched between the RPE and choroid, lies Bruch's membrane (BM). This consists of collagen, with a central layer of elastin fibres. The choroid itself sits just external to BM. It is a highly vascular tissue and consists of an inner capillary layer, the choriocapillaris and an outer large vessel layer. The capillaries within the choriocapillaris are fenestrated, allowing free passage of substances up to a certain size between the intra-capillary and the extravascular space.

The retina has a dual blood supply. The inner retina is supplied by its own vascular system, situated within the neurosensory retina. The retinal arteries emanate from the centre of the optic disc, then branch out in four diagonal directions to end in capillaries. These then drain into retinal veins that also form four branches running alongside the retinal arteries. These leave the eye through the centre of the optic disc. The endothelial cells of this vascular system together with tight junctions compose the inner blood–retinal barrier, corresponding to the blood brain barrier.

The choroid supplies the outer retina, via passive diffusion and active transport through BM and the RPE layer. Tight junctions between the RPE cells restrict movement and constitute the outer blood–retinal barrier. These barriers are important to ensure regulation of transport of fluids, nutrients and waste products. BM also acts as a physical barrier to restrict abnormal neovascularisation from the choroid (see below).

The macula is identifiable as an area about 3 mm in diameter, temporal to the optic disc. The temporal retinal artery branches arc around the macula (the 'arcades'). Histologically, the macula is defined as the area of the retina where the ganglion cell layer is more than one cell thick. The centre of the macula comprises the fovea. This is the point on which light rays from the external sources are focussed by the eye's optical system. The fovea appears darker clinically than the surrounding retina, since pigment levels are higher here. These include lutein and melanin. Lutein is a diet-derived yellow pigment found principally at the fovea. Melanin, found throughout the retina is maximal at the fovea in conjunction with larger RPE cells.

The fovea has evolved to allow maximal resolution of incoming images. Cone photoreceptor cells are at their highest concentration in the retina at the fovea.[8] Most other neurons within the neurosensory retina, including the ganglion cells, bipolar cells and nerve fibre layer, have been displaced away from the foveal region to reduce interference with incoming light. Furthermore, there are no retinal blood vessels at the fovea, the blood supply being derived from the outer-lying adjacent choroid.

AMD AND THE RETINA

Drusen are the earliest manifestation of AMD. These result from accumulation of extracellular material normally phagocytosed by the RPE cells. Drusen are of several types: (i) Hard drusen (HD) which appear as discrete yellow spots, (ii) Soft drusen (SD)

which are larger, more confluent and (iii) Reticular drusen (RD) which appear as a yellow interlacing network. HD and SD are located between the RPE and BM whereas RD are located above the RPE. Drusen are composed of a selective multitude of proteins and lipids many of which are associated with inflammation or the complement pathway.[11;12] SD and RD are associated with AMD progression.[13,14]

Both RPE atrophy and hypertrophy/hyperplasia often co-exist with drusen. RPE atrophy occurs due to apoptosis of RPE cells presumably as a result of local insult. RPE atrophy appears clinically as pale areas within the retina, with discrete edges. The underlying choroidal vessels may be visible. Large areas of RPE atrophy are termed "geographic atrophy" (GA). RPE hypertrophy/hyperplasia may be a reactive response to local insult and appears as irregular hyperpigmentation often located around areas of RPE atrophy or choroidal neovascular membrane (CNV—see below). These changes are associated with "dry" AMD. Most patients with this form of AMD will retain useful vision but may experience gradual visual deterioration. The advanced form of dry AMD (GA) can lead to blindness.

Unfortunately a small proportion of patients with AMD (the exact proportion varies according to how AMD is defined and the population studied) will develop sudden reduction of vision. This can be due to growth of abnormal blood vessels (CNV) under the retina, constituting "wet" AMD. CNV originates from the highly vascular choroidal layer. The proliferating vessels breach the normal barrier function of BM to proliferate under the RPE and neurosensory retina. The endothelia of these neovascular membranes are highly leaky and as a result these vessels are prone to extravasation of fluid and blood. Alternatively, neovascularisation can originate from within the retina ("retinal angiomatous proliferation," or RAP). Potential spaces for fluid and blood to collect include under the RPE (sub-RPE), between the RPE and neurosensory retina (sub-retinal) and within the neurosensory retina (intra-retinal). Haemorrhage is easy to identify clinically, whereas fluid leaking into the retinal layers needs careful stereoscopic examination to detect increased retinal thickening. If left untreated, CNV will eventually undergo fibrosis. The resulting macular scar is often referred to as "disciform" due to its characteristic disc-like shape. GA and macular scarring are the end-points of dry and wet AMD respectively; this occurs in about 3% of patients with AMD.[15] (Refer to Fig. 1 for a simplified diagrammatic cross-section of the macula and changes seen in AMD. Also refer to Fig 2 for the clinical findings seen in AMD.)

SYMPTOMS OF AMD

Early AMD may be asymptomatic and may only be picked up as an incidental finding on routine optometrist review. Dry AMD is associated with increased difficulty with central vision, especially with reading, and this tends to progress gradually. Wet AMD usually presents suddenly, with impaired central vision, distortion, metamorphopsia (change in size of objects) and a central scotoma (blind spot). Late AMD is associated with permanent impairment of central vision and may be sufficiently reduced to fall within the criteria of severe sight impairment (the legal term for "blindness"). However, it is important to note that patients with late AMD are not completely blind, since peripheral vision is usually preserved. This can provide useful navigational vision.

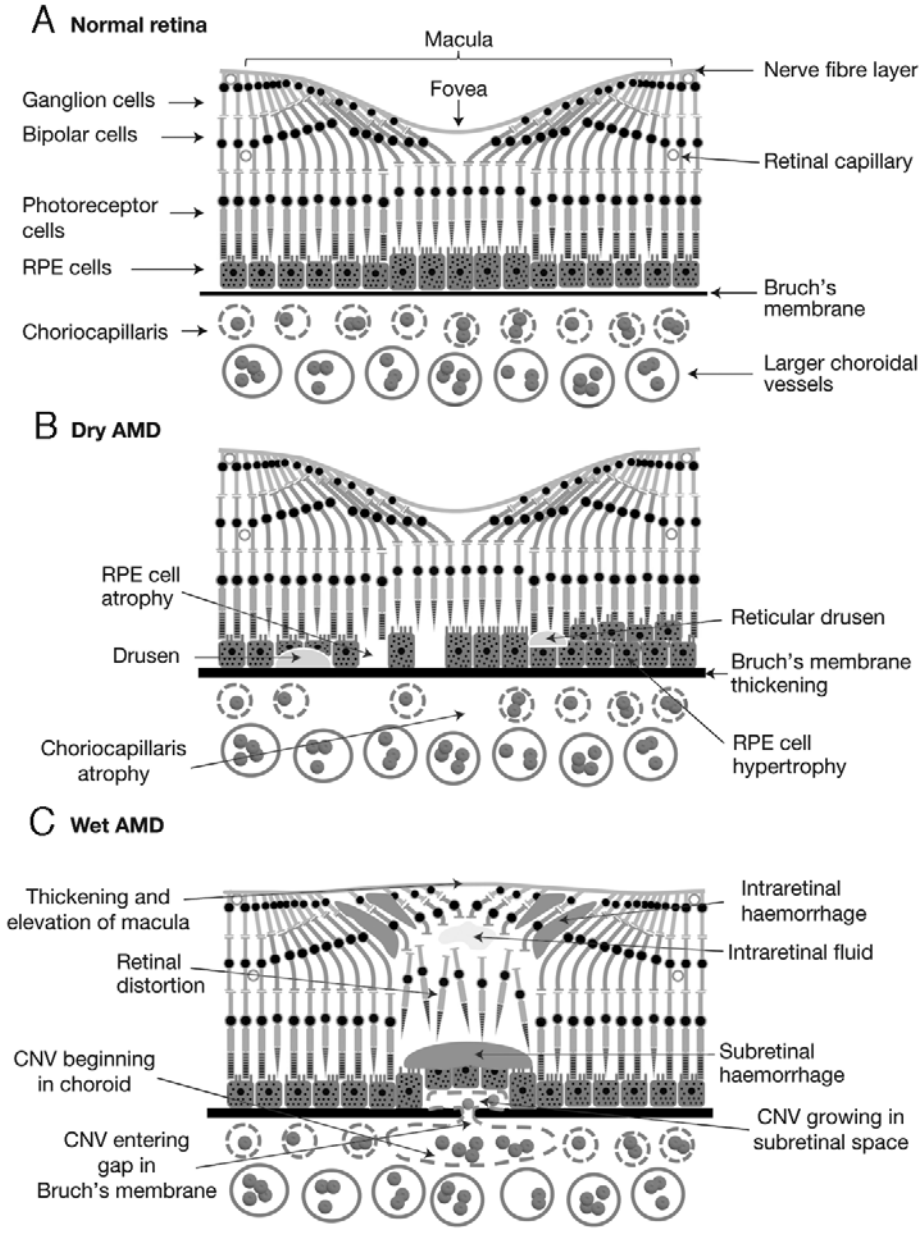

Figure 1. Changes seen in the retina in dry and wet AMD. A) Normal retina. B) Dry AMD. C) Wet AMD Reprinted with permission from: Khandhadia S, Lotery AJ. Expert Rev Mol Med 2010; 12, e34 (October 2010) ©2010 Cambridge University Press.

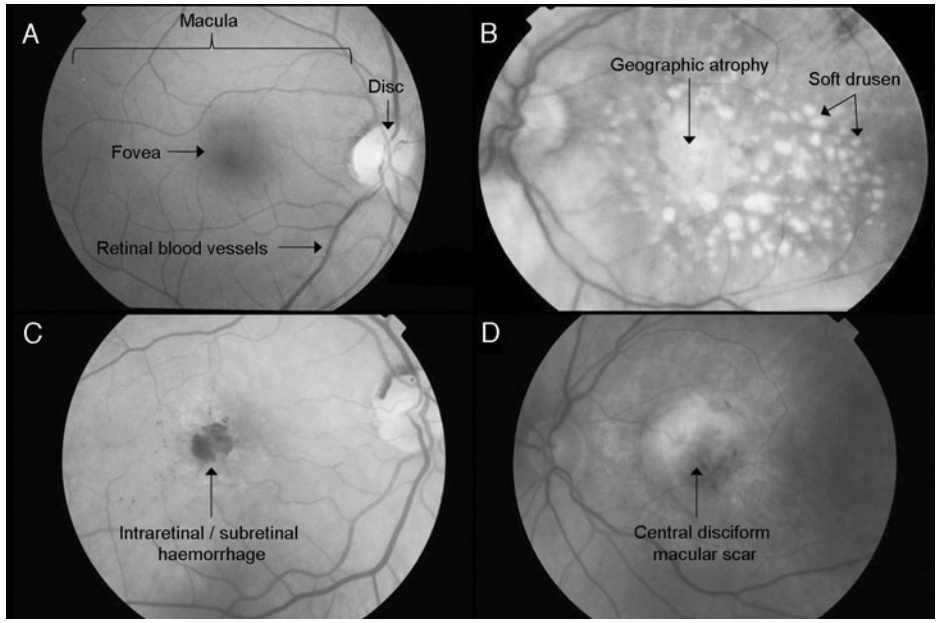

Figure 2. Retinal photographs depicting age-related macular degeneration (AMD). A) Normal. B) Dry AMD. C) Wet AMD. D) End-stage disciform macular scar. Reprinted with permission from: Khandhadia S, Lotery AJ. Expert Rev Mol Med 2010; 12, e34 (October 2010) ©2010 Cambridge University Press.

CLINICAL MANAGEMENT OF AMD

There is no definitive preventative measure for either dry or wet AMD. Furthermore, until recently no satisfactory treatment existed and patients inevitably irretrievably lost sight. In the last few years, the development of intravitreal injections of growth factor inhibitors has radically changed our management of wet AMD. This has meant the deteriorating sight for many patients can be stabilised, if not partially restored.

Management of Wet AMD

Early diagnosis and treatment of wet AMD is associated with a much better outcome. Fundus fluorescein angiogram (FFA) is performed to confirm the presence of CNV. This investigation involves injection of fluorescein (a fluorescent dye) intravenously, usually via the antecubital fossa. This dye passes through the systemic circulation and as it passes through the eye, photos are taken with a fundus camera equipped with barrier filters. Thus reflected light is excluded and a clear image of fluorescent light is obtained. Usually the dye passes through the retinal vessels without leaking. However, the presence of CNV is demonstrated by the presence of leakage from choroidal vessels at the macula. Currently the FFA is usually augmented by a non-invasive test called the Optical Coherence Tomogram (OCT). This uses low intensity laser to produce high resolution cross-sectional images of the macula. Evidence of CNV is inferred by observing the presence of intraretinal or subretinal fluid (Fig. 3).

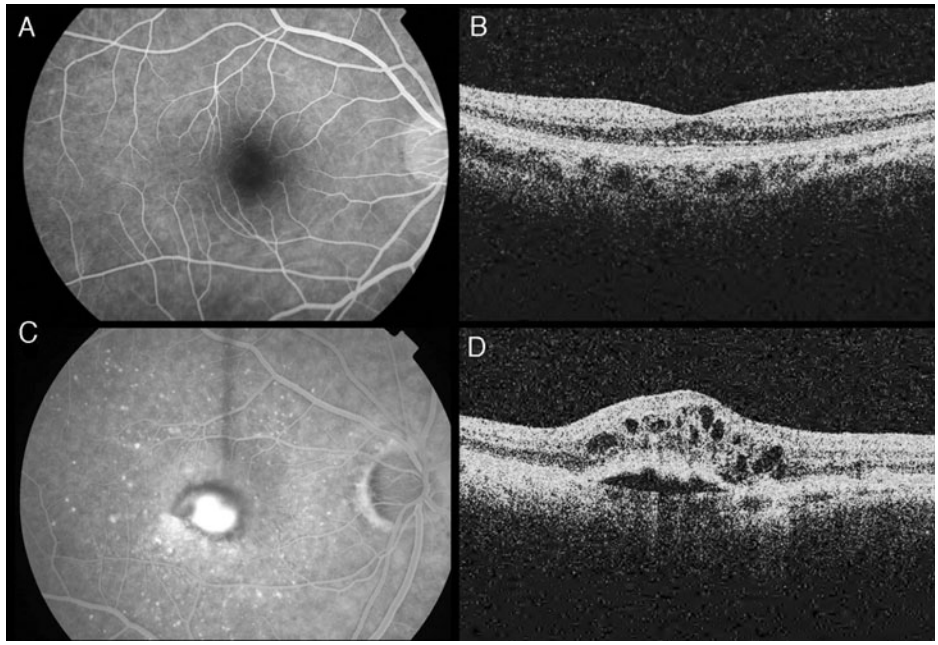

Figure 3. Fundus fluorescein angiograms (FFA) and Optical coherence tomograms (OCT) of wet AMD compared to normal. A) Normal FFA of macula. B) Normal OCT of macula. (see Fig. 1 for anatomy). C) FFA of eye with wet AMD. Note hyperfluorescent area at fovea, resulting from fluorescein dye leaking from choroidal neovascular membrane. D) OCT of eye with wet AMD. Note thickened retina, presence of intraretinal cysts full of fluid and sub-retinal pigment epithelial collection of fluid.

Once the presence of CNV is confirmed, current treatment consists of regular intravitreal injections of monoclonal antibodies which inhibit vascular endothelial growth factor (VEGF). Three injections are given as a preliminary course at four weekly intervals. Following this, patients are given further injections depending on the presence of active CNV, as demonstrated on ocular examination and OCT. Either ranibizumab (Lucentis®) or bevacizumab (Avastin®) are being used. Both work in similar ways, although comparative clinical trials are still ongoing. 0.05ml of the drug is injected 3.5-4 mm from the limbus (the junction between the cornea and sclera), perpendicular to the plane of the sclera. Serious adverse effects are rare (incidence <1%), but endophthalmitis (severe internal infection of the eye), internal haemorrhage, traumatic cataract and retinal detachment may occur. The number of injections required are variable, with some patients only requiring the minimum initial three injections, whereas others may require regular treatment for 2 years or more. All patients are usually monitored for a prolonged period of time even after stabilisation to ensure there is no recurrence of CNV.[16-18]

Patients may initially present with a large sub-macular haemorrhage, especially if on anticoagulant medication. In these cases, anti-VEGF intravitreal injections may not be effective. In addition, the presence of blood is toxic to the retinal cells and may lead to permanent extensive scarring. Removal of this blood is therefore beneficial. Intravitreal tissue plasminogen activator (TPA) and gas injections followed by head

posturing, can liquefy and displace any clotted blood away from the macula, although clinical improvement in this situation is rare.[19] A few patients develop vitreous haemorrhage due to bleeding breaking through the retina. If dense, this can be cleared with a vitrectomy, a surgical procedure involving removal of the vitreous.

Management of Dry AMD

As mentioned above, dry AMD is more insidious and is often picked up as a coincidental finding in the asymptomatic patient. At present there is no established way of preventing this condition (although there are several investigational products undergoing clinical trials, see below). Recently, clinical trials demonstrated oral anti-oxidant supplements may reduce the risk of progression. The Age-Related Eye Disease Study (AREDS) found patients with high risk dry AMD (presence of multiple SD and RPE changes) were less likely to exhibit AMD progression if taking high doses of oral vitamins A, C, E and zinc.[20] Other beneficial dietary modification includes increasing consumption of fresh fruit, vegetables and oily fish.[21-23]

Control of risk factors associated with cardiovascular disease may also be beneficial in reducing risk of AMD progression. These include reduction of smoking, serum cholesterol levels, systemic blood pressure and obesity.[24-28] In addition sunlight exposure may be implicated in AMD, especially since ultraviolet (UV) light is associated with RPE and retinal cell damage in vitro. However, this is contentious and there is no evidence that UV-blocking sunglasses are beneficial.[29-31] Lastly, when exposed to low-intensity laser, drusen can fade; however a clinical trial of more than a 1000 patients did not reveal any significant visual benefit.[32]

Unfortunately some patients with dry AMD can develop CNV, especially if high risk features are present.[14] Therefore patients are advised to report any new central visual symptoms, especially distortion. The Amsler grid, consisting of a grid of small squares, can be used regularly by the patient to detect new distortion and metamorphosia.

Management of End-Stage AMD

About 3% of all patients with AMD will reach “end stage” AMD and may fall within the legal criteria for partial or severe sight impairment. Impaired vision in AMD is associated with a reduced quality of life and these patients require socio-psychological support.[5] Magnifying aids, telescopes, closed circuit television (CCTV), talking books and domestic modifications may be beneficial. Some patients report benefit from intra-ocular placement of a magnifying intraocular lens.[5] This sits just behind the iris and can have the effect of increasing magnification as well as displacing images away from a damaged macula onto healthier peri-macular retinal tissue. Extensive retinal rotation surgery has also been attempted, but is associated with a high rate of complications.[33]

PROGNOSIS OF AMD

Wet AMD

More than 90% of patients with wet AMD treated with anti-VEGF intravitreal injections will retain stable vision, and out of these one-third will improve.[16,17] However,

wet AMD is often bilateral. The risk of a fellow eye being affected with a similar lesion is approximately 30% over a 6 year period.[34]

Dry AMD

Hard drusen is a common finding and is not associated with AMD progression. However soft drusen and RPE changes are associated with a 6.5% and 7.1% risk respectively of progression to late AMD over a 5 year period.[35] From the onset of GA, the mean duration to legal blindness is 5-9 years.[36,37] Furthermore, greater than 50% of fellow eyes are also afflicted with GA.[37]

PATHOLOGY OF AMD

AMD is a complex multi-factorial disease. It is likely that AMD develops clinically once an accumulation of risk factors exceeds disease threshold, based on an individual's repair and regenerative capabilities. Risk factors include advancing age, the effect of ongoing biological processes, genetic susceptibility and environmental/modifiable factors mentioned above (Fig. 4). Ageing is the most significant risk factor and is accompanied by alteration in gene expression and cellular functions. These include deteriorating mitochondrial function, increased protein degradation and apoptosis.[38,39] The main biological processes likely to contribute to the pathogenesis of AMD are described below.

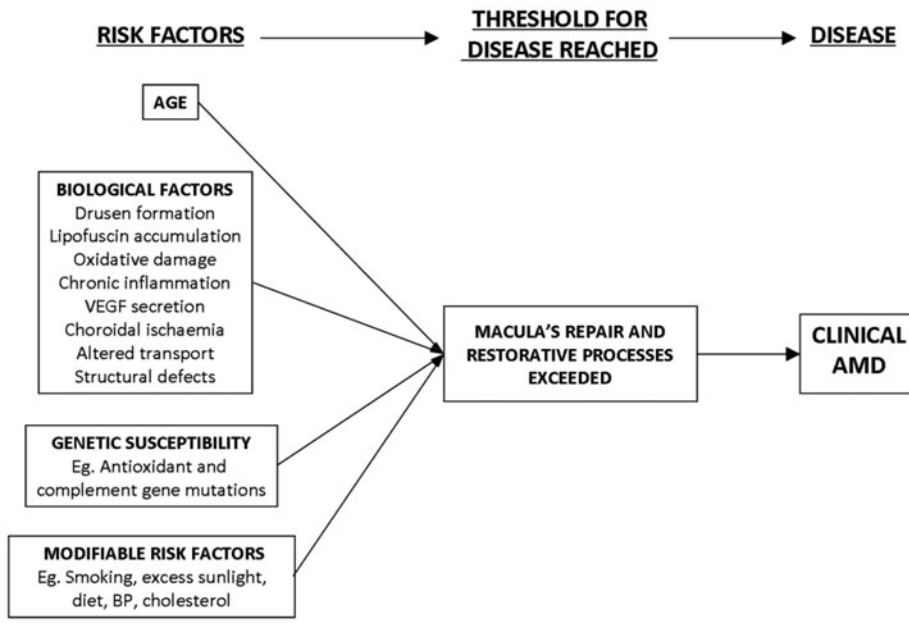

Figure 4. A model of AMD pathogenesis Modified from Swaroop et al 2009.[38]

Drusen Formation

At present it is unclear whether drusen contribute to the pathogenesis of AMD or if they are simply a manifestation of the underlying pathological processes. Drusen contain a range of lipids and proteins, the origins of which are as yet unknown.[11,12] Many of these are components of the inflammatory and complement system, suggesting drusen may play a key role as a focus of inflammation within the retina. Alternatively, drusen may accumulate as a result of ongoing inflammation elsewhere.

Lipofuscin Accumulation

A key function of RPE cells is phagocytosis of shed photoreceptor outer segments. This function diminishes with age.[40] As a result, undigested material accumulates within RPE and photoreceptor cells.[41,42] This material, called "lipofuscin", is composed of several toxic substances including retinoids, produced as by-products of the visual cycle, along with modified proteins and lipids.[43] *N*-retinylidene-*N*-retinylethanolamine (A2E), a fluorescent retinoid is a major component of lipofuscin and is associated with oxidative damage and complement activation.[44,45]

Inflammation

CNV development is associated with increased vascularisation, exudation and leukocyte chemotaxis; all these are features of the inflammatory response.[46] In particular, the complement system appears to play a central role. Mutations in genes coding for a range of complement proteins, factors and regulators have been associated with AMD. These include *Complement Factor H* (coding for a regulator of the alternate complement pathway), *CFHR1, CFHR3* (*CFH*-related genes), *Complement Factor B*, *Complement Factor I*, *Complement C3 and* the *SERPING1* gene (coding for C1 inhibitor, a regulator of the classic complement pathway).[47-56] Complement products have also been found in drusen and CNV membranes.[12,57]

Other inflammatory pathways may be implicated. Certain human leucocyte antigen (HLA) haplotypes have been associated with AMD.[58] Toll-like receptors (TLR) are involved in the innate immune system and *TLR* gene single nucleotide polymorphisms (SNPs) may be associated with AMD, although this is contentious.[59,60] Furthermore, chronic infections may provide a rationale for ongoing activation of inflammatory processes leading to macular damage. *Chlamydia pneumoniae*, for example, has been associated with increased AMD progression, although the link with AMD incidence is tentative.[61-63]

Oxidative Stress

The macula is particularly prone to oxidative stress especially generated by the UV wavelengths of incoming light. Furthermore, high metabolic demand at the macula produces further reactive oxygen species (ROS). This occurs from aerobic respiration within the electron cycle in mitochondria and from phagocytosis of outer segments by RPE cells. Antioxidant systems include the xanthophylls lutein and zeaxanthin, as well as antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase. Oxidative damage increases with age due to the body's declining repair and regenerative capabilities and build-up of toxic substances such as lipofuscin. This may be compounded by environmental factors such as smoking. SNPs in the *ARMS2* gene

are associated with AMD, and this may be via an increase oxidative stress, although this is speculative.[64-66] Finally, as mentioned above, antioxidant supplements in the form of vitamins A, C, E and zinc, decrease risk of AMD progression, as shown in the Age-Related Eye Disease Study (AREDS).[20] The dietary effects of lutein, zeaxanthin and omega-3 fatty acid are being investigated in an ongoing clinical trial (the "AREDS2" study).[67]

VEGF

Wet AMD is characterised by the development of CNV. Various growth factors may be involved, but the predominant stimulus appears to be VEGF-A, a cytokine produced by RPE cells which increases angiogenesis and vascular permeability.[68] Indeed as discussed above, monoclonal antibody fragments, blocking the action of VEGF-A at their receptors, are the present mainstay of treatment for wet AMD.[16,17] As yet it is unclear how VEGF production is stimulated, but it is likely to be a result of inflammatory activity.

Choroidal Ischaemia

The main watershed area of the posterior choroid lies between the fovea and optic disc and therefore the macula is vulnerable to ischaemia.[69] Choroidal blood flow reduces with age, presumably as a result of atherosclerosis or atrophy.[70] Choroidal ischaemia may be one factor contributing to the risk of AMD. Patients with lower choroidal blood flow are more likely to develop CNV.[71]

Alteration in Transport

With age, BM increases in thickness due to collagen remodelling and lipid deposition. This leads to decreased hydraulic conductivity impairing transport of solutes between the choroid and RPE.[72] Reduced RPE function can result, especially since RPE cells may already be compromised due to lipofuscin accumulation.

Structural Defects

Breaks in BM are a key factor in CNV development. The evidence for this is compelling. CNV growth is a risk of therapeutic thermal laser applied on the retina, due to BM disruption. Indeed, animal models of CNV are often created experimentally using retinal laser.[73] Breaks in BM are also features of non-AMD conditions associated with CNV growth, including high myopia, angioid streaks (seen, for example, in pseudoxanthoma elasticum) and eye trauma.[74] As mentioned above, the central component of BM is elastin. Interestingly, genetic variations in the fibulin-5 gene, which controls elastogenesis, have been associated with AMD.[75,76] This may lead to weakening of BM, thus increasing susceptibility to CNV.

The exact mechanism for the breakdown of BM in CNV formation is yet unknown. Present studies suggest that with age, BM may become increasingly fragile due to lipid-build-up, calcification and fragmentation.[77,78] Increased degradation of BM may occur from increased matrix metalloproteinase (MMP) activity, reduced activity of tissue inhibitors of MMP (TIMP) and from increased cytokine release from macrophage build-up.[79-81] Of note, SNPs in the *TIMP-3* gene have been associated with AMD.[82] In contradiction, decreased MMP activity is observed in dry AMD and may explain the characteristic accumulation

in extracellular matrix and BM thickening.[83] However CNV formation may be associated with a more localised increase in MMP activity to initiate BM rupture.

AMD AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a common heterogeneous neurodegenerative disease strongly associated with age. Several population based studies suggest intriguing associations between AMD and AD.

The Blue Mountains Eye Study by Pham et al (n = 3509, age 49-97) used a Mini- Mental State Examination, modified to exclude the 5 items needing vision. They found a multivariate adjusted association between late AMD and cognitive impairment with an odds ratio (OR) of 2.2 (95% Confidence Interval (C.I.) 1.0-5.0). They concluded that there was a significant cross-sectional association between late AMD and cognitive impairment, independent of visual impairment in this population.[84] The Atherosclerosis Risk in Communities Study by Wong et al (n = 9286, age 51-70) showed an OR of 1.6 (95%C.I. 1.1-2.2) for patients with severe cognitive impairment having early AMD. The grading of cognition was based on Word Fluency Test scores. However, two other cognitive test scores used by the study did not show an association between severe cognitive impairment and early AMD. The authors suggested a weak association existed between AMD and AD.[85] The population based Rotterdam Study by Klaver et al (n = 1438, age 75+) found patients with advanced AMD at baseline had a controlled relative risk (RR) of 1.5 (95%C.I.0.6-3.5) of incident AD. They concluded some overlap of pathogenesis between AD and AMD.[86]

Amyloid and Activation of the Immune System

A hallmark of AD is the deposition and aggregation of misfolded protein as amyloid fibrils or plaques, including amyloid-associated protein tau, beta-amyloid (beta-A) and amyloid precursor protein (APP).[87] Interestingly, the drusen in AMD eyes also contain beta-A fibrils and prefibrillar amyloid oligomers, with none found in age-matched control eyes without drusen.[88] Where GA is present, the distribution of beta-A is at the periphery of the lesions.[88-90] Deposition of beta-A is thought to be toxic to the local RPE and photoreceptors, causing degeneration and may induce damaging levels of inflammation in them. Beta-A increases RPE monocyte chemoattractant protein-1 (MCP-1) and thereby recruits macrophages and microglia.[91] Beta-A also increases both macrophage and microglia IL-1 beta and TNF-alpha production. These cytokines result in significant RPE cell-mediated up regulation of factor B, the main alternative complement pathway activator.[91]

Proteins found in drusen also suggest an association with AD. These include vitronectin (known to produce amyloid fibrils when misfolded), the complement membrane attack complex (C5b-9), serum APP and apolipoprotein E (ApoE)..[92,93] Primary complement cascade activation at sites of beta-A deposition and the presence of C5b-9 suggests that chronic inflammation is a mechanism of neuro-degeneration in both AMD and AD.[94]

Apolipoprotein

Late onset AD is a multi-factorial disease. Its strongest genetic linkage is with the *ApoE* gene. Apolipoprotein is a major protein of the central nervous system and regulates cholesterol and lipid transport. It is ubiquitously found in AMD drusen.

The *ApoE* gene has 3 major isoforms, namely ApoE 2, 3 and 4, coded by the alleles epsilon 2, 3 and 4 respectively. Most common is the ApoE epsilon 3 allele, which is not linked to AD nor to AMD. ApoE epsilon 4 is associated with an increased risk of AD but appears protective for AMD.[95,96] In addition, ApoE epsilon 2 is associated with an increased risk of AMD.[96] Further research is needed to investigate the mechanism of the allelic associations of ApoE with both AMD and AD.

ONGOING RESEARCH AND ANTICIPATED DEVELOPMENTS

The breakthrough of anti-VEGF therapy has improved the prognosis of many patients with AMD. Furthermore this appears to have stimulated research interest in AMD as is evident in the recent proliferation of clinical trials. Tables 1 and 2 present a range of the ongoing/recently completed trials. Of note is the wide spectrum of mechanisms of action, including targeting the immune system, reducing growth factor activity, reducing oxidative stress, reducing lipofuscin deposition, neuroprotection, plasmapheresis, direct radiation therapy and replacing damaged RPE tissue. Methods of administration are also diverse, and include topical eye drops, subcutaneous/intravitreal/intravenous injections, oral medication and laser treatment. A likely development is the use of combination and adjuvant therapy with anti-VEGF agents, with the intention of reducing the frequency of injections required.

Genetics is likely to play an increasing role in the management of human disease. Genetic analysis may predict response to specific treatments. This implies future treatment could be tailor-made to an individual's genotype ("personalised medicine"). Gene therapy is another intriguing prospect. Patients could be screened for AMD-associated genes and faulty genes replaced with normal copies to reduce overall AMD risk. Alternatively gene therapy could enable sustained drug/monoclonal antibody delivery. Presently clinical trials are underway with the aim of delivering gene therapy to patients with Leber's Congenital Amaurosis, a rare retinal dystrophy.[97] As experience with ocular gene therapy increases, the hope is that more common and complex diseases such as AMD may benefit.

One of the exciting results of the AMD/AD copathology theory is the investigation of the use of putative neurodegenerative disease therapies in AMD. For example, systemic anti-beta-A immunotherapy of an AMD mouse model demonstrated attenuation of pathology and improvement in electroretinogram readings.[98] Reduced drusen area has also been noted in a murine AMD model treated with Copaxone, a T-cell-based vaccination undergoing clinical trials in AMD (Table 1).[99] Another area under investigation is the use of direct optical imaging of the retinal beta-A plaques to evaluate AD non-invasively. Potentially AD could then be diagnosed at an early sub-clinical phase, creating an opportunity for pre symptomatic treatment. Such imaging could also be used as a biomarker to evaluate response in clinical trials.[100] This could significantly reduce the cost of such clinical trials. A recent animal study by Koronyo-Hamaoui et al administered a safe beta-A-labeling systemic fluorochrome to an AD mouse model. It showed that retinal disease was detectable earlier than brain disease and was undetectable in controls. Beta-A-labeling progressed with the disease and was significantly reduced on administration of an immune-based therapy effective in reducing brain disease.[101]

As greater understanding develops of both the pathogenesis of AMD and systemic neurodegenerative diseases, further common aetiological factors may be discovered. This may lead to novel treatments for either of these conditions. The need for interdisciplinary research is therefore compelling.

Table 1. Clinical trial of investigational products for dry AMD

Therapeutic Agent	Mechanism of Action	Details	Route	Phase	Sponsor	CT Identifier
Sirolimus	Anti-inflammatory	mTOR (mammalian target of rapamycin) inhibitor	Subconjunctival injection	1/2	NEI	NCT00766649
Glatiramer (Copaxone)	Anti-inflammatory	T-cell immono-modulation	Subcutaneous injection	1	The New York Eye and Ear Infirmary	NCT00541333
Fluocinolone Acetonide Intravitreal Insert	Anti-inflammatory	Steroid	Intravitreal insertion of implant	2	Alimera Sciences	NCT00695318
Eculizumab	Complement inhibition	Binds and inhibits cleavage of C5	Intravenous	2	University of Miami/Alexion Pharmaceuticals	NCT00935883
ARC1905	Complement inhibition	Anti-C5 Aptamer—C5 inhibitor	Intravitreal	1	Ophthotech Corporation	NCT00950638 NCT00709527
Rheopheresis	Reduction of immune-related proteins	Double filtration plasmapheresis of high molecular weight proteins	External removal/ filtration with subsequent return of plasma	4	Apheresis Research Institute	NCT00751361
Fenretinide	Reduction of lipofuscin accumulation	Retinoic acid analogue—reduces accumulation of A2E by reducing systemic levels of retinol (vitamin A), a precursor of A2E	Oral	2	Sirion Therapeutics	NCT00429936
ACU-4429	Reduction of lipofuscin accumulation	"Visual cycle modulator" Inhibition of RPE65, a key enzyme involved in visual cycle in rods, reducing A2E build-up	Oral	2	Acucela/Otsuka Pharmaceutical	NCT01002950

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Table 1. Continued

Therapeutic Agent	Mechanism of Action	Details	Route	Phase	Sponsor	CT Identifier
Retinal Transplantation	Replacement of lost tissue	Transplantation of human foetal neural retinal tissue and RPE	Subretinal surgical procedure	2	National Neurovision Research Institute	NCT00346060
Encapsulated Human NTC-201 Cell Implant	Neuro-protection	A small capsule containing RPE cells genetically engineered to release Ciliary Neurotrophic Factor (CNTF) through the capsule membrane	Intravitreal insertion	2	Neurotech Pharmaceuticals	NCT00447954
Brimonidine	Neuro-protection	Slow-releasing brimonidine implant	Intravitreal injection of implant	2	Allergan	NCT00658619
OT551	Anti-oxidant	Anti-oxidant eye drops	Topical eye drops	2	NEI	NCT00306488 NCT00485394
Lutein/ zeaxanthin/ Omega-3 long-chain polyunsaturated fatty acids	Anti-oxidant	Increases antioxidant capacity	Oral	3	NEI	NCT00345176
RNG65	Reduction of amyloid accumulation	Anti-amyloid beta antibody	Intravenous	1	Pfizer	NCT00877032
MC-1101	Increase of choroidal blood flow	Vasodilator—increases choroidal blood flow	Topical eye drops		MacuCLEAR	NCT01013376

CT = ClinicalTrials.gov
NEI = National Eye Institute, USA
siRNA = Short interfering ribo-nuclease acid
Information obtained from www.clinicaltrials.org on 25th September 2010

Table 2. Clinical trial of investigational products for wet AMD

Therapeutic Agent	Mechanism of Action	Details	Route	Phase	Sponsor	CT Identifier
Everolimus	Anti-inflammatory	mTOR inhibitor	Oral	2	Novartis	NCT00857259
Infliximab	Anti-inflammatory	Monoclonal antibody against TNF-alpha	Intravenous infusion	2	NEI	NCT00304954
Sirolimus	Anti-inflammatory	mTOR inhibitor	Oral	2	NEI	NCT00304954
Daclizumab	Anti-inflammatory	Monoclonal antibody vs interleukin-2, therefore limiting T-cell signalling. Binds to CD25, the alpha chain of the IL2 receptor	Intravenous infusion	2	NEI	NCT00304954
Volociximab	Anti-inflammatory	Alpha 5 Beta 1 Integrin Antagonist	Intravitreal injection	1	Ophthotech Corporation	NCT00782093
POT-4	Complement inhibitor	C3 inhibitor A derivative of the cyclic peptide Compstatin, which binds and inhibits C3.	Intravitreal injection	1	Potentia Pharmaceuticals	NCT00473928
AAV2-sFLT01	Anti-VEGF	Gene delivery of sFLT01, a novel chimeric VEGF-binding molecule, using adeno-associated virus (AAV) serotype 2	Intravitreal injection	1	Genzyme	NCT01024998
VEGF Trap	Anti-VEGF	A soluble VEGF receptor fusion protein which binds all forms of VEGF-A and placental growth factor (PGF).	Intravitreal injection	3	Bayer	NCT00637377
Bevasiranib	Anti-VEGF	siRNA of VEGF	Intravitreal injection	2	Opko Health	NCT00259753
PTK787	Anti-VEGF	VEGF receptor tyrosine kinase inhibitor	Oral	1,2	Pfizer	NCT00138632
AL-39324	Anti-VEGF	VEGF receptor tyrosine kinase inhibitor	Intravitreal injection	2	Alcon Research	NCT00992563
MP0112	Anti-VEGF	DARPin (Designed ankyrin repeat proteins)—based VEGF-A antagonist	Intravitreal injection	1	Molecular Partners AG	NCT01086761
Sirna-027	Anti-VEGF	siRNA vs VEGF receptor 1	Intravitreal injection	1,2	Allergan/Sirna Therapeutics Inc.	NCT00363714

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Table 2. Continued

Therapeutic Agent	Mechanism of Action	Details	Route	Phase	Sponsor	CT Identifier
Vaccination by VEGFR1 and VEGFR2 – derived peptide	Anti-VEGF	Vaccination induces cytotoxic T-lymphocytes (CTLs) with potent cytotoxicity against cells expressing VEGFR1 and 2	Subcutaneous injection	1	Osaka University/ Human Genome Centre, Tokyo	NCT00791570
AdGV-PEDF.11D	Increases level of Pigment Epithelial Derived Growth Factor (PEDF)	E1, E3 and E4 deleted adenovirus vector containing PEDF gene	Intravitreal injection	1	GenVec	NCT00109499
E10030	Anti-platelet-derived growth factor (PDGF)	Anti-PDGF Pegylated Aptamer	Intravitreal injection	1,2	Ophthotech Corporation	NCT01089517 NCT00569140
iSONEP (Sonepcizumab LT1009)	Multiple growth factor inhibitor	A monoclonal antibody, which blocks action of sphingosine 1-phosphate (S1P), reducing levels of a range of growth and survival factors for multiple cells	Intravitreal	1	Lpath	NCT00767949
Pazopanib	Multiple growth factor inhibitor	Tyrosine kinase inhibitor of multiple receptors (including VEGF and platelet-derived growth factor receptors.)	Topical/oral	1,2	GlaxoSmith-Kline	NCT01134055 NCT01154062
ATG003 (mecamylamine)	Reduction of angiogenesis	Nicotinic acetylcholine receptor inhibitor	Topical eye drops		CoMentis	NCT00607750
CGC-11047	Reduction of cell proliferation	A polyamine analogue. Targets hyper-proliferating cells and halts cell growth/induces apoptosis	Subconjunctival injection	1	Cellgate	NCT00446654
Palomid 529	Reduction of cell proliferation	Dual TORC1/2 inhibitor of the PI3K/Akt/mTOR pathway. Suppresses angiogenesis and cell proliferation.	Intravitreal/ subconjunctival injection	1	Paloma Pharmaceuticals	NCT01033721

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Table 2. Continued

Therapeutic Agent	Mechanism of Action	Details	Route	Phase	Sponsor	CT Identifier
JSM6427	Reduction of cell adhesion/migration	Integrin α5β1-antagonist (this integrin normally mediates cell adhesion and migration)	Intravitreal injection	1	Jerini Ophthalmic	NCT00536016
PF-04523655	Reduces photoreceptor apoptosis	siRNA against RTP801	Intravitreal injection	2	Quark Pharmaceuticals/Pfizer	NCT00713518
Strontium90 Beta radiation	Radiation	Intravitreal radiation delivery by Epi-Rad system	Intravitreal delivery	3	NeoVista	NCT00454389
X-ray radiation	Radiation	Noninvasive robotically-guided delivery of radiation via 3 beams	External, via contact lens	1	Oraya Therapeutics	NCT01016873
WST11 (Stakel®)	Activation of photosensitiser	Becomes active on exposure to infrared laser light, causing occlusion of CNV	Intravenous, with external laser activation (photodynamic therapy)	2	Steba Biotech S.A.	NCT01021956

CT = ClinicalTrials.gov
NEI = National Eye Institute, USA
siRNA = Short interfering ribo-nuclease acid
Information obtained from www.clinicaltrials.org on 25th September 2010

CONCLUSION

AMD is still a distressing disease for many of the elderly population. A multi-faceted approach is required in the future to cumulatively reduce both intrinsic and extrinsic risk factors, to prevent onset of this blinding condition. With the current interest in research and a wealth of clinical trials, the future is promising. The intriguing overlap between AMD and AD suggests that therapies targeted at treating AD may also result in treatment for AMD and vice versa. Such developments are urgently needed for this devastating and prevalent disease.

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