

# Age-related Macular Degeneration

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## Abstract

*Age-related macular degeneration (ARMD) is defined as an ocular disease leading to loss of central vision in the elderly. The disorder is characterized by both primary and secondary damage of macular retinal pigment epithelial (RPE) cells, resulting in formation of drusen (deposits lying beneath the RPE), choroidal neovascularization (CNV), and atrophy of photoreceptors and choriocapillaris layer of the choroidea. ARMD is regarded as the leading cause for reading disability in individuals of 65 years and older in predominantly Caucasian populations. The clinical course of the disease is divided into two stages: the early ARMD stages characterized by macular drusen and late ARMD stages with neovascular complications (CNV) and disciform scarring. Early forms of ARMD are reported to occur in 30% of the population of 75 years and above, and late forms in 4-8% of the individuals over 70 years. The current etiopathogenic model is based on oxidative damage that influence negatively the metabolism of photoreceptors and RPE. Age, smoking, arteriosclerosis and genetic factors predispose to ARMD. Numerous loci segregate in ARMD families, suggesting complex oligogenic patterns of inheritance for the disease. Current therapy encompasses nutritive antioxidants, laser treatment, surgery and magnifying devices.*

## Keywords

Macula, age-related macular degeneration (ARMD), drusen, choroidal neovascularization (CNV), age, antioxidants, laser, photodynamic therapy (PDT), angiography

## Definition

Age-related macular degeneration (ARMD) is defined as an ocular disease leading to loss of central vision in the elderly. The disorder is characterized by both primary and secondary damage of macular retinal pigment epithelial (RPE) cells, resulting in:

- formation of drusen (yellow deposits that form between the RPE and the underlying Bruch's membrane);
- formation of new choroidal vessel membranes, termed choroidal neovascularization (CNV);

- atrophy of photoreceptors and choriocapillaris layer of the choroidea.

### Excluded diseases

The term ARMD does not refer to macular dystrophies related to drusen, such as Stargardt's disease or Sorsby fundus dystrophy, since these diseases are not acquired and follow a different pathogenic mechanism. Other causes of CNV, such as ocular histoplasmosis or "presumed ocular histoplasmosis" syndrome, traumatic choroidal rupture, excessive myopia, angioid streaks, chorioretinal scars caused by photocoagulation, and inflammatory diseases of the choroid (e.g. multifocal choroiditis) must be excluded. Excluded diseases include also choroidal tumors (melanomas, osteomas, hemangiomas, metastases) and inflammatory conditions (Vogt-Koyanagi-Harada's disease, posterior scleritis, uveal effusion syndrome), which are other pathological conditions leading to rupture of the Bruch's membrane, subretinal fluid and hemorrhages. Central scotoma resulting from ARMD must be differentiated from those associated with diseases of the optic nerve. All hereditary macular dystrophies occurring in earlier life should be also excluded.

### Frequency

ARMD is regarded as the leading cause for reading disability in individuals of 65 years and older in predominantly Caucasian populations. Early forms of ARMD are reported to occur in 30% of the population of 75 years and above, and late forms in 4-8% of the individuals over 70 years.

### Clinical description

The clinical course of the disease is divided into two stages. Early stages of ARMD are characterized by macular drusen, and irregular proliferation and atrophy of the RPE. The late stages of ARMD present with geographic RPE atrophy, RPE detachment and rupture, CNV and fibrovascular, disciform scarring. The first symptoms manifested in patients are metamorphopsia and/or general central vision loss resulting in reading disability and difficulties in detecting faces. Late stages of ARMD cause central scotoma, which is extremely disabling if occurrence is bilateral. Three late forms of ARMD causing vision loss can be characterized: First, in more than 80% of the cases, forms with vascular complications are the main cause for vision loss; second, forms with a geographic choroidal pigment epithelial atrophy, which prevent the overlying photoreceptors from functioning properly. The third form corresponds to a pigment epithelial tear occurring after

serous pigment epithelial detachment above drusen or choriovascular membranes. The loss of pigment epithelium causes an immediate impairment of photoreceptors.

The early and late clinical stages of ARMD are also commonly referred to as "dry" and "wet" ARMD, respectively. The so-called wet form is mostly related to the vascular complication of ARMD. However, as the detachment of the RPE might also be caused by fluid that is not derived from a neovascular membrane, the term "wet" is not very helpful in the differentiation of the three different clinical types of late stage ARMD.

### Treatment

Therapy of ARMD is three-fold. First, there is an increasing body of evidence regarding the efficiency, in the early stage of ARMD, of a preventive therapy that is based on antioxidants and laser treatment, used for RPE protection and drusen reduction, respectively. Secondly, other forms of therapy in late stages of ARMD aim to stabilize or slow down the course of ARMD with neovascular complications by either obliteration or resection of the neovascular membrane. Third, magnifying reading helps towards visual rehabilitation of patients with ARMD.

Oral treatment with antioxidants (micronutrients) like vitamins C, E, beta-caroten, genistein, lutein, zeaxanthin and minerals (zinc, copper) helps protect against ageing RPE and photoreceptors. Statistical analysis of AREDS study (Mc Bee *et al*, 2003) indicate that patients with large drusen and eccentric geographic atrophy of the RPE, as well as patients with a neovascular complication or geographic atrophy on the other eye, may benefit from the antioxidative therapy by reduction of CNV risk by 25%.

Drusen photocoagulation may provide another prophylactic therapy for late forms of ARMD. Mild perifoveal photocoagulation is used to reduce drusen by activating neighbouring phagocyte RPE cells, which ingest these cellular debris. Whether this therapy really reduces the incidence of neovascular choroidal membranes in the long term remains to be established.

The macular photocoagulation study group (MPS) has shown that the risk of significant visual function loss in parafoveal, juxtafoveal and subfoveal membranes (200-2500 µm, 1-200 µm, and under the geometric center of the foveal avascular zone, respectively) in late stages of ARMD with neovascular complications can be reduced on the long term by direct laser photocoagulation. However, the recurrence rate of CNV after laser therapy remains high.

Another form of photocoagulation, the feeder vessel treatment guided by indocyanine green

angiography (ICG) of the neovascular membrane, may be used when the feeder vessel is not wider than 130 µm.

Photodynamic therapy (PDT), which is based on the combination of a red, low energetic (cold) laser and a photosensitive agent (verteporfin), has been shown to be effective in reducing exudative activity caused by ARMD in classic subfoveal CNV membranes (situated above the RPE) by inducing oxydative damage in the CNV endothelium (Sharma *et al*, 2004). Similarly, occult membranes (situated beneath the RPE) of a defined size seem to respond favorably to PDT. However, this therapy is associated with a high recurrence rate, and thus requires to be repeated during the disease course.

Anti-vascular growth factor therapy using aptamers (Eyeteck Study Group, 2003) or antibodies (Novartis) by intravitreal injection seems to be an aiding device to prevent the activation of vaso-endothelial growth factor (VEGF) by PDT (Schmidt-Erfurth *et al*, 2003). This therapy would aid to lower recurrence rate or further CNV growth under PDT therapy.

Injection of angiostatic substances, such as anecortave acetate (in Tenon's space) or Triamcinolone (intravitreally), has been shown to stop CNV growth (Soubrane *et al*, 2003; Fauser *et al*, 2003). Multicenter and safety studies are underway to prove long-term efficacy.

The use of a low-energetic diode laser called transpupillary thermotherapy (TTT) may be useful in the occlusion of subfoveal occult CNV membranes. TTT creates a localized hyperthermia, which result in denaturation of proteins, including heat-shock proteins. Occult membranes represent 70% of the neovascular complications in ARMD. The effectiveness of TTT in the treatment of late stage ARMD patients is currently under investigation in masked multicenter studies.

Surgical procedures aim to remove the CNV or to rotate the macular retina away from the CNV locus to a locus with healthier RPE. These procedures are invasive, as a *pars plana* vitrectomy and retinotomy have to be performed, and intra- and postoperative complications may arise. In addition, macular rotation is combined with surgery on the extraocular muscles, as the rotation causes a tilted image in the cerebral cortex. These procedures are still regarded as experimental with a rate of postoperative proliferative vitreo-retinopathy ranging from 30% to 50%.

Radiation therapy at a dose of 8x2 Gy has not proved to change the course of the disease in classic CNV (Bellmann *et al*, 2003).

Recurrences occur in all the therapies mentioned above for treating the neovascular

stage, since in ARMD the whole RPE and choriocapillaris are involved in the degenerative process. Only 20% of patients with late stages of ARMD are treated with only one type of therapy.

If therapy cannot be carried out or if it is not successful the prescription of magnifying aids may be the only rehabilitative therapy for patient with ARMD and no healthy eye left. These aids range from simple magnifying glasses to combined video-screen devices. They share the same principle, which is based on the magnification of the image in the near distance on the patient's retina in order to enable the non-CNV-involved neighbouring RPE to replace the damaged foveal or macular RPE area. Audio libraries and acoustic devices (watches, reading computers) are available to complement the visual aids.

### Etiology

Several factors are responsible for the development of ARMD. The current pathogenic model is based on oxydative damage that influences negatively the metabolism of photoreceptors and RPE. Light damage, free radicals and hemodynamic changes have cumulative effects resulting in cell apoptosis. Subsequently, inflammatory mediators such as prostaglandines, cytokines, leucotriens and others trigger inflammation and chemotaxis of macrophages and lymphocytes. The concentration of non-saturated fatty acids is high in the photoreceptor outer segments. Light damage induces a chemical change (mainly oxygenation) in the metabolism of these lipids, which then start to accumulate as lipofuscin granula in the RPE. This leads to the formation of soft and large drusen (basal linear deposits), which degrade the layer of Bruch's membrane.

Proteome analysis of drusen isolated from ARMD donor eyes detected oxidative protein modifications that may also be causally involved in drusen formation (Crabb *et al*, 2002). High drusen concentrations may lead to the damage of the RPE, which is then amenable to phagocytosis, and geographic areas of atrophy appear. In some eyes, angiogenic growth factors, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are secreted in response to the inflammatory degenerative process and stimulate growth of choroidal capillaries into the Bruch's membrane. These capillaries differentiate into arterioles and venules. They are covered by fibrous tissue, and neovascular membranes are formed, resulting into further degeneration of the RPE and photoreceptors.

Genetic predisposition is an established fact in ARMD. Among patients with late ARMD cases,

60% have a relative with a similar disease. Bilateral drusen and disciform scars are most often symmetric. Some families showing an autosomal dominant inherited ARMD inheritance pattern have been found to be associated with mutations in the *ABCR* gene (1q21-p13), which encodes a retinal rod protein. Patients with Stargardt's disease also have this defect. Genomewide scan and genetic linkage analysis in ARMD families found evidence of new loci contributing to AMD, at 4q32 and 9q33, 1q31, 10q26, and 3p13 (Majewski *et al*, 2003). A major ARMD locus was recently identified on 15q21. In view of the complex nature of the genetics of AMD, all of these loci have the potential to harbor genes that cause AMD, either alone or in combination, or genes that act as modifiers to the age at onset, degree of severity, or eventual phenotype (Iyengar *et al*, 2004). Age, smoking, arteriosclerosis, white skin colour (reduced amount of melanins in skin, choroid and RPE), and reduced levels of antioxidants (e.g. betakarotin) seem to be extrinsic risk factors of ARMD. In addition, high fat diet combined with plasma hyperlipidemia seem to predispose to formation of sub-RPE deposits (Espinosa-Heidmann *et al*, 2004)

### Diagnostic methods

Ophthalmoscopy and fluorescein angiography are the main diagnostic methods used to visualize, detect and differentiate different forms of ARMD. Fluorescein angiography is performed by injecting a bolus of 10-20% of Na-fluorescein intravenously and by taking a series of analog or digital pictures of the fundus, which enable the visualization of the CNV membrane. ICG is performed in a way similar to that of fluorescein angiography and provides a more accurate image of the choroid and the pathology of the CNV membrane. Laser treatment, PDT, TTT, and surgery are performed on the basis of the clinical findings obtained with these diagnostic imaging methods. It has to be emphasized that angiography is an invasive method involving contraindications and complications. Optical Coherence Tomography (OCT, Zeiss-Jena) could aid to visualize edema non-invasively in the macula, but has not been proved to replace angiographic methods.

### Genetic counseling

To date, there are very few indications for genetic counseling, and only family history of ARMD will prompt an early ophthalmologic examination of younger relatives.

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