Abstract
Age-related macular degeneration (AMD) is one of the main causes of visual deterioration in the developed nations. AMD comes in many forms but the most devastating form is the exudative (wet) type. Over the years, research into the pathophysiology of AMD has led to the discovery of multiple therapies such as the intravitreal injection of anti-vascular endothelial growth factor. The diagnostic tools to assess the type and progress of AMD have also evolved from slit lamp ophthalmoscopy examination to high resolution imaging of the retina with optical coherence tomography (OCT), fundus fluorescein angiogram, and OCT angiogram. In the future, the field of treating AMD will continue to expand with new drug therapies to slow the progression of dry AMD and limit the retinal photoreceptor damage from wet AMD.

Epidemiology
Age-related macular degeneration (AMD) is one of the leading causes of visual disability in individuals over 60 years of age in developed countries. Although neovascular (exudative), or more commonly wet, AMD is the type of advanced AMD with the most rapid and severe course, it fortunately accounts for only 10–15% of the disease. According to the earliest studies (Framingham Eye Study and Beaver Dam Eye Study), wet AMD was estimated to affect only about 1.5% individuals aged 52 years or older. Nevertheless, the global prevalence is expected to increase by the year 2040 [1, 2]. This high prevalence, indeed, represents a real economic burden, leading to an annual expenditure of USD 4.6 billion in the US alone [3].

The risk factors that facilitate the development of AMD can be divided in:
- Non-modifiable – for example, age (most important), ethnicity (non-Hispanic whites), family history (20–30%) and light;
- Modifiable – smoking, body mass index, diet and blood lipid level [4].

AMD is a complex neurodegenerative disease with intensive genetic, epidemiological and molecular studies beginning to uncover the mechanism of this pathology. Various associated genes were identified, including MMP9, CFH, CFB, C3, ARMS2, HTRA1, and APO-E. Despite the identi-
fication of various genetic and environmental factors involved in the development of AMD, some aspects of the pathophysiological mechanism remain unknown.

Pathophysiology and Natural History

Exudative AMD is characterized by choroidal neovascularization (CNV) that denotes the pathologic growth of new blood vessels from the pre-existing choroidal vessels into the subretinal space. The importance of CNV is that it is the determinant of the disciform process; the disc-shaped, subretinal, fibrovascular membrane ultimately progresses to cicatrisation, an loss of macular function.

The process of CNV formation in AMD can be divided in 5 steps:

Aging and Senescence of the Retinal Pigment Epithelium (RPE). A decrease in lysosomal activity of RPE accompanies aging, and age-related progressive accumulation of lipofuscin, a byproduct of photoreceptor outer-segment digestion by lysosome. This results in disturbance of RPE function.

RPE Basal Laminar/Linear Deposit (Drusen) Formation. Two types of drusens have been described: hard (nodular drusen) and soft drusen. The latter tend become confluent and, unlike hard drusen, appear to be an important associated and predisposing feature of CNV. Deposit between the RPE and Bruch’s membrane may block the diffusion of oxygen and nutrients from choriocapillaris to the photoreceptors.

The resulting hypoxia induces the expression of vascular endothelial growth factor (VEGF) to promote the formation of new blood vessels.

Enzymatic and Mechanical Disruption of Bruch’s Membrane. When the balance between proteolytic enzymes, such as matrix metalloproteinases and their inhibitors favors a proteolytic environment the Bruch’s membrane can be disrupted, allowing CNV to reach the sub-RPE space. Studies in transgenic mice support the contention that Bruch’s membrane disruption is required for the development of CNV.

CNV Membrane Formation. Choroidal angiogenesis is a multistep process that includes degradation of vascular basement membrane, proliferation and migration of choroidal endothelial cells, choroidal endothelial cell tube formation, and restoration of the vascular basement membrane. CNV occurs when there is an imbalance between proangiogenic factors and antiangiogenic growth factors.

Cicatricial Membrane Formation. CNV gradually evolve into paucicellular cicatricial membranes. The loss of cellularity is most likely due to apoptosis, or programmed cell death of stromal cells [5].

Conditions such as inflammation, complement activation, oxidative stress and lipid homeostasis have also been identified to be involved in the pathogenesis of AMD [6–12].

Classification of Neovascular AMD

The hallmark of the neovascular form of AMD is the presence of CNV. Any alteration of the BM, such as drusen, thickening of the BM’s inner aspect, or conditions similar to the non-neovascular changes associated with AMD can directly or indirectly increase the probability of BM disruption. This consequently allows buds of capillaries emerging from the choriocapillaries to gain access to the BM’s inner collagenous layer and/or subretinal space. Histologically, CNV is classified into 3 neovascular growth patterns:

- Type 1 neovascularization originates from the choriocapillaris and it is localised under the RPE (Fig. 1).
- Type 2 neovascularization also originates from the choriocapillaris but extends through the RPE and is localized in the subretinal space (Fig. 2).
• Type 3 neovascularization originates from the deep retinal capillary plexus and is located in the outer retina (Fig. 3).

While the origin, anatomic location and imaging features of both type 1 and 2 neovascularization are well established [13], type 3 neovascularization is more controversial [14]. The term type 3 neovascularization essentially encompass 2 previously described lesions: retinal angiomatous proliferation (RAP) and chorioretinal anastomosis. The first consists of a focal neovascular proliferation from the deep retinal capillary plexus, extending into the subretinal space and possibly communicating with a CNV. The latter, on the contrary, is defined as an intraretinal extension of type 1 neovascularization [15, 16].

**Diagnostic and Follow-Up Tools in Neovascular AMD**

Ophthalmoscopic examination remains the first approach to patients with suspected neovascular AMD. Clinical signs may include:
- Subretinal fluid (SRF).
- Subretinal or sub-pigment epithelial blood.
- Intraretinal hemorrhage (possible sign of RAP).
- Subretinal or intraretinal lipid.
- Subretinal pigment ring.
- Irregular elevation of RPE.
- Subretinal gray-white lesion (CNV lesion itself).
- Cystoid macular edema.
- Sea fan pattern of subretinal vessels.

Patients usually describe sudden onset of decreased visual acuity (VA), metamorphopsia and paracentral scotomata. Amsler grid self-testing by patients can be effective for detecting early neovascular AMD.

Fundus Fluorescein Angiography (FFA) is the gold standard for diagnosing CNV. Two major patterns are visible on FFA:

1. Classic CNV, which is an area of bright, fairly uniform hyperfluorescence identified in the early phase of the FFA that gradually increases

![Multimodal imaging pictures of right eye type 2 CNV.](image)