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Age-related macular disease

Part 1 - Classification of AMD

In the first of a three-part series, **Dr Frank Eperjesi** looks at the classification of and nomenclature used in describing age-related macular degeneration. C7680, one general CET point, suitable for optometrists and DOs

The macula has been defined as that part of the retina centred on the foveola in which the ganglion cell layer is more than one cell in thickness and has an approximate diameter of 5.5mm.[1] Age-related macular degeneration (AMD) is a common, chronic, progressive degenerative disease of the macular area, usually bilateral and most often clinically apparent after 50 years of age.

Despite its widespread prevalence and its extensive ocular morbidity, the pathogenesis of AMD remains poorly understood. It is, however, widely accepted that the primary loci of the disease are the choriocapillaris, Bruch's membrane and the retinal pigment epithelium (RPE), and that the visual loss results from dysfunction and death of the overlying photoreceptors.[2]

This article will describe the classification of age-related macular disease, the leading cause of visual loss in the 50-plus age group in the developed world. There is even dissension as to the definition of this disease but one which the author finds useful is 'any eccentrically located atrophic or exudative process capable of lowering visual acuity if it spreads into fixation, as well as excessive numbers or softening and confluence of drusen that predispose to these complications'.[3]

Terminology

As in many other areas of medicine and paramedicine the terminology used to classify and describe the clinical features of age-related macular disease is confusing; several terms are used synonymously by some authors, researchers and clinicians but are used to mean different things by others.

For example, it seems that epidemiologists prefer to use the term age-related maculopathy (see below for a definition of this term) for the overall disease process and to reserve the term age-related macular degeneration for the late stage only. In eye care literature the term age-related maculopathy is most often used solely to describe the very early stages of the disease. The inconsistency in terminology combined with different definitions and severity scales has limited comparisons of findings among clinical and epidemiological studies. There is a great need for standardisation of nomenclature in this area.

Until this is achieved, when studying research and clinical articles on age-related macular disease it is important for the reader to establish what terminology the author(s) is using and what that terminology is exactly referring to.

TABLE 1

Summary of the International classification system of age-related maculopathy and age-related macular degeneration[5]

Preferred terminology	Preferred abbreviation	Synonym	Clinical features
Age-related maculopathy	ARM	Age-related changes Early AMD	Drusen > 64 µm, hypo- and hyperpigmentation
Age-related macular degeneration	AMD	Late ARM	Dry-hypopigmentation, visible, choroidal vessels Wet-RPE detachments, sub-retinal or sub-RPE neovascular membrane(s), fibrin-like deposits, sub-retinal not related to other retinal vascular disease

Classification of age-related disease

There is no generally agreed definition of, or a uniform diagnostic criteria for, age-related macular disease.

The condition has been defined for a number of clinical and epidemiological studies using varying degrees of drusen, pigmentary change, atrophy and other associated changes such as sub-retinal neovascularisation.[4]

Classification systems for age-related macular disease can be divided into two types: firstly, the classification used by lab-based researchers as well as eye care practitioners taking part in clinical trials; and, secondly, the classification used mainly by eye care practitioners working in primary, secondary and tertiary settings.

Classifications of age-related macular disease used in research and clinical trials

Many researchers and clinicians looking for improved detection and management strategies for age-related macular disease have adopted the International Classification System of Age-related Maculopathy and Age-Related Macular Degeneration.[5]

International Classification System of Age-related Maculopathy and Age-related Macular Degeneration

Age-related maculopathy

Age-related maculopathy (ARM) has been defined as a disorder of the macular area of the retina, often clinically apparent after 50 years of age, characterised by the presence of any one or combina-

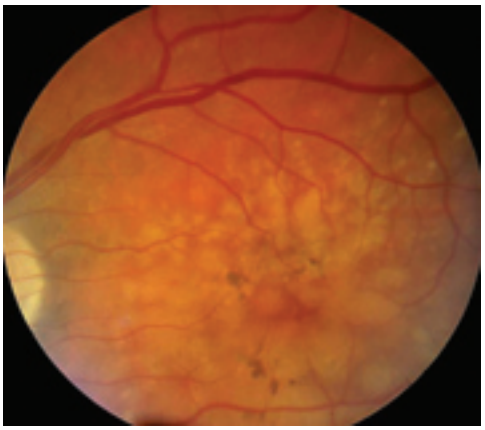


Figure 1 Soft drusen with areas of hyper- and hypopigmentation this is an example of ARM

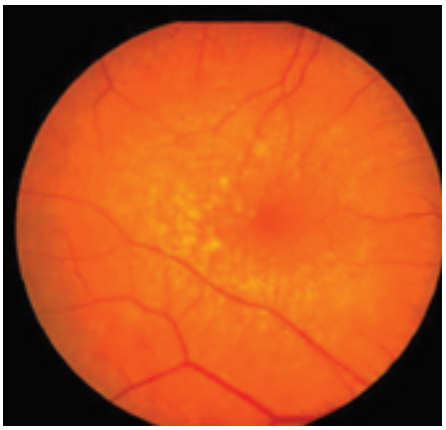


Figure 2 Age-related changes with hard drusen in the macular area only

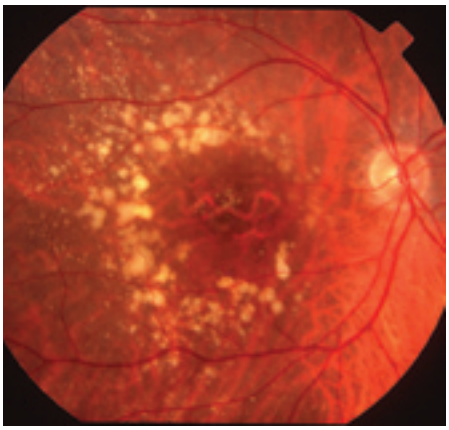


Figure 3 Dry AMD with geographic atrophy

tion of the following clinical features without indication that they are secondary to another disorder such as retinal detachment, high myopia or an inflammatory process:

- Discrete whitish-yellow spots identified as drusen (German for crystalline bumps or bodies at least >64 microns in greatest linear dimension),[1] focal whitish-yellow excrescences under the retina, generally clustered in the posterior pole, but can occur anywhere in the retina external to the neuroretina or the RPE. They may be confluent, often with indistinct borders. They have decreasing density from the centre outwards with fuzzy edges. Note, hard drusen, usually present in eyes with, as well as those without, ARM, do not themselves characterise the disorder. Eyes that have hard drusen only are probably best described as undergoing age-related changes and not as having ARM or AMD.

Small hard drusen (<64 microns in the greatest linear dimension) are extremely common – about 80 per cent of the population over the age of 30 years manifests at least one.[1]

- Areas of increased pigment or hyperpigmentation (in the outer retina or choroid) associated with drusen
- Areas of depigmentation or hypopigmentation of the RPE, most often more sharply demarcated than drusen, without any visibility of choroidal vessels associ-

ated with drusen.[5] (Figure 1)

Interestingly, visual acuity is not a criterion for the presence or absence of ARM.[5]

Age-related macular degeneration (AMD)

The late stages of ARM are described as age-related macular degeneration (AMD) and this includes both dry and wet AMD. The average age of onset of visual loss is about 75 years.[1]

Dry AMD or geographic atrophy (GA) is characterised by:

- Any clearly defined leision that is approximately round or oval in shape with hypopigmentation or depigmentation, or apparent absence of the RPE in which choroidal vessels are more visible than in surrounding areas.

Wet AMD is characterised by any of the following:

- RPE detachments which may be associated with neurosensory retinal detachment, associated with other forms of ARM
- Subretinal or sub-RPE neovascular membrane(s)
- Epiretinal, intraretinal, subretinal or sub-pigment epithelial scar/glial tissue or fibrin-like deposits
- Sub-retinal haemorrhages that may be nearly black, bright red, or whitish yellow and that are not related to other retinal vascular disease.

Late ARM is diagnosed in the presence of GA (defined as atrophic macular scarring) within 3,000µm of the fovea, an RPE detachment or choroidal neovascularisation (and/or its sequelae),[5] and is henceforth referred to as age-related macular degeneration (AMD).

In other words, according to this classification system late ARM and AMD are synonymous, with AMD being the preferred term. Just to add to the terminology mêlée, ARM is sometimes referred to as early AMD but in this text the term ARM is preferred.

Table 1 shows a summary of the terms and clinical features of the International Classification System of Age-related Maculopathy and Age-related Macular Degeneration.

Age-related macular disease

The term age-related macular disease is used in this text to encompass both ARM and AMD. The abbreviation ARMD for age-related macular degeneration is slowly falling out of vogue and will not be further mentioned here.

Clinical classification of age-related macular disease

Some eye care practitioners prefer to use a less cumbersome form of classification than that proposed by the aforementioned international classification system.

A simpler classification that is more user-friendly in optometric and ophthalmological clinical practice for clinicians, patients and carers is often adopted. In this clinical classification, age-related macular disease is divided into two main types: dry and wet. Each of these AMD manifestations is associated with age and decreased central visual acuity.

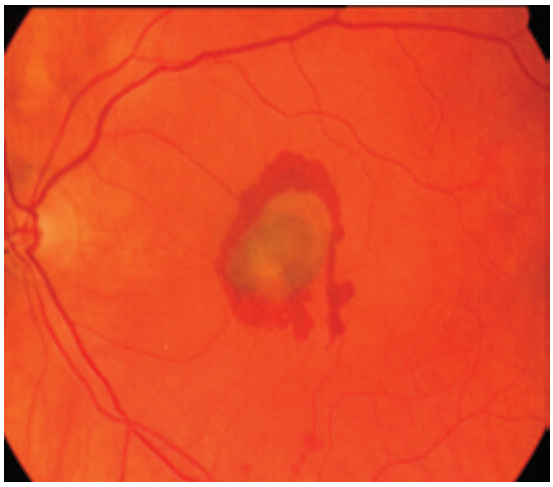
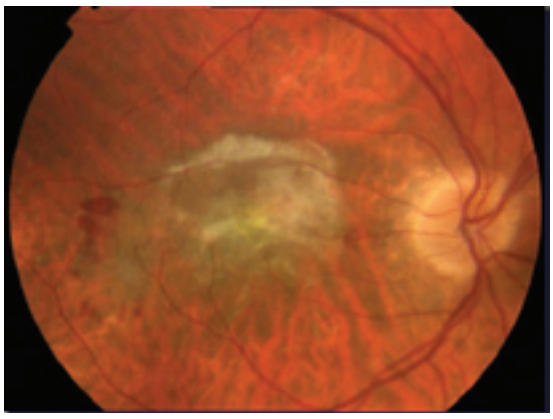
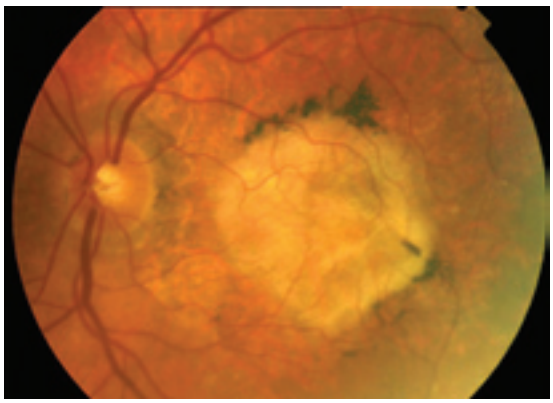


Figure 4 Early stage wet AMD depicting a sub-retinal haemorrhage and circinate pigmentation





Figures 5 and 6 Late stage wet AMD with clinical features of a disciform scar

Dry type of age-related macular disease

To complicate the terminology situation even more, the dry type of age-related macular disease is often referred to as non-neovascular or non-exudative.

The dry type from this clinical classification would map to both ARM and AMD in the international classification system, but only to AMD that did not involve any sub-retinal neovascularisation. The clinical features of the dry type of age-related macular disease are:

- Discrete yellow spots at the macula (drusen)
- Hyperpigmentation of the RPE
- Sharply demarcated areas of RPE depigmentation (hypopigmentation).

Focal hyperpigmentation of the RPE is a high-risk feature for subsequent wet AMD development.

Some eye care practitioners may describe a patient who has a few small (<64µm) well defined hard drusen and very little impact on visual acuity (6/6- to 6/9) as having ARM. However, under the international classification system the term ARM refers to the presence of soft drusen (>64µm) and not hard drusen. In the author's opinion a patient presenting with hard drusen only is probably best described as having age-related changes and not ARM or AMD (Figure 2).

In the initial stages of dry AMD it is seen clinically as one or more well-delineated areas of atrophy of the RPE. The areas typically are small (less than one disc area) and may ring the fovea, but eventually will coalesce or manifest as one large central lesion up to 7mm across.[1]

The end stage of this form of the disease is often termed geographic or atrophic and is often referred to as GA, which in this context has been described as atrophy of the retina spread over a wide area (hence the term geographic) centred on the macula (Figure 3).

Dry AMD is the most common form of the disease and accounts for around 85-90 per cent of all cases. It is characterised by GA and usually associated with a build-up of drusen under the RPE.

Atrophic AMD could be described as the chronic form of the disease since its progression is slow and causes the gradual deterioration of central vision over many (up to 20) years. One of the often-ignored findings of the Age-related Eye Disease Study is that ARM and dry AMD are conditions that progress very slowly.[6]

Presently there is no widely accepted treatment modality for this the most commonly occurring type of AMD, although some studies have shown that ocular nutritional supplements may have a role to play in the management of dry and wet AMD.[6,7]

Wet type of age-related macular disease

To further complicate the terminology the wet type of age-related macular disease is often referred to as neovascular or exudative, since the main clinical feature is sub-retinal neovascularisation, which is also known as choroidal neovascularisation (CNV) or a choroidal neovascular membrane. These new vessels often haemorrhage blood and/or lipid intra-retinally, or into the sub-retinal or pre-retinal space, hence the term exudative (Figure 4).

The clinical features of the wet type of AMD are:

- GA of the RPE with visible underlying choroidal vessels
- Pigment epithelial detachment (PED) with or without neurosensory detachment
- Subretinal or sub-RPE neovascularisation
- Fiborglial scar tissue, haemorrhage and exudates.[8]

Some authorities suggest that the term GA should only be used to describe the advanced form of dry AMD;[9] however, it seems the majority of experts in this area agree that the term can be used to describe one of the clinical features of wet AMD.

Associated elements of ARM and dry AMD, which include drusen, RPE atrophy and focal areas of depigmentation or hyperpigmentation typically are present in eyes affected by wet AMD as well as in contralateral eyes. However, wet AMD may occur without any of these precursor lesions.[1]

Choroidal neovascularisation, the formation of new blood vessels from the choriocapillaris, usually results in serous or haemorrhagic detachment of the RPE or sensory retina, eventually accompanied by fibrous tissue with RPE or sensory retina, eventually accompanied by fibrous tissue with RPE proliferation and atrophy.

The end stage of this form of age-related macular disease is also often described as GA, as well as disciform (having a round or oval shape like a disc) and this form is characterised by retinal pigment epithelial detachments, choroidal neovascular membranes and disciform scars (Figures 5 and 6).

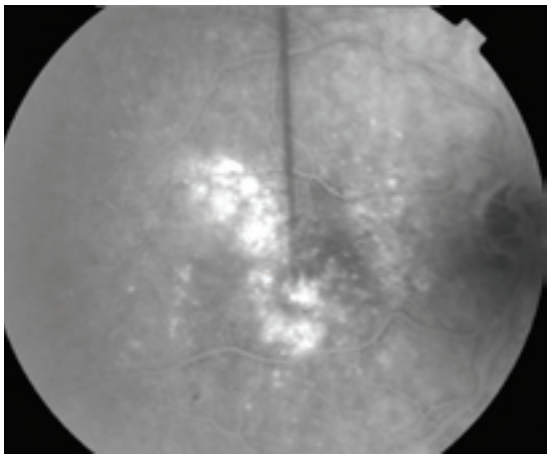


Figure 7 Fluorescein angiography of classic CNV in wet AMD

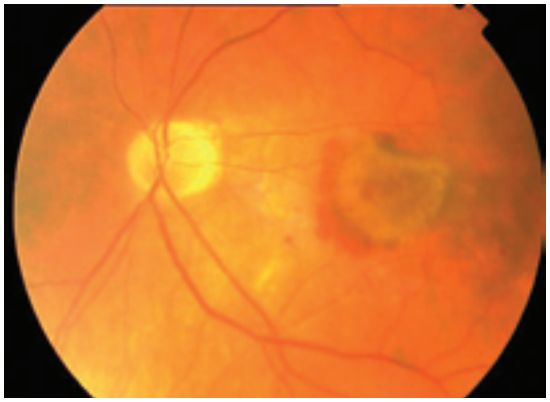


Figure 8 Clinical appearance of classic wet AMD using ophthalmoscopy

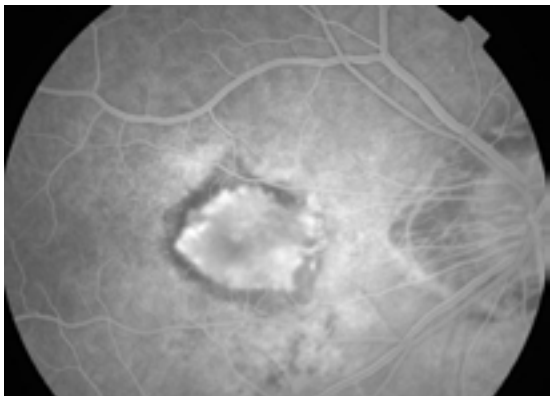


Figure 9 Fluorescein angiography of occult CNV in wet AMD

The wet type of AMD, although less common (10-15 per cent of all cases) than dry AMD, is a more aggressive or 'acute' type of AMD. It can result in severe vision loss in a very short period of time (one to six months). Wet AMD is characterised by angiogenesis (the growth of new blood vessels). New blood vessels form in the choroid, and are therefore referred to as choroidal neovascularisation. The new blood vessels that develop are abnormal; when they leak, an accumulation of blood and/or lipid within and beneath the retina results in a sudden loss of central vision. Permanent loss of vision occurs sometime later as the outer retina (including the photoreceptors) becomes atrophic or replaced by fibrous tissues.[1]

Extent and composition of a CNV lesion

Determination of the presence and evaluation of the extent and composition of a CNV lesion are critical to deciding if photocoagulation is indicated and if so where to apply the treatment. If the lesion is demarcated well, its location may be determined by the closest point of the lesion to the centre of the foveal avascular zone (FAZ).

The lesion location is classified angiographically as:

- Extrafoveal (closest extent ± 200µm from the centre of the FAZ
- Juxtafoveal (closest extent 1 to 199µm from the centre of the FAZ); or
- Subfoveal (under the centre of the FAZ).[1]

Based on angiographic patterns of fluorescence, components of CNV lesions may be further categorised into classic and occult CNV. This differential diagnosis can only be safely and accurately made following the conduction of fluorescein angiography, and although the features of clinical presentation may offer clues, diagnosis in this way is inappropriate.[1]

Classic CNV in wet AMD

Classic CNV is characterised by an area of well-demarcated, discrete, bright choroidal fluorescence that is discerned in the early phase of the angiogram.

Initially, the borders are well demarcated but in the later phases of the angiogram, fluorescein leakage from the CNV obscures the boundaries of this area (Figure 7). There are some

clinical features that can be used to determine whether the wet AMD lesion is classic or occult. For example, sub-retinal haemorrhage or pigmentation in a circular pattern generally (but not always) indicates a predominantly classic sub-retinal neovascular membrane[10] (Figure 4 and Figure 8). The pigmentation is due to RPE hyperplasia (an abnormal increase in the number of cells) surrounding the sub-retinal neovascular membrane.

Occult CNV in wet AMD

Occult CNV is recognised angiographically as one of two patterns:

- Fibrovascular PED
- Late phase leakage of an undetermined source.

Fibrovascular PED is characterised on fluorescein angiography by an area of irregular elevation of the RPE, which is neither as bright nor as discrete as areas of classic CNV, often with stippled hyperfluorescence present in the mid-phase of the angiogram and leakage or staining of this area by the late phase (Figure 9).

Late leakage of an undetermined source usually appears as speckled hyperfluorescence with dye pooled in the sub-sensory retinal space in the late phase, for which the source of leakage does not correspond to classic CNV or a fibrovascular PED in the early or mid-phase of the angiogram.

Identification of occult CNV, therefore, is facilitated by late phase photographs (up to 10 minutes after fluorescein injection) and stereoscopic photographs which may detect the irregularity of a fibrovascular PED.[1]

Eyes that change from dry to wet AMD – natural history

There are relatively few longitudinal, observational studies of the changes in macular signs of ARM over time. The high-risk characteristics for the development of wet AMD are number of drusen, presence of larger, confluent or soft drusen and focal hyperpigmentation. Eyes that have signs of ARM are likely to develop signs of more severe AMD with time, although the timescale is variable. Results of one study suggest that the cumulative risk of developing wet AMD in patients with bilateral drusen is 8 per cent within a three-year period. Eyes with signs of ARM may develop areas of larger and confluent drusen, greater drusen area, or additional pigmentary changes. An area with one or two soft drusen may develop additional drusen, with some confluence, or may be replaced with small drusen, pigmentary changes, or an area having a normal appearance.[12]

MULTIPLE-CHOICE QUESTIONS – take part at opticianonline.net

1 Which one of the following is a synonym for early age-related macular degeneration?
A Choroidal neovascularisation
B Age-related maculopathy
C Confluent drusen
D PED

2 According to the International Classification System of Age-Related Maculopathy and Age-Related Macular Degeneration which one of the following characterises wet AMD?
A RPE detachments
B Hard drusen
C Soft drusen
D GA

3 Age-related macular disease can be used as an umbrella term for which of the following?
A Wet AMD and sub-retinal haemorrhage
B Dry AMD and GA
C ARM and AMD
D Age-related changes and late ARM

4 Which one of the following is likely to progress most rapidly?
A Dry AMD
B CNV
C Change of hard drusen to soft drusen
D Change of soft drusen to hard drusen

5 Differentiation between classic and occult CNV is best made using which one of the following?
A Ophthalmoscopy
B Symptoms
C Rate of visual acuity loss
D Fluorescein angiography

6 Which one of the following best applies to the natural history of AMD?
A All patients with dry AMD will convert to wet AMD given time
B Confluent drusen are a high risk for wet AMD
C Bilateral drusen indicate a cumulative risk of 50 per cent for wet AMD within a three-year period
D Soft drusen never spontaneously regress

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Acknowledgements
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