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Review

Age-related macular degeneration

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INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative macular disorder most often clinically apparent after 50 years of age, characterized by certain fundal features and after exclusion of other disorders e.g. high myopia etc. Drusen (deposits of extracellular material lying between retinal pigment epithelium (RPE) and the inner collagenous zone of Bruch's membrane – *Figure 1*), hyperpigmentation and hypopigmentation of the RPE, without visibility of choroidal blood vessels are regarded as features of early AMD. Although drusen are the hallmark of AMD one or more hard drusen were found in at least 95% of the aged populations assessed in the larger Caucasian studies with small hard drusen being the most common in all age groups. The two stages of late AMD include exudative/neovascular (wet) and non-exudative/geographic atrophy, GA (dry) with an 80:20 ratio being observed in the majority of AMD prevalence studies (*Figures 2* and *3* respectively). Exudative AMD, which is characterised by choroidal neovascularization and

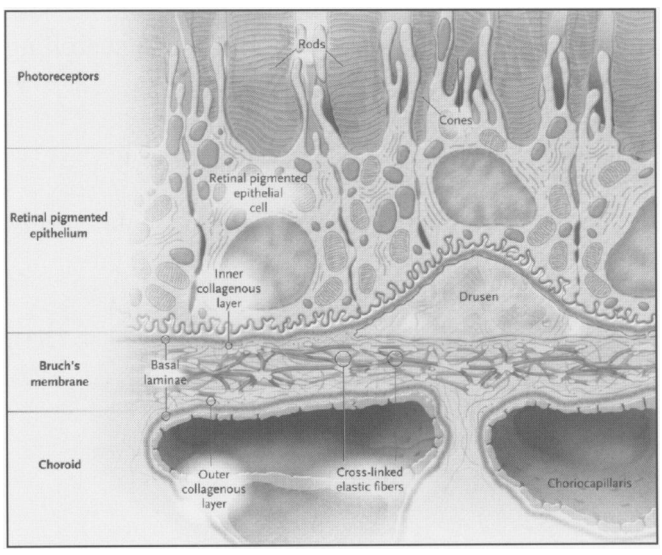

Fig 1. Interface between retinal pigment epithelium and Bruch's membrane demonstrating drusen location.

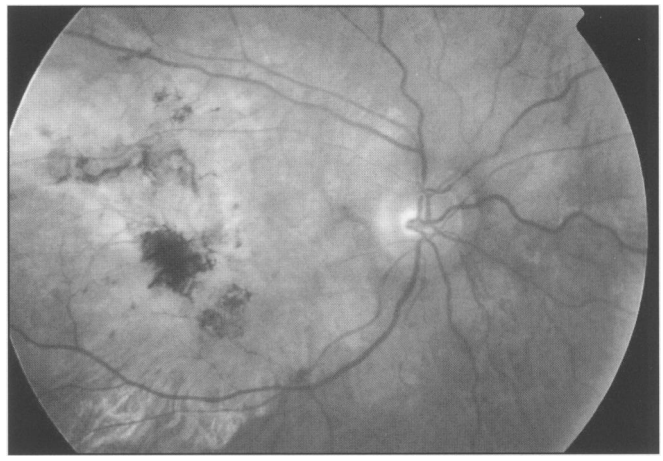

Fig 2. Retinal stereoscopic fundal photograph illustrating the features of wet AMD.

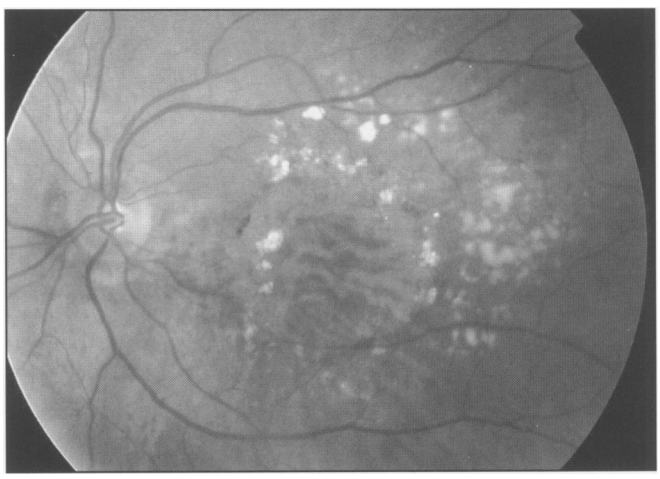

Fig 3. Retinal stereoscopic fundal photograph illustrating the features of dry AMD.

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fibrous scarring of the macula, is responsible for 80% of the AMD-related blindness.

AMD is the leading (54.4%) cause of blindness in Caucasians, compared to only 4.4% and 14.3% of cases in black and Hispanic persons, respectively.[1]

The prevalence (1.6%[2]) and incidence of late AMD (1.1% over five years[3]), in association with the increasing longevity of populations, is impacting significantly on patients, their carers and National Health Service. AMD affects 420,000 people in the United Kingdom with an estimated 214,000 people having registrable visual impairment secondary to AMD.[4] Apart from the more obvious disabling effects of AMD associated with loss of central vision, a frequently overlooked effect is depression (33% of affected individuals), which becomes particularly high on involvement of the second eye.[5]

Age is the most consistent and significant association with AMD and related lesions and is widely supported in population-based AMD prevalence and epidemiology studies, irrespective of ethnic/racial background.[2] This increase is less significant for non-white groups. A steep rise in prevalence rates of early and late AMD occur in the ≥70years.

Although numerous studies have failed to detect a significant gender difference in the prevalence of early or late AMD, females appear to have a slightly increased risk of developing late AMD.[2]

AMD is a multifactorial disease involving the interaction of genetic and environmental factors. Difficulties in classification of AMD phenotype continues to be problematic with a negative impact on unravelling the complex genetic aetiology.

HISTORICAL BACKGROUND

Hutchinson and Tay in 1875 were probably the first ophthalmologists in the English literature to describe what is presently called AMD, when they described the symmetrical fundal changes in senile patients. It was not until 1885 that AMD was recognized as a discrete clinical entity by Otto Haab and called "senile macular degeneration (SMD)". This term has been extensively used through the generations by ophthalmologists to describe the very common macular changes observed in the elderly. Various names have been used over the years for SMD,[6] with age-related maculopathy (ARM) and AMD being the interchangeable terms used today.

AMD has been difficult to classify and until recently a lack of standard classification has made it difficult to compare and review progress in the research field. The publication of an international classification and grading system for ARM and AMD in 1995,[7] based on the morphological changes observed on stereoscopic (30° or 35°) colour fundus transparencies in individuals ≥50 years has facilitated this to a certain extent. This system is based on the Wisconsin age related maculopathy grading system with the macula area being defined by a standard grid facilitating the locations and measurements of the previously mentioned AMD features[8] (refer *Figure 4*). Although this was the first standardised

TABLE I

Classification of mutually exclusive stages of AMD taken from van Leeuwen et al, 2003[9]

Stage	*Definition*
0a	No signs of AMD
0b	Hard drusen (< 63μm) only
1a	Soft distinct drusen (≥ 63μm) only
1b	Pigmentary abnormalities only, no soft drusen (≥ 63μm)
2a	Soft indistinct drusen (≥ 125μm) or reticular drusen only
2b	Soft distinct drusen (≥ 63μm) with pigmentary abnormalities
3	Soft indistinct (≥ 125μm) or reticular drusen with pigmentary abnormalities
4	Atrophic or neovascular AMD

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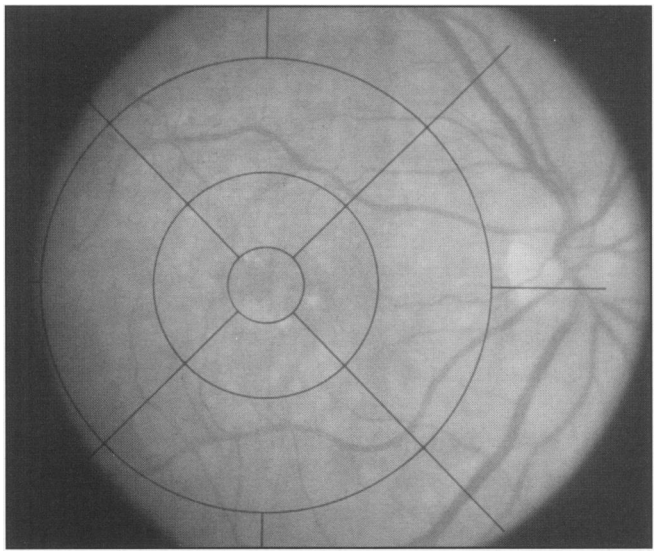

Fig 4. Standard retinal fundus grid for classification and grading of AMD.

classification and grading system for AMD, a more practical AMD phenotyping system with "affected" AMD status being designated as stage ≥ 2a i.e. soft indistinct drusen (≥ 125μm) or reticular drusen was developed recently (*Table 1*).[9]

GENETICS

Evidence of the genetic basis to AMD is well established as a result of many different types of studies over the preceding twenty years.

Case reports of concordance for AMD phenotypes within monozygotic twin pairs were perhaps the earliest indication of a genetic basis for AMD.[10]

Numerous twin studies have significantly supported the genetic component of AMD[11] with late AMD having a higher heritability (quantitative measure of innate genetic predisposition to a disease) in addition to a moderate to large unique environmental component in the largest twin study involving 840 elderly male twins.[12]

Familial aggregation studies have also demonstrated the genetic component to AMD with a lifetime risk ratio of 4.2 for late AMD in relatives.[13]

Loci on chromosomes 1q31 and 10q26 have been consistently identified in AMD genome wide scans and supports the hypothesis of genes within these loci contributing to AMD.[14-15]

The first disease locus for non-exudative AMD, (gene symbol ARMD1),[16] on chromosome 1q25-31 was discovered in a multigenerational pedigree in which ten members were affected with non-exudative /dry AMD. Subsequently a Gln5345Arg mutation in the gene Hemicentin-1 was shown to segregate with this AMD phenotype.[17] Hemicentin-1 (also known as Fibulin 6/FBNL6), a member of the fibulin protein family, encodes for extracellular matrix proteins with a potential role in drusen formation and therefore AMD pathogenesis. However, mutations in Hemicentin-1 have not been found to be associated with AMD in three other separate studies.[15,18-19] Although support for the ARMD1 locus, is substantial in the genome wide scans, it seems likely that another gene other than Hemicentin-1 may be responsible.

The first putative disease locus for exudative AMD was detected between 17-19.35 megabases (Mb) on chromosome 16p12-13 using familial linkage in a large Northern Irish pedigree.[20] The familial mutation remains undetected. Association studies in a case-control study of sporadic AMD cases from Northern Ireland added slight support to this identified linkage region.[20]

Three other genes, Fibulin 5, APOE and Complement Factor H have been reported to be associated with AMD phenotypes.

Missense mutations in the Fibulin 5 gene were found in 1.7% of 402 patients with AMD in a case-control study.[21] Further studies analyzing fibulin 5 are required in order to verify the significance of this. Fibulin 5 is a candidate gene for AMD due to its role in extracellular matrix proteins and in particular the polymerization of elastin which is a major component of Bruch's membrane and involved in AMD pathogenesis.

There is substantial evidence to show that the APOE ε4 allele has a protective effect with AMD, while APOE ε2 allele is associated with a modest increase in risk of exudative AMD.[22] APOE is a functional candidate gene due to its role in lipid transport and distribution, involvement in drusen formation and high expression levels in the retina. The opposite effect of APOE in AMD to its role in coronary heart disease remains unexplained at present.

Recently a 2.45-5.57 increased risk for AMD with a Tyr402His polymorphism in the gene encoding Complement Factor H (CFH) has been reported by independent research groups, although the existence of other coding or splice site variants within CFH that may modulate the AMD risk could not be excluded .[23-26] CFH is involved in the complement pathway and in particular impacts on C3 convertase enzyme. Evidence for deposition of components of

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this complement pathway in drusen and choroid of eyes with AMD is extensive.[27,60-61]

Despite the phenotypic similarities between the hereditary monogenic macular dystrophies and AMD e.g. Best disease, with the exception of ABCA4, none of the causative genes was found to be responsible for a significant percentage of AMD cases. The ABCA4 screening consortium[28] assigned a threefold and fivefold risk of AMD in D2177N and G1961E ABCA4 carriers respectively, however replication of these findings have not been possible, leading to much controversy surrounding its potential role in AMD. The observation that some inherited macular dystrophies may have widespread retinal dysfunction, and the possibility of several genes acting synergistically or being ubiquitous, are among the suggestions by Michaelides *et al*, 2003[29] for the non-significant role of these genes in the genetic predisposition to AMD.

The above studies have clearly established that genetic predisposition plays a major role in the aetiology of AMD. Despite this, genetics of AMD are regarded as complex with the possible involvement of one or more genes enhancing an individual's susceptibility for developing the condition. The possibility that there may be other genes that modify the age of onset or phenotypic features of AMD has also to be considered. These genes may act independently or in conjunction with environmental factors e.g. smoking.

Genetic studies of AMD involve consideration of the clinical heterogeneity associated with AMD and correlation with genetic heterogeneity i.e. dry and wet AMD may have different genetic aetiology and specific phenotypes within AMD pedigrees may run true within families.[30] The recent surge in genetic studies from 2000 with nine AMD genome-wide screens published within the last eighteen months may be attributed to the growing awareness of genetics in a number of other complex late-onset medical disorders e.g. Alzheimer's disease. Unravelling the genetics of AMD will facilitate the possible expansion of the knowledge of the pathophysiology of AMD, identification of at risk individuals prior to the onset of clinical findings, and the development of preventive treatments and therapeutic strategies.

NON-GENETIC RISK FACTORS

In addition to age, gender and race/ethnicity, there are several other risk factors which have been implicated in AMD.

Evidence for a significant association between smoking and late AMD is extensively provided in numerous types of studies.[31-32] Current smokers had the highest risk of AMD compared to ex-smokers or non-smokers across all studies. This was particularly highlighted in the meta-analysis of three prospective studies,[32] the association with current smoking being stronger with exudative AMD (OR=4.55, 95% CI, 2.74-7.54) than with non-exudative AMD (OR=2.56, 95%CI, 1.26-5.2). In addition, current smokers had about a 2.5 fold increased risk of developing AMD[33-34] and were more likely to show progression of early AMD (RR=1.34, 95% CI, 0.94-1.91), to develop pigmentary abnormalities (RR=1.32, 95% CI, 0.89-1.98) and large soft drusen (≥250μm) (RR=2.19, 95% CI, 1.44-3.32) than ex smokers.[35] A significantly earlier age of developing AMD (67 years) in current smokers than in ex (73years) or never smokers (77years) was detected in the Blue Mountain Eye Study population.[36] In addition a trend for increased risk of AMD with increasing number of smoking pack years, with the risk of AMD remaining increased until at least 20 years after smoking cessation was observed .[34] The causal relationship of smoking with AMD can be explained by its recognised ability to increase oxidative stress either directly or indirectly with lowering dietary intake of vitamin C and ß-carotene, and the associated lower macular pigment density.

Population-based incidence studies have provided useful predictors of progression to AMD which include soft distinct/indistinct (≥ 125-250μm) and reticular drusen and hyperpigmentation.[9,37-38] Additional AMD risk factors highlighted by these studies included ≥10% macular area involved by drusen, ≥ 5-10 drusen and depigmentation. Two of these studies, demonstrated an increased risk between 3-11 fold of large areas of small hard drusen developing into large (≥125μm) drusen.[37-38]

A J-shaped relationship between body mass index (BMI) and AMD development and rate of progression has been illustrated with the leanest (BMI< 22) and particularly the obese (BMI>30) being at significantly increased risk.[31]

Although evidence is conflicting, there may be an association with hyperopia with AMD, albeit minor, which would alert ophthalmologists to this slightly increased risk group of individuals. There is no hypothesis for this association at present.

It would appear that cataract, particularly the nuclear type, is associated with a moderate risk of early AMD.[31] Although cataract surgery can exacerbate

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AMD[39] removal of the cataract improves quality of life and visual function improvement even in end-stage disease.[40] The association of AMD in eyes that have undergone cataract surgery may be due to better detection secondary to easier visualisation of the fundus, the increased risk of photic retinal damage from the lights of operating microscopes[41] and lastly the possible inflammatory changes post cataract surgery that may predispose to the increased exudative AMD risk.[39]

Assessment of the relationship of light exposure and AMD has been fraught with many difficulties. However sunlight exposure appears to increase AMD risk, but ultimately this may be through the increased incidence and progression of early AMD and related lesions i.e. soft indistinct drusen and retinal pigment. Advice about protective gear and length of sunlight exposure may help reduce this risk.

A significant number of studies have demonstrated a weak association between hypertension and AMD which may be attributed to the various methods and definitions used.[31-32] Overwhelming evidence does not support an association with cardiovascular disease and AMD prevalence [32,43] and development and progression despite some common risk factors.[44]

Dietary fat intake may influence the risk of developing AMD by predisposing to atherosclerosis and altering the composition of Bruch's membrane rendering it less permeable to diffusion of nutrients and waste products to and from the RPE.[45-46] In addition there is a protective association (OR= 0.52, 95% CI, 0.22-1.24) between higher fish consumption and AMD.[46] There is sufficient evidence therefore to recommend dietary alterations in those individuals with mild to moderate signs of AMD to reduce progression with the added benefit to the cardiovascular system.

The effect of statins in AMD remains unresolved-with some studies reporting an inverse relationship between statins and AMD i.e. protective with individuals taking statins having a 1/11 risk of AMD[47] but unsupported in other studies.[48]

There are conflicting reports of the effect and type of alcohol consumption on the development of AMD.[49-50] The different relationships that have been identified between AMD and types of alcohol may be indicative of dietary (antioxidants) or life style factors e.g. smoking has been strongly associated with heavy drinking[50] or alcohol consumption patterns of different populations studied.

PATHOGENESIS OF AMD

Physiological ageing in humans is a generalised process associated with cumulative oxidative stress. The retina and RPE are particularly susceptible to oxidative stress due to their high oxygen consumption and levels of cumulative irradiation exposure in addition to proportion of polyunsaturated fatty acids and chromophores.[51]

Oxidative stress is the most likely primary event in AMD pathogenesis, in addition to inflammation and angiogenesis on the background of genetic and environmental influences as depicted in Figure 5.

Evidence for the role of inflammation in AMD is extensive and is inclusive of anatomical[52] and molecular studies and more recently animal models.[53] However, it is largely the molecular studies that have contributed to the current understanding of the

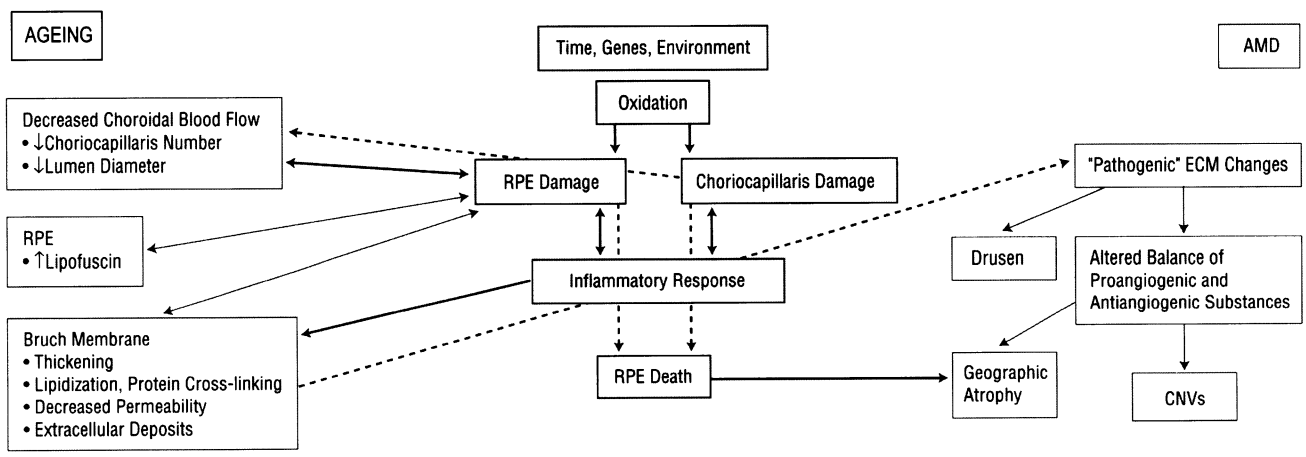

Figure 5 Ageing versus AMD (Taken from Zarbin MA, 2004[27])

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TABLE II

Major molecular constituents of drusen (from Zarbin et al, 2004[27])

α_1 Antichymotrypsin
α_1 Antitrypsin
Alzheimer amyloid ß peptide
Advanced glycation end products
Amyloid P component
Apolipoproteins B and E
Carbohydrate moieties recognised by wheat germ agglutinin, Limax flavus agglutinin, concanavalin A, Arachis hypogaea agglutinin, and Ricinis communis agglutinin
Cholesterol esters
Clusterin
Complement factors (C1q, C3c, C4, C5, C5b-9 complex)
Cluster differentiation antigen
Complement receptor 1
Factor X
Heparin sulphate proteoglycan
Human leucocyte antigen DR
Immunoglobulin light chains
Major histocompatibility complex class II antigens
Membrane cofactor protein
Peroxidized lipids (derived from long-chain polyunsaturated fatty acids ie. linolenic acid and docosahexanoic acid, which are usually found in photoreceptor outer segments)
Phospholipids and neutral lipids
Tissue inhibitor of matrix metalloproteinases-3
Transthyretin (major carrier of vitamin A in the blood)
Ubiquitin
Vitronectin

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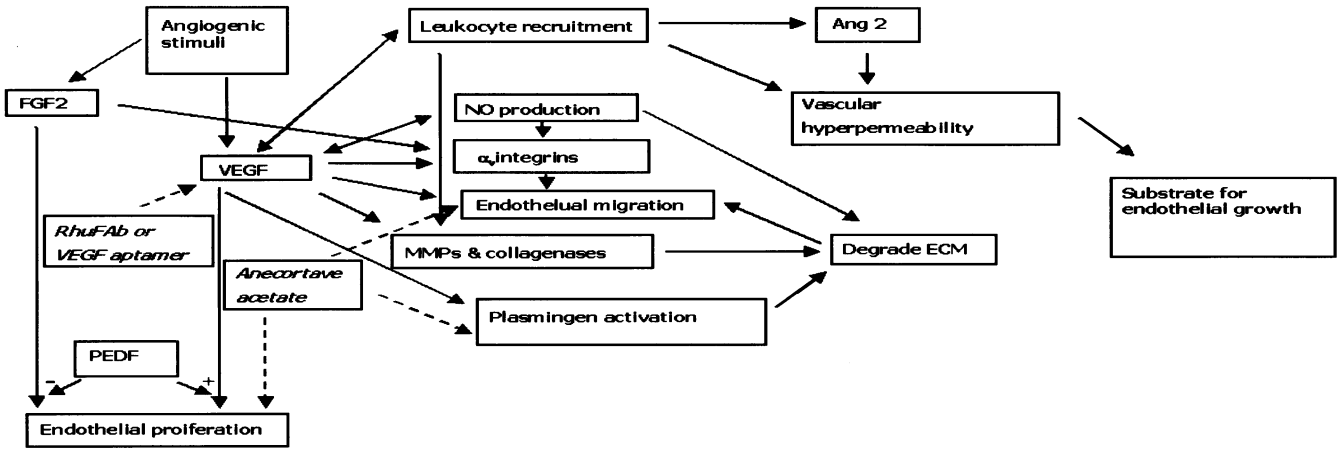

Figure 6 Angiogenesis in choroidal nevascularisation (Taken from Ambati *et al* 2003[53])

inflammatory role in AMD and the development of a local inflammation model of drusen biogenesis.[54-55] The extensive range of inflammatory constituents identified in drusen further support this (*Table 2*). AMD has been postulated to represent another chronic age-related inflammatory disease due to the striking compositional similarities between drusen and the deposits or plaques associated with Alzheimer disease, atherosclerosis and glomerular membrane disease.[56-57]

The role of angiogenesis in AMD is well documented although much remains unknown. A summary of angiogenesis in CNV is provided in Figure 6. CNV, which represents a non-specific response to a specific stimulus in nearly forty ophthalmic conditions, including AMD is a result of an altered balance between proangiogenic and antiangiogenic factors.[58]

AMD pathogenesis has been extensively investigated in an attempt to unravel the disease, however much remains unknown.

CLINICAL ASPECTS OF AMD

A degree of overlap between the two types of late AMD is well recognised, with both sometimes occurring in the same eye or at once in different eyes in the same person.

A typical history of a patient with non-exudative AMD is of a lengthy process of gradual visual loss interrupted by periods of deterioration. Sparing of the foveal centre occurs late in the course of the disease[59] with the primary visual impairment arising from scotomas (blind spots) which correspond to geographic atrophy (GA). In the early stages of GA, the patient's ability to read and recognise faces is compromised, with the size and position of the atrophic area determining the level of impairment.[60] Sudden loss of central vision in a patient with GA may indicate the presence of an exudative component or the final involvement of the central macula in geographic atrophy.

The primary event in exudative AMD is choroidal neovascularization (CNV), referring to the growth of new choroidal blood vessels, usually located beneath the RPE or rarely in the subretinal space. CNV is usually classified by both its location relative to the foveola i.e. subfoveal, juxtafoveal or extrafoveal and its pattern of fluorescence (classic, occult or mixed) on fluorescein angiography (Figure 7). CNV appears as a greenish–grey lesion on ophthalmoscopy, often accompanied by sensory

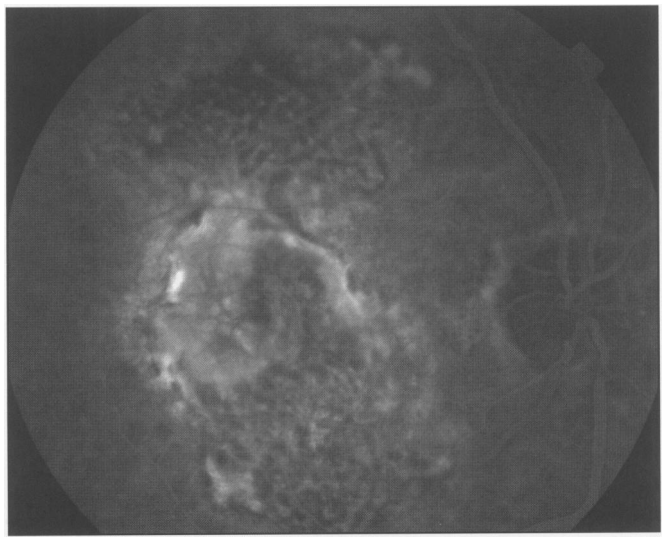

Fig 7. Fluorescein angiogram illustrating wet AMD.

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retinal detachment. There may be additional signs of subretinal exudate and blood. Although the patient may be asymptomatic, the majority complain of the sudden onset of distortion and loss of central vision. CNV may precipitate detachment and tears in the RPE. Fibrovascular disciform scar tissue formation occurs with repeated leakage of blood and serum from the CNV, and represents the end-stage. The degree of RPE and photoreceptor degeneration is proportional to the diameter and thickness of the disciform scar.

TREATMENT

Treatments in AMD can be divided into the well recognised categories of preventative, established and innovative.

Lifestyle changes demonstrated to be beneficial in reducing occurrence and progression of AMD include cessation of smoking and antioxidant vitamin and mineral supplementation. A modest benefit of antioxidant vitamin and mineral supplementation in people with moderate to severe signs of AMD was the conclusion of the Cochrane review.[61] However it has been shown that individuals without AMD could not delay or prevent the onset of disease by taking antioxidant and mineral supplements.[62] Other lifestyle factors such as more exercise, alteration in type and amount of alcohol consumed, use of sun protective measures and a diet of regular fish consumption, low total and altered fat dietary intake await further research prior to any recommendations. Screening using the Amsler grid facilitates early detection of choroidal neovascularisation AMD signs in the patient with pre-existing disease particularly in the other eye and can as such be regarded as preventative.

Presently the five-year results of the Complications of Age-related Macular Degeneration Prevention Trial, evaluating the effect of low-intensity laser treatment as prophylaxis in high-risk patients with numerous large drusen in both eyes is eagerly awaited.

Presently there is no established treatment for non-exudative AMD.

Laser photocoagulation is a well-established and widely accepted treatment for CNV, largely as a result of the Macular Photocoagulation Studies.[63] This treatment is only beneficial when the CNV lesion is well demarcated and located in the juxtafoveal or extrafoveal regions, although small subfoveal lesions may benefit. Approximately 10-15% of patients with exudative AMD are eligible for this treatment. Despite persistent and recurrent CNV in over 50% of laser-treated eyes within 3-5 years of treatment,[63] laser photocoagulation continues to remain the standard of care for these lesions.

Photodynamic therapy (PDT) with verteporfin has recently been acknowledged as an approved treatment for classic subfoveal CNV.[64] NICE guidelines provide eligibility criteria for NHS funded PDT.[65] There are a number of advantages to PDT, including the ability to treat subfoveal lesions due to less destruction of the retina compared to conventional laser photocoagulation, and minimal ocular and systemic side effects. However, at best PDT seems to stabilize vision. The high persistence and recurrence rate following PDT leads to multiple repeat treatments, and adds to the cost of treatment.

Numerous experimental therapeutic interventions are under investigation including surgical intervention, anti-angiogenic and angiostatic agents, transpupillary thermotherapy and gene therapy. To date until further large scale, controlled clinical trials have been completed no consensus of the risks and benefits of such treatments can be reached.

CONCLUSIONS

AMD is the leading cause of blindness in elderly Caucasians, impacting significantly on patients, their carers and National Health Service. Treatment is limited mainly to reducing the disease progression. The multifactorial aspect of AMD is well established with age, smoking and genetics being the most consistent associations. The difficulties of phenotyping AMD have been well recognised for many years and may explain the limited progress in identifying the underlying complex genetic aetiology. Presently the debate continues as to whether non-exudative AMD is a separate disease and perhaps a different aetiology to exudative AMD or whether they both represent a continuous spectrum of AMD i.e. clinical heterogeneity. However drusen size of $\geq$125μm appears to be the most discriminating feature in AMD phenotyping for progression to AMD.

AMD impinges on the practice of medical practitioners from various specialities, particularly ophthalmology, geriatrics, psychiatry and general practice. The recognition of the familial and sporadic forms of AMD by medical practitioners is paramount with the relevant preventive and screening interventions.

AMD was first recognized 130 years ago, however much remains unknown. It will continue to present a major challenge to clinicians and researchers in the future.

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