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Review Article

Age-Related Macular Degeneration – Clinical Therapeutic Etiopathogenic Considerations

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Abstract

Age-related macular degeneration – AMD – is a primary irreversible condition, with macular localization, which is accompanied by profound alteration of central macular vision in people over 65 years of age. Senescent changes in the macula affect the retinal pigment epithelium, Bruch's membrane, choriocapillaries and are associated with the presence of retinal pigment epithelium (RPE) detachment, RPE rupture, choroidal neovascularization (CVN). AMD has 2 forms: atrophic (more common, 85%) and exudative. The atrophic form is accompanied by a slow decrease (approximately 5 years) of central vision, with preservation of peripheral vision, the patient having difficulty reading, spatial orientation. The specific lesion of this form of AMD is Drusen. Exudative AMD is accompanied by choroidal neovascularization (classical, occult), after detachment and RPE rupture. The etiopathogenic treatment of AMD is complex and prolonged, attacking multiple aspects: periodic control of risk factors, treatment of oxidative stress, control of lipid metabolism dysfunction, antiangiogenic treatment, corticosteroids. Regulation of the extracellular matrix by laser photocoagulation treatment can be effective for juxta and extrafoveal MNVC. Photodynamic therapy with verteporfin, gene therapy, surgical treatment, artificial vision and, if necessary, combined therapies have also been used to improve visual prognosis. Atrophic or exudative AMD are disabling, progressive conditions with irreversible loss of central vision.

Keywords: age-related macular degeneration (AMD); atrophic exudative; choroidal neovascularization; classic; occult (NVC); drusen; retinal pigment epithelium (RPE); choroidal neovascular membrane (CNM); anti VEGF; Bevacizumab; ranibizumab; triamcinolone acetonide; laser photocoagulation; photodynamic therapy; gene therapy; artificial vision

Introduction

Age-related macular degeneration – AMD is a common cause of irreversible vision loss in patients over 65. The risk of developing AMD increases with age (after 75 years the risk of AMD is 1/3).

AMD is a multifactorial condition that develops in adults over 60 years of age, which includes a set of degenerative, non-inflammatory, progressive, acquired lesions of the macular region occurring in a normal anterior eye.

AMD generates a central scotoma (a central black spot) in the area of the fixation point in the center of the macula, without alteration of peripheral vision.

AMD is responsible for blindness in approximately 11-18% of patients over 65 years of age with eye disease, in which age adjusts the prevalence of the disease.In patients with AMD, the quality of life in daily activity decreases due to quantitative/qualitative changes in central visual perception, with progressive difficulties in reading, driving, and spatial orientation.

AMD is the most common cause of irreversible vision loss in people over 65 years of age in industrialized countries, with the number of AMD patients increasing over the past 15 years.[1,2]

- Macular degenerative lesions cause progressive or rapid loss of central vision, which over time leads to blindness, while maintaining lateral peripheral vision.
- Frequently asymptomatic, AMD becomes symptomatic when vision decreases.
- 64.5% of patients have the same stage of disease in both eyes, but they are asymmetrical forms with different stages of evolution in the two eyes.
- Many patients are diagnosed with AMD in one eye, with the disease in the second eye possibly occurring within the next 5 years.

- AMD frequency is increasing with ethnic and regional differences: Caucasians 12.3%, Europe 7.38%, Asia 7.53%, affects less the African American population
- women more frequently develop exudative AMD, atrophic AMD affects women and men equally
- Genetic predisposition with mutations in the ABCR8 gene, the short arm of chromosome 1, has been confirmed.

Etiology of AMD

Etiology of macular degeneration Although the cause of age-related macular degeneration is still unknown, genetic factors play an important role alongside other risk factors. A combination of risk factors interact to alter the Bruch's membrane/choroid complex, the retinal pigment epithelium, and the photoreceptor cells of the retina in the macular region.

- Initial events affect one or all of these components
- The retina progressively degenerates into the exudative form accompanied by retinal pigment epithelium (RPE) detachment, rupture, and choroidal neovascularization (CVN).

AMD is thought to be caused by an aging process in the retinal pigment epithelium (RPE), which has limited possibilities for regeneration, with the accumulation of lipid material, through the degradation of the external segmental discs of the photoreceptors. These accumulations increase with age and lead to tissue dysfunction with changes in choroid perfusion. Secondary to hypoxia, VEGF (vascular endothelial growth factor) expression occurs, which contributes to the development of the neovascular form of AMD – the exudative form of AMD.

In the process of AMD formation, an important factor is physiological aging, which causes a series of changes in the macula, many of which are clinically undetectable, affecting the retinal layers, the pigment epithelium, Bruch's membrane, and the choriocapillaries.

All these changes do not represent macular degeneration itself, but just a normal aging process. Macular degeneration involves the appearance of abnormalities with or without neovascularization: detachment, rupture, EPR, choroidal neovascular membrane (NVC).

Risk factors

- ***Generali***
  - age - the prevalence of AMD increases with age: 10% in patients 65-75 years old, 25% over 75 years old
  - sex – women have a higher incidence of the exudative form of AMD, but there are no sex differences in the atrophic forms
  - race – the exudative form is more common in Europeans
    – the atrophic form is more common in light-colored eyes, with a increased incidence in Asians
  - systemic diseases: hypertension, atherosclerosis, diabetes, obesity
  - longsightedness
  - environmental factors: smoking, alcohol, polluted environment
- ***genetic***
  - Genetic factors have a strong impact on the pathogenesis of AMD, interacting with environmental factors for the development of AMD. These factors are: alcohol, smoking, environmental pollution, which increase the risk of developing AMD.
  - A genome-wide study of 43,000 people identified 52 genes associated with AMD. Mutations in these genes affect various biochemical pathways including: the complement cascade, lipid metabolism and transport, modulation of the extracellular collagen matrix, all-trans-retinaldehyde clearance from photoreceptors, and angiogenesis[3].
  - Among these, two genes with major susceptibility to AMD are distinguished: CHF, which encodes factor H of the complement system, and ARMS2, whose function is poorly known. The Complement pathway is implicated in the pathogenesis of macular degeneration as complement proteins have been identified in drusen in patients with AMD[4].
  - ARMS2/HTRA1 and MMP20 genes are associated with the size of choroidal neovascularization lesions in AMD.
  - Genetic tests: can be performed and include tests for the detection of several alleles known in the etiopathogenesis of AMD. These tests are controversial because lifestyle, with associated risk factors, increases the risk of AMD regardless of the genome identified with the associated risk genes. Pharmacogenetic tests are also available and they provide answers regarding the therapy to be followed in a particular individual. The field of genetic testing in AMD is in continuous development and research.

Pathogenic changes in AMD

- ***senescence changes***at the macula level, it affects the outer retina, retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaries, with advanced age producing[2,5,6]:
  - thickening of the basement membrane
  - thinning of the choroid
  - decreased photoreceptor density
  - reduction of choriocapillaries by reducing VEGF diffusion
  - involutional changes in Bruch's membrane
  - accumulation of lipofuscin, at the level of the EPR, with apoptosis and the appearance of drusen, decreased blood flow, production of vascular growth factor VEGF and hyperplasia of neovascularization
  - increase in free radicals, accumulation of unsaturated fatty acids, decrease in antioxidant capacity, favors the development of AMD
  - decreased lysosomal activity, with inhibition of autophagy
- **Atrophic AMD**is associated with lipofuscin accumulation in the RPE through dysfunctions of protein metabolism, with photoreceptor degradation and the formation of small subretinal deposits – drusen
  - **Lipofuscin accumulated in the RPE with age favors the development of AMD**
- **Wet AMD**is associated with:
  - subretinal fluid accumulation
  - retinal pigment epithelial detachment (RPE)
  - Classic and occult choroidal neovascularization (CVN)[2]

- ***oxidative stress*** plays an important role in AMD, where an imbalance occurs between the production and elimination of oxygen, the retina being a major consumer of oxygen;

- lipid homeostasis – increased high-density lipoprotein cholesterol is associated with increased risk of AMD, low-density lipoprotein reduces risk of AMD

  - The accumulation of ALEs in lipofuscin in AMD patients interferes with proteins and promotes apoptosis of photoreceptors and EPR cells.

- inflammation and immunity

  - drusen contain a variety of proinflammatory factors indicating the existence of possible inflammation in early AMD (CRP is higher in AMD)
  - inflammation and immunity influence the progression of AMD[3]

- neovascularization - is generated by VEGF, which is a determining risk factor for AMD, VEGF playing an important role in the occurrence of neovascularization

- other mechanisms

  - **lysosomal autophagy**with cytoplasmic protein degradation with age through decreased lysosomal enzyme activity, reduced autophagy, and lipofuscin accumulation with the development of AMD; autophagic flux in the RPE in AMD has been found to be lower than normal
  - **hemodynamic dysfunctions**leading to choroidal vascular dysfunction in AMD with age through choroidal vascular sclerosis, vascular wall thickening through atherosclerosis, vascular sclerosis with decreased choroidal flow, insufficient perfusion of the RPE and damage to Bruch's membrane, factors favoring the development of AMD
  - **disorders in protein homeostasis** can promote AMD

AMD Clinic

Clinically, AMD is:

- Dry atrophic AMD
- Wet exudative AMD

Atrophic Amd

Atrophic AMD is a condition with vision loss, with slow progression, approximately 5 years, with preservation of peripheral vision, because the degenerative process affects the central foveolar region of the macula, an area with high spatial resolution[7,8].

  - The patient has difficulty reading and recognizing objects, with poor spatial orientation, while maintaining functionally intact peripheral vision.

- ***The specific lesion of this retinal disease is DRUSEN.***

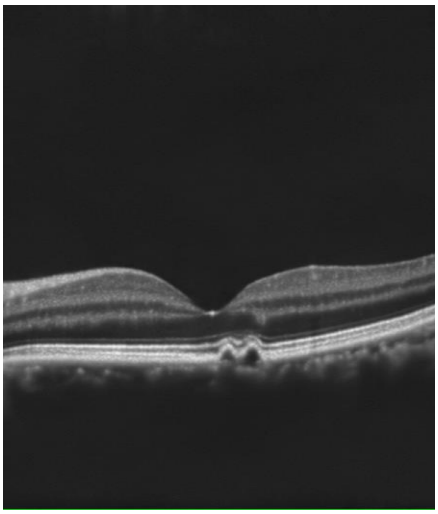
Clinically, drusen are small, round, yellow lesions located on the basal surface of the RPE and give a thickened appearance to Bruch's membrane.

They can be in the form of basal laminar deposits – they have a granular appearance, rich in lipids and collagen fibers between the basement membrane of the pigment epithelium and the plasma membrane or in the form of linear deposits – dense granules with phospholipid vesicles in the internal area of Bruch's membrane. These deposits can cause detachments of the pigment epithelium.[9]

According to their size, drusen can be: - small under 63 microns in diameter, intermediate between 63-124 microns, large over 125 microns.

Drusen can coalesce, causing drusenoid detachments of pigment epithelium over 350 microns in diameter.

Drusen are: miliary, serous (represents the major sign of age-related macular degeneration), reticular, (reticular pseudodrusen), pigmentary migrations.



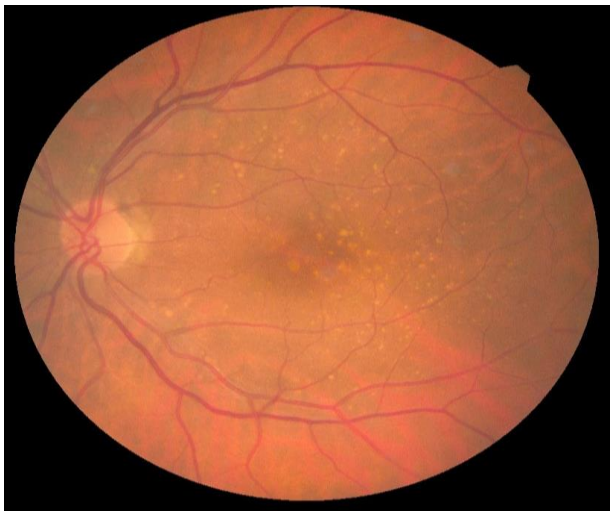


Figure 1: (left) Macular Drusens-CT view, they occur as waves and elevations of the pigmentar epitelium with hyporeflective material underneath.
Figure 2: (Right) Milliary drusens

Their evolution over time may be towards multiplication and their confluence transforming into serogranular drusen. An evolution towards atrophy or choroidal neovascularization is rare.

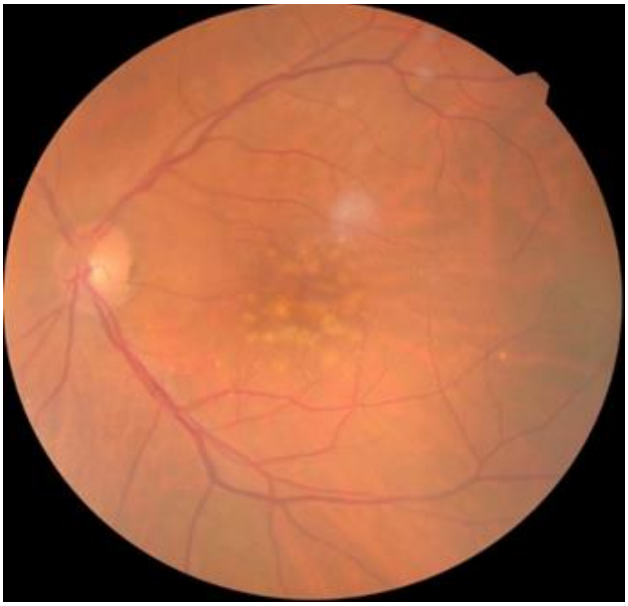


Figure 3: Serousal macular drusens

Atrophic AMD is the most common form of AMD, approximately 85% of cases, characterized by the disappearance of photoreceptors, pigment epithelium, and choriocapillaries.

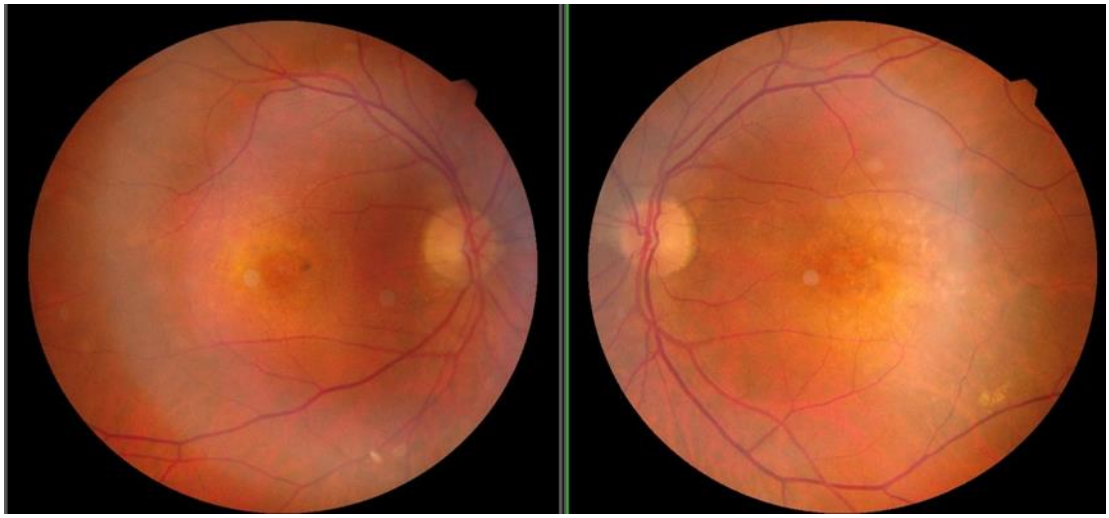


Figure 4: Pigmentary migration in the macula

Atrophy may be the consequence of drusen regression and pigmentary changes.

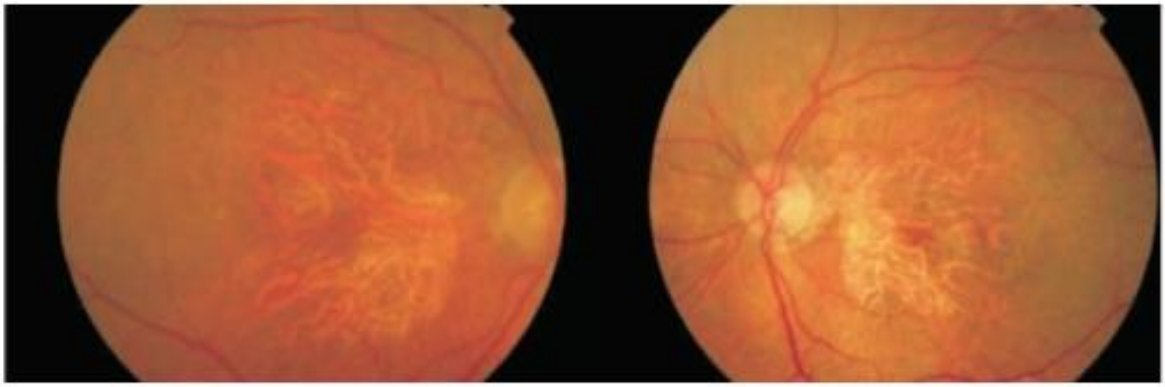


Figure 5: Geographic atrophy - atrophy of retinal pigmentar epitelium with view of coroidian circulation

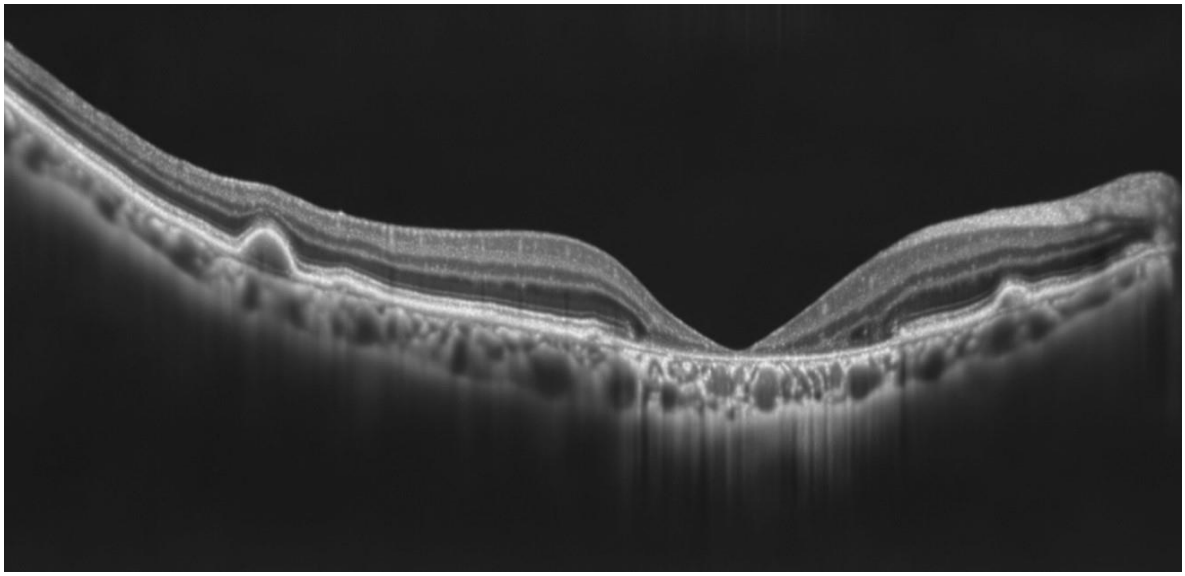


Figure 6: Geographic atrophy-CT view, lack of photo-receptors and atrophy of retinal layers in the macula

Differential diagnosis is made with atrophic changes in the RPE induced by central serous chorioretinopathy, hereditary macular dystrophies, late-onset vitelliform dystrophy of the macula, and toxic chloroquine maculopathy.

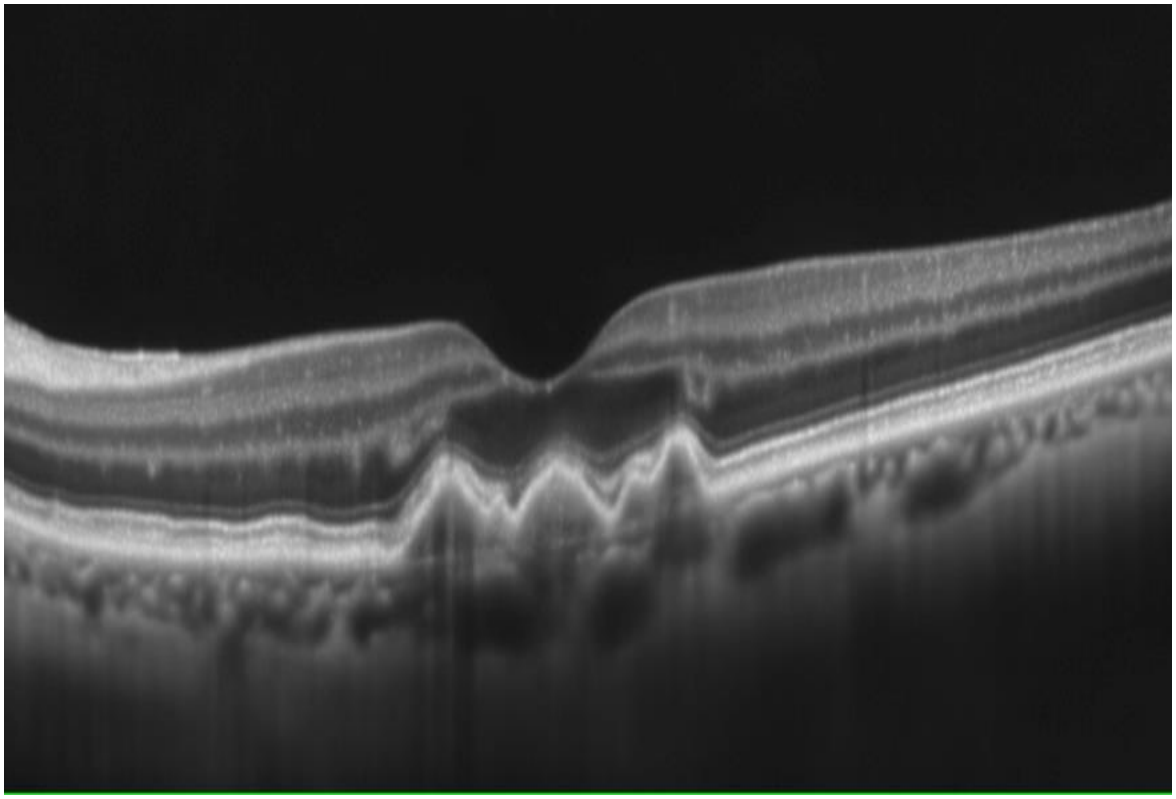


Figure 7: Retinal drusens behind the foveolar

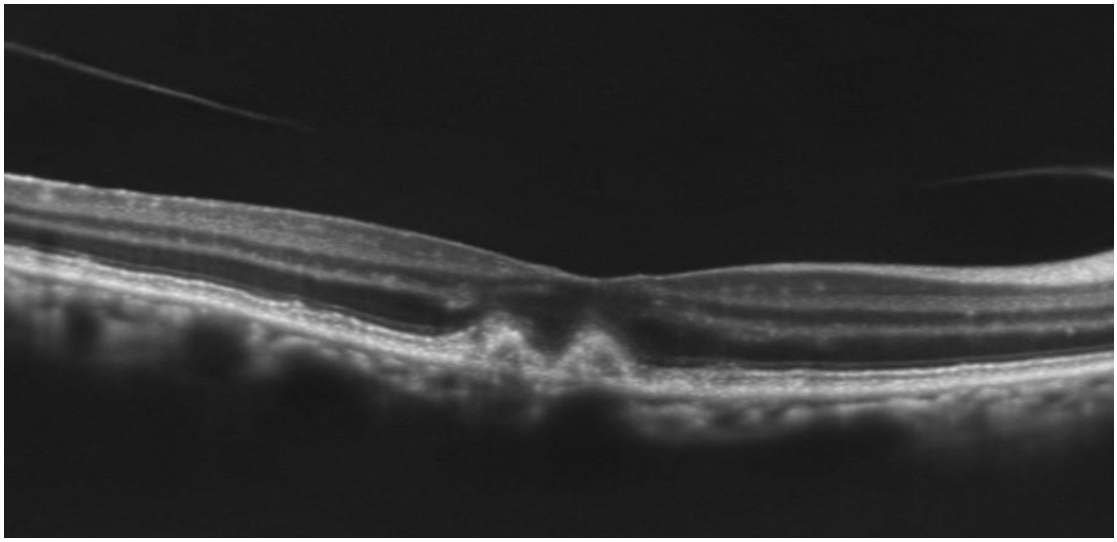


Figure 8: Pseudo-drusens, located above the pigmentar epitelium and immediately underneath the photo-receptors that are hyper-reflective

Clinically, in atrophic AMD it is highlighted:

- round or oval areas of hypopigmentation or depigmentation with visible choroidal vessels and areas of atrophy approximately 175µm in diameter
- areas of geographic atrophy that may expand over time and become bilateral
- patients with unilateral atrophic AMD may develop wet AMD with neovascularization in the second eye
- Drusen precede geographic atrophic AMD with large, confluent drusen, refractile deposits, with hyperpigmentation that can progress to geographic atrophy[1,2].

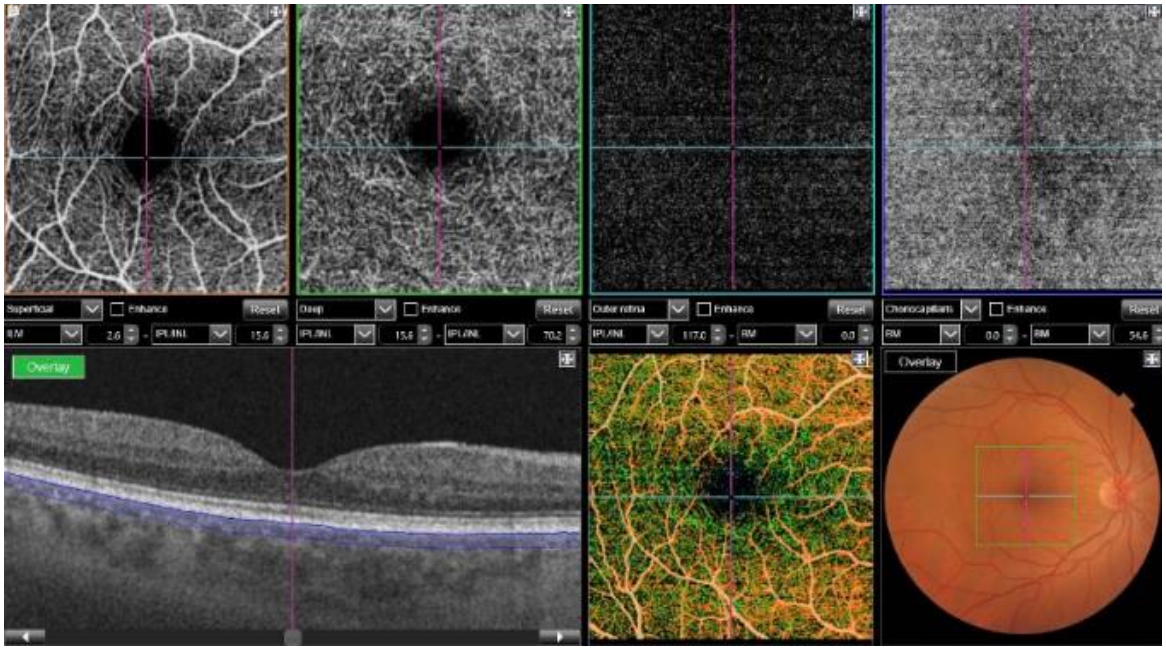


Figure 9: Ocularangiographic computer tomograp imagesh-upper images (from left to right) superficial plexiform strata, deep plexiform strata, external avascular retina, and coriocapilaries, lower images various aspects of ocular CT and ocular angiographic CT

Investigations

Optical coherence tomography (OCT)It is a noninvasive method that makes sections of the retina and precisely locates lesions.

- Drusen appear as nodular elevations under the pigment epithelium without sub- or intraretinal fluid.
- Reticular pseudodrusen appear on OCT above the pigment epithelium line and immediately below the line represented by the photoreceptor cell layer[10].

Optical coherence tomography with OCTA angiography

- uses a new technology that also detects the movements of red blood cells and thus blood vessels can be visualized in vivo.

Fundus autofluorescence FAF - is due to the accumulation of fluorophores in the retina that accumulate in the lysosomes of EPR cells as lipofuscin. Retinal areas lacking EPR cells cause a lack of autofluorescence and appear as dark areas.

Patient monitoringwith macular diseases can be done with the AMSLER test

Amd Exudative – Wet – Neovascular Form

Exudative AMD:

- is frequently associated with rapid progression of vision loss, compared to the atrophic form, with decreased ability to read
- the decrease in visual acuity is due to the development of neovascularization in the macular area
- aggressive evolution with rapid deterioration of central vision, with neovascular growth, bleeding, fibrosis and RPE rupture
- Untreated, patients lose 3 lines of visual acuity in 2 years
- the patient has difficulty recognizing objects, spatial orientation, and reading, while central vision is absent, with peripheral vision preserved

Exudative AMD is accompanied by detachment and rupture of the RPE with the development of choroidal neovascularization – NVC [3,8]

- ***Retinal pigment epithelial detachment (RPED)*** It is produced by the accumulation of lipids in Bruch's membrane, which make it hydrophobic and block the flow of ions and fluids from the retinal pigment epithelial cells.
  - AFG early hyperfluorescence that increases progressively
  - ophthalmoscopically, yellowish prominence with smooth edges;
  - The prognosis is reserved in retrofoveolar location.

The evolution of DEPR is towards: spontaneous resolution in young people, geographic atrophy with atrophic AMD or sensory retinal detachment with passage of subretinal fluid and development of classic and occult neovascularization, in the presence of spontaneous RPE rupture with neovascularization.

- ***Retinal pigment epithelial tear (RPER)*** with sudden onset, it is clinically evident by decreased central vision, at the ophthalmoscope by a crescent-shaped dehiscence with free, folded edges and retractions located at the level of the PRD;
  - ➢ AFG hypo fluorescence below the free edge with progressive adjacent hyper fluorescence.
- ***Choroidal neovascularization – NVC.*** The development of the choroidal neovascular membrane induces deterioration of central visual acuity, through the destruction and dysfunction of photoreceptors in the macular region[11].
  - **Classic NVC** It is a well-defined membrane that fills with dye, has a bright fluorescence and can be located relative to the center of the macula
    - ➢ extrafoveolar, over 200 microns from the center
    - ➢ subfoveolar, below the center of the fovea with reserved visual prognosis
    - ➢ juxtafoveolar, close to 200 microns from the center but does not affect it
  - **Occult NVC** It is a poorly defined membrane with a poorly defined contour on AFG, with the presence of the "notch" sign, which is a single or multiple indentation, located at the level of the serous detachment of the RPE, which appears as a central round hypofluorescent spot, surrounded by a hyperfluorescent ring[2,12,13].
  - ***Retinal angiomatous proliferation*** is a particular form of CNV associated with retinal capillary proliferation and telangiectatic response with a frequency of 10-15% in AMD - it is more common in the elderly with bilateral symmetrical neovascular damage, more common in women.

Exudative AMD is characterized by the presence of choroidal neovascular membrane (CNMV)

- neovessels can rupture and cause hemorrhages in the macula with secondary scarring
- The aggressive evolution of visual function is accompanied by rapid deterioration of central vision; parallel with the growth of friable neovessels, bleeding, hemorrhages, fibrosis.
- At the same time, degenerative changes occur in the Bruch membrane; the presence of proangiogenic factors stimulates the growth of abnormal neovessels in the choriocapillaries, which perforate the Bruch membrane and affect the photoreceptor/EPR complex, forming a fibrovascular complex under the EPR - **MCNV type 1 or the EPR ruptures and the neovessels reach the subretinal space, developing type 2 MCNV**[1,2,12].

- **Symptoms in wet AMD** include macular syndrome, with major changes in central vision[1,2,13]
  - **central vision impairment** is the main sign present in exudative AMD, the patient announcing the presence of a spot "in central vision" - positive scotoma with progressive or rapid decrease in central vision, acute or insidious until the total absence of central vision.
  - metamorphopsia is the distorted perception of images
  - distorted "foggy" vision especially for close-up vision
  - progressive (rapid) decrease in central vision acutely or insidiously with positive central scotoma, with absence of central vision
  - micropsia is the reduction in the size of the visual image due to the displacement of the foveal cones (rare)
  - macropsia represents the increased perception of the size of images, which is caused by the crowding of foveal cones (very rare)
  - **different sizes of visual images in the 2 eyes**
  - change in color vision, especially in the blue-yellow axis, with late onset

Differential diagnosis of neovascular AMD

- Degenerative causes: severe myopia, angioid streaks
- Heredodegenerative causes: vitelliform maculopathy, fundus flavimaculatus, optic nerve drusen
- Inflammatory: ocular histoplasmosis, multifocal choroiditis, serpiginous choroiditis, toxoplasmosis, toxocariasis
- Tumorous: choroidal nevus, choroidal hemangiomatosis, choroidal metastases
- Traumatic: choroidal rupture, intense photocoagulation
- Idiopathic

Paraclinical evaluations in wet AMD[10]

AFG-highlights EPR dehiscence with long-term fluorescein retention, highlighting the edges of the lesion, with intense hyperfluorescence with rapid diffusion of fluorescein through the permeable Bruch membrane and pooling under the EPR

- ➢ Classic MCNV, with hyperfluorescence in the early phase, with increasing intensity and likeage, highlighting subretinal fluid if present
- ➢ Occult MCNV - early hyperfluorescence of neovessels, diffusion or "leakage" with fibrovascular detachment of the RPE and late leakage of

undetermined source, with stagnation of fluorescein in the subretinal space

- ***Indocyanine green angiography***It is useful in highlighting occult NVC, where well-demarcated hyperfluorescent areas called "hotspots" appear.
- ***Tomography****in optical coherence*OCT in which there are direct signs of the presence of choroidal neovascularization, and indirect signs (intensely reflective fusiform thickening between the retina and the external, hyperreflective band which is the EPR complex of the choroidal Bruch membrane)
  - occult forms may appear with protrusions of the RPE or with irregularities of the hyperreflective outer band; indirect signs are retinal thickening evaluated quantitatively, OCT provides additional information compared to other diagnostic methods and is a test for confirming and monitoring AMD pre and post therapy
- ***Optical coherence tomography angiography – angioOCT*** detects changes in light dispersion in a series of scans taken in rapid succession.

Therapeutic objectives in AMD [5,8,14,15,16]

AMD treatment is an adjuvant treatment to limit the major decrease in visual function, as there is no effective medical treatment for the recovery of visual function. AMD treatment is a treatment that blocks inflammation, blocks free radicals, inhibits the release of vasoforming factors, stimulants of choroidal neovascularization.

AMD treatment includes[2,6,14,15]:

- anti-VEGF treatment
- anti-inflammatory treatment
- antioxidant treatment
- laser photocoagulation
- radiotherapy
- transpupillary thermotherapy
- photodynamic therapy
- gene therapy
- surgical treatment
- artificial vision

AMD occurs through the correlation between primary degenerative lesions, related to the patient's age, associated with disturbances in cellular homeostasis. Cellular senescence is the initiating factor of AMD, and the progression of the disease is associated with multiple other, correlated mechanisms: oxidative stress, inflammatory factors, changes in immunity.

AMD treatment is a complex, prolonged treatment that must control the multiple disorders of the factors that generate serious eye disease.[15,17]

- **treatment must be individualized depending on the evolutionary stage of AMD**

Etiopathogenic treatment in AMD

- Periodic control of risk factors in people over 65 years of age.
- Treatment of oxidative stress and apoptosis
  - nutritional supplements – vitamins and minerals according to the AREDS study for the prevention of AMD progression: vitamin C 500 mg, vitamin E 400 mg, beta-carotene 15 mg, zinc 80 mg, cupric oxide 2 mg, omega 3 fatty acids, lutein/zeaxanthin.
- Control of lipid metabolism dysfunction with antilipemic medication.

Anti-VEGF medication It is a complex, sustained treatment and requires permanent therapeutic administration after a rigorous periodic ophthalmological check-up.

- **AMD with neovascularization has devastating effects on visual function**
- During the development of AMD, the balance between activator and inhibitor factors of angiogenesis changes with the appearance of neovascularization.
- Angiogenesis inhibitors - antiVEGF - reduce the growth of the neovascular membrane and help with edema resorption
- **AntiVEGF medication allows vision to be maintained in approximately 50% of patients** (it is possible up to 90%, but the elderly patient has multiple comorbidities and treatments, and AMD must be monitored and controlled periodically every 1-2 months to preserve vision, which is difficult for the elderly.
- **AntiVEGF medication allows for vision stabilization by inhibiting neovascular proliferation.**[2,8,18]

AVASTIN – Bevacizumab (2005)

- is a humanized monoclonal antibody that binds VEGF and suppresses angiogenesis, thus inhibiting neovascularization
- is indicated in: lesions below 2DP, moderately low VA, patient without FDT laser treatment, no scars, no occult CNV, good VA on the fellow eye
- used "off label", administered intravitreally every 4 weeks with favorable visual prognosis in early stages improves vision in 30% of patients, in advanced stages can stabilize vision
- OCT reveals decreased macular retinal thickness
- blocks the growth of neovascularization and leakage
- ranibizumab-like effect
- safe and effective in early and intermediate stages of wet AMD
- Side effects (minimal): eye redness, foreign body sensation, dry eye, itching, ocular discomfort, temporary blurred vision, myodesopsis, rare light sensitivity, eye infection, DR, cataracts.

LUCENTIS – Ranibizumab

- It is a recombinant human antibody fragment that inactivates all VEGF isoforms
- By blocking VEGF, it blocks the growth of new vessels and reduces leakage, major factors that cause vision loss in AMD
- is indicated in AMD with classic, minimal occult CNV
- intravitreal 0.3-0.5 mg every 24 months
- AV increases to 24% with 0.3 mg and to 33% with 0.5 mg and is maintained for 24 months
- The indication for treatment is limited by the high cost of the drug and the need to repeat the intravitreal injection at short intervals (1 month)

EYLEA – Aflibercept

- is a fusion protein with human portions of VEGFR-1 and 2
- ranibizumab-like effect
- 2 mg is administered every 2 months, after 1 year, every 12 weeks

MACUGEN – Pegaptamide (2004 (first used)

- is limited due to high cost, requires repeated injections, and sometimes must be combined with PDT
- AV can be preserved in 33% of patients

BROLUCIZUMAB – Beovu

- has small molecule with high affinity for VEGF A isoform
- inhibitor of CEGF receptor activation
- 6 mg every month for 3 months, then every 2-3 months
- similar to aflibercept

PEGAPTANIB – intravitreal 0.3mg every 6 weeks

SUTINIB

CONBERCEPT, Abicivar, OPT-302, RG 7716

Anti-inflammatory treatment

CorticosteroidsIt acts by stabilizing the blood-ocular barrier, blocking inflammation, blocking angiogenesis by inhibiting macrophages that release angiogenic factors.

Intravitreal implants:

- Retisert - fluocinolone acetonide
- Porsudex, Ozurdex – dexamethasone with effect from 6 months to 2-3 years
- Kenalog, triamcinolone acetonide

Anecortav is a corticosteroid derivative that inhibits angiogenesis by interfering with proteinases that promote vascular proliferation and endothelial migration.

- It is indicated in classic CNV and dry AMD to reduce the risk of lesion progression.

Inhibitive C3, C5 - ZIMURA

Reduction of apoptosis, angiogenesis – (VEGF A) Risutegamib

Reducing blood viscosity – rheopheresis
Extracellular matrix regulation - Laser photocoagulation treatment

Laser photocoagulation aims to destroy neovessels to limit their proliferation and extension, thus limiting the progression of AMD.

- The disadvantage of laser FC is related to the possible recurrence (39-76%) in the first 2 years after laser therapy, because the neovascular membrane is incompletely inactivated.
  - Occult NVC that is NOT visualized by AFG cannot benefit from laser treatment.
  - Thermal burns after laser application denature tissue proteins through coagulation necrosis; over time, pigmentary scar tissue develops; by destroying the ischemic extramacular retina, FC reduces the area of ischemia, which secondarily reduces the total production of vascular endothelial growth factor VEGF and reduces the stimulus for the occurrence of neovascularization[19]

Laser FC is indicated in juxta and extrafoveal NVC

Radiotherapy

- External beam radiation, proton radiation, brachytherapy with "palladium, strontium" plates
- The neovista system places the radiation source on the MNVC through an intravitreal approach.

Photodynamic therapy with verteporfin – PDT

It consists of the intravenous administration of a photosensitizing drug that localizes in the choroidal neovessels followed by local activation of the drug with a nonthermal laser.

- FDT is indicated in classic subfoveal MNVC, occult MNVC with signs of recurrent progression, rapid visual deterioration
- repeating the treatment
- therapeutic efficacy focused on the lesion
- currently rarely used
- FDT cannot restore lost vision, but it can slow the deterioration of central vision.

Gene therapy

It consists of implementing a functional gene to correct a genetic error or to introduce a new function into a pre-existing cell for the treatment of disease.

- In AMD, the correct choice of transfer genes that can inhibit neovascularization is necessary[20].

Surgical treatment

- ***Macular translocation*** limited or with 360 degree retinotomy (complete TMC)

  The macular surgery approach remains a promising therapy in well-selected cases despite possible postoperative complications, achieving clearer vision.

  - surgical treatment requires complex surgical maneuvers with lens extraction and implant, posterior vitrectomy, total retinal detachment, retinotomy, retinal rotation, retinal reattachment
- ***Surgical removal of subfoveal CNV***
  - has the best prognosis because it is kept free of RPE
  - after retinotomy, subretinal tissue plasminogen activator, air/fluid exchange
  - After surgical excision of subfoveal CNV associated with AMD, vision improves slightly and stabilizes in most patients.
- ***Autologous RPE transplantation***
  - It can partially restore vision in AMD with neovascularization, but surgical complications are important.

Combined treatments

- The basic medication in AMD is anti-VEGF medication, but there are also other therapeutic targets: PDGF, TNFα, PDGF
- Combination treatments aim to block angiogenesis and improve long-term visual prognosis. Treatment in AMD is a conservative treatment for prognostic improvement.

Artificial vision

Artificial vision with cortical, retinal prostheses.

There is no effective medical treatment at this time for AMD. Treatment in AMD is an adjunctive treatment to limit risk factors, block inflammation, block free radicals, inhibit the release of vasoforming factors, stimulators of neovascularization.

Conclusions

Age-related macular degeneration – AMD is a common cause of irreversible, progressive vision loss over the age of 65. AMD causes profound impairment of visual functions through degenerative lesions in the macula. AMD is caused by senescent degenerative lesions of the macular retina (decrease in photoreceptors, thickening of the Bruch membrane, thinning of the choroid) associated with subretinal fluid accumulation, detachment damage and RPE rupture with the appearance of classic and occult choroidal neovascularization (NVC), the atrophic form of AMD is more common (85%) and is accompanied by slow,

progressive loss of central vision. Exudative AMD is accompanied by subretinal fluid accumulation, the presence of neovascular choroidal membrane, detachment with RPE rupture, classic or occult choroidal neovascularization. Exudative AMD is associated with progressive irreversible loss of central vision. Current treatment of AMD is etiopathogenic and attempts to limit the anatomical/functional degradation of the eye in order to limit the rapid degradation of vision loss. Complex and prolonged treatment, single or combined, includes: risk factor control, oxidative stress treatment, antiangiogenic treatment, anti-inflammatory treatment, C3, C5 inhibitor, laser photocoagulation treatment, photodynamic therapy, surgical treatment, gene therapy.

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