Review

Implications of the anatomical classification of the neovascular form of age-related macular degeneration

R. Gallego-Pinazo a,b,*, L. Monje-Fernández c, N. García-Marín a,b, M. Andreu-Fenoll a,b, R. Dolz-Marco a,b

a Unidad de Mátula, Servicio de Oftalmología, Hospital Universitario y Politécnico La Fe, Valencia, Spain
b Red Temática de Investigación Cooperativa OFTARED, Instituto de Salud Carlos III, Madrid, Spain
c Servicio de Oftalmología, Complejo Universitario Hospitalario de León, León, Spain

ARTICLE INFO

Article history:
Received 21 February 2016
Accepted 17 May 2016
Available online 23 September 2016

Keywords:
Age-related macular degeneration
Angiography
Optical coherence tomography
Choroidal neovascularization
Geographic atrophy
Antiangiogenics

ABSTRACT

Objective: To present the clinical relevance of the anatomical classification of the neovascular form of age-related macular degeneration (AMD).

Methods: Critical analysis of the current situation in the management of patients with neovascular AMD, by reviewing the available scientific evidence with regard to the classification of the types of neovascular lesion by angiography and optical coherence tomography (OCT).

Results: The classification of the neovascular lesion type secondary to AMD by OCT in type 1 (under the pigment epithelium), type 2 (subretinal), and type 3 (retinal angiomatous proliferation) lesions provides an added value in allowing to establish a long-term visual prognosis, an estimate of the number of treatments that a certain case may require, and a stratification of the risk for secondary geographic atrophy.

Conclusions: Incorporating OCT to the initial qualitative analysis of cases with neovascular AMD offers an added value superior to that provided by the angiography, with the relevant clinical implications.

© 2016 Sociedad Española de Oftalmología. Published by Elsevier España, S.L.U. All rights reserved.


* Corresponding author.
E-mail addresses: robertogallegopinazo@yahoo.es, robertogallego@comv.es (R. Gallego-Pinazo).

2173-5794/© 2016 Sociedad Española de Oftalmología. Published by Elsevier España, S.L.U. All rights reserved.
Implicaciones de la clasificación anatómica de la forma neovascular de la degeneración macular asociada a la edad

RESUMEN

Objetivos: Presentar la relevancia clínica de la clasificación anatómica de la forma neovascular de degeneración macular asociada a la edad (DMAE).

Métodos: Análisis crítico de la situación actual de la gestión de pacientes con DMAE neovascular revisando la evidencia científica disponible respecto a la clasificación de los tipos de lesión neovascular por angiografía y por tomografía de coherencia óptica (OCT).

Resultados: La clasificación del tipo de lesión neovascular secundaria a DMAE mediante OCT en lesiones de tipo 1 (por debajo del epitelio pigmentario), de tipo 2 (subretinianas) y de tipo 3 (proliferación angiomatosa retiniana), aporta un valor añadido permitiendo establecer un pronóstico visual a largo plazo, una estimación del número de tratamientos que un caso pueda requerir y una estratificación del riesgo de atrofía geográfica secundaria.

Conclusiones: Incorporar la OCT en el análisis cualitativo inicial de los casos de DMAE neovascular ofrece un valor añadido superior al de la angiografía con implicaciones prácticas relevantes.

© 2016 Sociedad Española de Oftalmología. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

The point has been reached in which discussing the neovascular form of age-related macular degeneration (AMD) has become totally ambiguous and abstract. New imaging techniques and the advent of intravitreal vascular endothelial growth factor inhibitors have modified the natural history of the disease from a progressive and inevitable deterioration of vision from diagnostic to the stabilization, and even improvement, of patients’ visual function.1,2

However, the group of neovascular AMD patients comprises many variables and variants that at this stage are impossible to identify, preventing us from establishing an adapted prognostic and therapeutic algorithm. The much touted “individualization” of treatments would then be closer to reality. In this context, the main role is played by optical coherence tomography (OCT).

Angiography with sodium fluorescein

In 1991 a classification of neovascular membranes associated to AMD was proposed on the basis of sodium fluorescein angiography (FAG) findings.3 This proposal was made in the context of the Macular Photocoagulation Study (MPS) registered as NCT00000158. At that time, it was proposed to classify lesions as follows:

- Classic choroidal neovascularization: choroidal hyperfluorescence areas with well-defined margins, distinguishable since early angiogram phases and characterized in late phases by pooling of contrast that blurs the limits of the neovascular membrane.
- Hidden neovascularization, comprising 2 possibilities:
  - Fibrovascular pigment epithelium detachment (PED): areas that are not as hyperfluorescent or as well defined as classic lesions in the transient angiographic phase, which at 60–120 s evidence stippled hyperfluorescence, and finally at approximately 10 min leakage or staining occurrences.
  - Late leakage of undetermined origin: late hyperfluorescence (2–5 min) speckled with contrast pooling, the origin of which was impossible to identify in previous angiogram phases.

Together with the above criteria, additional characteristics were defined that made it unfeasible to classify neovascular lesions by means of FAG, such as a significant hemorrhages, RPE hyperplasia or fibrotic tissue and serous PED. The researchers in charge of establishing said angiographic criteria in the MPS admitted encountering difficulties in highly relevant areas such as the ability to clearly differentiate lesion types in some patients, defining the precise limits of PED or identifying the specific areas of the neovascular lesion, among others. It is surprising that, with so many limitations, this classification survived and even today remains as the gold standard for classifying neovascular membranes in clinical trials with AMD patients.

Angiography with indocyanine green

The development of angiography with the inclusion of indocyanine green (IGA) partially improved the ability to recognize and define hidden lesions and contributed new concepts to angiographic semiology of neovascular AMD,4,5 including:

- Plaque: hypercyanescent areas larger than a disc area that could be adequately or poorly differentiated.
- Hot spot: hypercyanescent areas smaller than a disc area.
Fig. 1 – Tomographic sections of type I lesions secondary to age-related macular degeneration, showing the location of the neovascular complex between the retina pigment epithelium and Bruch’s membrane, as well as the subretinal fluid as the characteristic tomographic expression of this lesion type.

In addition, IGA allows the identification of 2 new entities associated to neovascular AMD: (1) polypoid choroidal vasculopathy, characterized by the presence of pseudoaneurismatic dilatations in the choroidal vessels comprised within a hypercyanescent plaque and (2) retinal angiomatous proliferation, characterized by intraretinal hypercyanescence and the eventual formation of retinchoroidal anatomosis.

Tomographic classification

In 2010, Bailey K. Freund published a brilliant editorial that dramatically changed the understanding of neovascular disease associated to AMD. By combining concepts known through histopathological studies with detailed visualization of OCT images, said author proposed a new classification of the lesions in secondary to neovascular AMD:

- Type I neovascular lesions, where tomographic sections evidence neovascularization confined to the space between the RPE and Bruch membrane, typically associated to the presence of subretinal fluid without cystic intraretinal fluid (Fig. 1). These are the hidden lesions defined by MPS with FAG, both fibrovascular PED and a late leakage of undefined origin, and with the lesions in the IGA plaque (Fig. 2). Eventually, type I neovascular lesions can develop polypoid dilatations in the neovascular tissue, giving rise to polypoidal choroidal vasculopathy (Fig. 3).

Fig. 2 – Multimodal image analysis of a patient with type I neovascular lesion, where sodium fluorescein angiography shows the presence of a hidden lesion.
- Type II neovascular lesions, where tomographic sections evidence neovascularization located in the subretinal space, between the neurosensory retina and the RPE, which has been eroded by fibrovascular proliferation (Fig. 4). These lesions are typically associated to the presence of intraretinal fluid, predominant also with variable density subretinal fluid component. It matches classical lesions defined by MPS by means of FAG and are difficult to identify in IGA (Fig. 5).
- Type III neovascular lesions, where tomographic sections evidence cystic intraretinal fluid and eventually serous or fibrovascular PED spotted hyper-reflective lesions (Fig. 6). These lesions match retinal angiomatous proliferation (Fig. 7).

**Clinic implications of the tomographic classification of neovascular age-related macular degeneration**

Initially, the classification proposed by Freund based on OCT\textsuperscript{16} seems much more precise and reproducible, but it also has other advantages. A laborious and detailed study has contributed a number of conclusions to neovascular AMD scientific literature that are summarized due to their significant clinical value.

Neovascular lesions secondary to AMD can be classified in a more precise and reliable manner combining FAG with OCT. Accordingly, despite the notable agreement between both

---

Fig. 3 – Multimodal image analysis of a patient with polypoid choroidal vasculopathy, in which indocyanine green angiography shows the presence of polypoid choroidal dilatations.

Fig. 4 – Tomographic sections of patients with type II lesions secondary to age-related macular degeneration, showing the location of the hyper-reflective neovascular complex in the subretinal space, between the neurosensory retina and the retina pigment epithelium, as well as cystic intraretinal fluid.
diagnostic systems, sensitivity for type III lesion detection, i.e., retinal angiomatous proliferation, is much higher with OCT when compared to FAG. Of 266 analyzed eyes, the prevalence between the different types of neovascular lesions was 39.9% for type I lesions, 9.0% for type II lesions and 34.2% for type III lesions. Overall, 16.9% of cases exhibited mixed neovascularization with 2 or more components in the lesion.

Similarly, the funduscopic characteristics of contralateral eyes of patients with unilateral neovascular AMD could provide information about signs of risk for developing each neovascular lesion type. The type I lesions could present in eyes with increased subfoveal choroidal thickness and without reticular pseudo-drusen (subretinal drusen-like deposits); the type II lesions in eyes with significant retina mentation increase, and type III lesions in eyes with diminished subfoveal choroidal thickness and abundance of reticular pseudo-drusen. This information is highly valuable for screening and early diagnostic procedures.

The anatomic classification of neovascular AMD could also enable more specific visual prognosis. The impact of associated geographic atrophy is well known in these patients, but the risk this involves changes in accordance with the type of lesion. Even though over half of patients with neovascular AMD treated with antiangiogenics develop RPE geographic atrophy, those with type I neovascular lesions are less prone to this complication, whereas patients with type III lesions exhibit a significantly higher risk. However, patients with type I neovascular lesions preserve better vision in the long-term than the rest, the worst visual prognosis being for type II.

Fig. 5 – Multimodal image analysis of a patient with type II neovascular lesion, where sodium fluorescein angiography shows the presence of a classic lesion.

Fig. 6 – Tomographic sections of patients with type III lesions secondary to age-related macular degeneration, showing communication between the neurosensory retina and the retina pigment epithelium with cystic intraretinal fluid and variable retina pigment epithelium detachment.
Conclusion

Considering the high burden of care that ophthalmology services must manage, largely due to the treatment on follow-up of patients with neovascular AMD, it is reasonable to generally utilize OCT as a tool for diagnostic and follow-up due to its reliability and sensitivity, thus preventing an invasive and time-consuming test such as FAG.

Similarly, the classification of the neovascular lesion type in patients with AMD provides an estimate of the long-term visual prognostic and accordingly to approach a more effective therapeutic strategy, being aware of the risk of developing geographic atrophy. The objective of OCT technicians should strive for excellency in the assessment of tomographic images of neovascular AMD patients due to the clinic implications that precise assessments involve.

In accordance with the above, FAG is left in a possibly residual background role in the context of the differential diagnostic of exudative maculopathies in elderly patients with doubts related to etiology. The advent of new angiography technology with OCT (OCT-A) paves the way for a new field of study of patients with neovascular AMD because, without having to administer endovenous contrast, a representation of the vascular pattern can be obtained in a matter of seconds, for the superficial and deep retinal capillary plexus as well as for the choriocapillary. The Coscas group has published a series of OCT-A patterns that allow differentiation between active and quiescent neovascular lesions based on the morphology of the neovascular mesh, the ramification pattern, vascular terminations, presence of anastomotic loops and perilesional halo. However, we are still far from being able to use the signs that OCT-A provides about neovascular AMD patients, while the OCT-based anatomic classification of these cases has already demonstrated its significant clinical value.

Conflict of interests

No conflict of interests was declared by the authors.

REFERENCES


13. Chang TS, Freund KB, de la Cruz Z, Yannuzzi LA, Green WR. Clinopathologic correlation of choroidal neovascularization demonstrated by indocyanine green angiography in a patient with retention of good vision for almost four years. Retina. 1994;14:114–24.


