Review

Towards the new spectral-domain optical coherence tomography based classification of age-related macular degeneration☆

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Abstract

Introduction: Age-related macular degeneration (AMD) is major social and health problem in industrialised societies. The contribution of the new diagnostic techniques, mainly spectral-domain optical coherence tomography (SD-OCT), has led to a better understanding of this disease.

Aim: To review the current clinical classification of AMD, to describe the new tomographic classification of wet AMD, and to review the new topographical findings in dry AMD.

Development: There are two classically described forms of AMD: dry and wet; there are also three progressive stages of severity: early, intermediate and advanced. This purely clinical stratification does not take into account any criteria based on SD-OCT. On the other hand, a new SD-OCT based classification has been proposed for choroidal neovascularisations secondary to AMD: types 1 (equivalent to occult), 2 (equivalent to classic), and 3 (equivalent to retinal angiomatous proliferation). Finally, SD-OCT offers exclusive and valuable information on the evaluation of dry AMD as regards subretinal drusenoid deposits, drusenoid pigment epithelium detachments, drusen coalescence, or the appearance of subretinal fluid in absence of choroidal neovascularisation.

Conclusions: Dry AMD exhibits a range of tomographical signs that also have their own relative risk of progression to advance stages of the disease. We need an international consensus in order to follow-up and treat in the best way all those patients with AMD, not only with the wet but also with the dry form.

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Hacia la nueva clasificación de la degeneración macular asociada a la edad basada en la tomografía de coherencia óptica de dominio espectral

Resumen

Introducción: La degeneración macular asociada a la edad (DMAE) es un problema sociosanitario de primer orden en las sociedades industrializadas. La aportación de las nuevas técnicas diagnósticas, fundamentalmente la tomografía de coherencia óptica de dominio espectral (SD-OCT), ha ayudado a comprender mejor esta enfermedad.

Objetivo: Recordar la clasificación clínica vigente de la DMAE, exponer la nueva clasificación tomográfica de la DMAE exudativa, y revisar los nuevos hallazgos tomográficos de la degeneración macular seca.

Desarrollo: Clásicamente se distinguen dos formas de DMAE: seca y exudativa; asimismo existen tres estados progresivos de severidad: precoz, intermedio y tardío. Esta estratificación puramente clínica de la enfermedad no hace referencia a criterios basados en la SD-OCT. Por otra parte, se ha sugerido una nueva clasificación de las neovascularizaciones coroideas secundarias a DMAE fundamentada en la SD-OCT: tipos 1 (equivalente a la oculta), 2 (equivalente a la clásica) y 3 (equivalente a la proliferación angiomatosas retiniana). Por último, la SD-OCT aporta una valiosa y exclusiva información en la evaluación de la DMAE seca sobre los depósitos drusenoides subretinianos, los desprendimientos drusenoides del epitelio pigmentario, la coalescencia de las drusas, o la aparición de flúido subretiniano en ausencia de neovascularización coroidea.

Conclusiones: La DMAE seca presenta un espectro de signos tomográficos que además pueden existir tres estadios progresivos de severidad: precoz, intermedio y tardío. Esto facilita la precisión de la enfermedad y puede ser un consenso internacional para poder seguir y tratar de la mejor manera a todos los pacientes englobados dentro del espectro de la DMAE, no solo en su forma exudativa, sino también en su forma seca.

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Introduction

Age-related macular degeneration (ARMD) is a social and health problem of first order in industrialized societies all over the world. Fortunately, it is one of the diseases which has seen the highest development of therapies in the last decade. The development of Spectral Domain Optic Coherence Tomography (SD-OCT) and the revolution brought about by antiangiogenic intravitreal treatments (mainly ranibizumab, Lucentis®; Novartis) have modified the diagnosis, follow-up and prognosis of ARMD patients, although mainly in the exudative or neovascular form. Without a doubt, knowledge about the dry or atrophic forms of ARMD must be updated in order to develop effective treatments for these forms.

Development

Clinical classification of age-related macular degeneration

Typically, 2 forms of ARMD can be differentiated: dry and exudative.1 Dry ARMD accounts for 9 out of every 10 cases of this entity and its typical changes consist in Bruch membrane thickening, drusen formation and progressive degeneration of the retina pigment epithelium (RPE). On the other hand, neovascular ARMD represents one out of every 10 cases of ARMD and is characterized by the development of choroidal neovascularization (CNV).

In addition, ARMD comprises 3 evolutionary severity stages6: the early stage is characterized by the presence of small or intermediate drusen (<124 μm, hard) and/or pigmentedary alterations of the retina pigment epithelium (RPE); clinically, it is generally asymptomatic or with very few visual symptoms. The intermediate stage is characterized by the presence of some large drusen (>124 μm, soft) and/or geographic atrophy of the macular RPE with central foveal involvement. At the clinical level, it courses with slight or moderate vision reduction, sub-optimal adaptation to darkness, loss of sensitivity to contrast or paracentral scotomae. Finally, in the case of dry ARMD the advanced stage is defined by the presence of geographical atrophies of the macular RPE with central foveal involvement that gives rise to a vision loss which, although being progressive and not acute, is certainly severe. In the case of neovascular ARMD, the development of CNV causes acute and severe visual loss, and this type of ARMD is included in the advanced stage of the disease.

The above purely clinical division of the disease does not make any reference to criteria based on the findings of SD-OCT, an instrument with which the analysis of the changes at the level of the interface between the external retina and the underlying choriocapillary can be done in a quick, simple and noninvasive manner. In our viewpoint said classification is insufficient to understand ARMD at this point in time.
Fig. 1 – Left column: neovascularization type 1 (NVC1). (A) showing neuroepithelium detachment in the retinograph. (B and C) fluorescein angiography (FA) depicts juxtafoveal hidden choroidal neovascularization. High resolution horizontal and vertical tomographic sections centered in the fovea, both in grayscale (D1–D2) and in color (E1–E2), show the subretinal fluid in the irregularity of the surface corresponding to the retina pigment epithelium. The 3D reconstruction of the neurosensory retina volume (F1) shows the alteration produced by neurosensory detachment (in yellow). On the other hand, the displacement map of the retina pigment epithelium against its natural position evidences a smaller volume of the retina pigment sub-epithelium neovascularization (F2).

Center column: neovascularization type 2 (NVC2). (A) showing macular vitelliform lesion in the retinograph surrounded by drusen. (B and C) fluorescein angiography shows a predominantly classic choroidal neovascularization. High resolution horizontal and vertical tomographic sections centered in the fovea show both in the grayscale (D1–D2) and in color (E1–E2) subretinal hyper-reflectiveness and the retina pigment epithelium defect in its location. The 3D reconstruction of the neurosensory retina volume (F1) illustrates the significant alteration produced by neovascularization. On the other hand, the retina pigment epithelium displacement map evidences against its natural position the volume of subretinal neovascularization (F2).

Right column: neovascularization type 3 (NVC3). (A) Macular thickening in the retina graph with outward lipidic exudation. (B and C) Fluorescein angiography shows retinal angiomaticus proliferation. High resolution horizontal and vertical tomographic sections centered in the fovea show both in grayscale (D1–D2) and in color (E1–E2) retinal pigment epithelium detachment with intraretinal cysts and subretinal fluid in the form of neuroepithelium detachment in the vertical sections (D2–E2). 3D reconstruction of the neurosensory retina volume (F1) illustrates the significant alteration produced by neovascularization. On the other hand, the displacement map of the retina pigment epithelium against its natural position evidences a discrete volume corresponding to the detachment area of said epithelium (F2).

**Tomographic classification of choroidal neovascularization**

Recently, Freund et al. have suggested the necessity of classifying neovascular ARMD according to the images obtained with SD-OCT (Fig. 1). On the basis of Gass' histological classifications, the authors propose the following tomographic types of CNV:

- **Neovascularization type 1**: located below the RPE without signs of infiltration of fibrovascular proliferation towards the subretinal space. This is the most frequent type of CNV in ARMD. The dysfunction of the external hemoretinal barrier (HRB) causes the accumulation of fluid and hemorrhages within and below the retina. Possibly, this could have a long evolution originated as a compensation to external neurosensory retina hypoxia but which, at a given point in time, begins to induce pathological changes due to increases in the size and flow of these choroidal neovessels. On the other hand, when type 1 neovascularizations mature, they could associate polypoid dilatation of some of the choroidal vessels, giving rise to the appearance of polypoidal choroidal vasculopathy. A highly relevant hypothesis suggests that it is not convenient to destroy said type 1 neovascularizations to the extent that their origin is benign and aims at supplementing the supply of oxygen to a retina which needs it. Its loss could produce the atrophy of the overlying neuronal tissue which would entail severe visual loss.

- **Neovascularization type 2**: located in the subretinal space above a damaged RPE invaded by fibrovascular proliferation. The association of this type of neovascularization with type I by means of SD-OCT is very frequent. The focal loss of HRB means that the recurrence of intraretinal fluid or chronification thereof occurs much more frequently.

- **Neovascularization type 3**: this type corresponds to retinal angiomaticus proliferation (RAP) with tomographic findings...
including the presence of serous RPE detachment with cystic retinal edema associated or not to subretinal fluid. The hyper-reflectiveness induced by the intraretinal neovascularization, typically extra foveal, can be evidenced.

**New tomographic findings of dry macular degeneration**

Drusen constitute the sign of identity of dry ARMD. The classification of drusen based on size is well-known (small <63 μm, intermediate; hard >124 μm) or based on its funduscopic characteristics (hard or well defined; soft or with undefined edges). To this we must add reticular pseudo-drusen or subretinal drusenoid deposits (SDD). Whereas genuine drusen are located typically below the RPE (between the baseline membrane of the RPE cells and the internal collagen layer of Bruch’s membrane), the SDD can be seen by means of SD-OCT in the subretinal space above the hyper-reflective strip corresponding to the RPE (Fig. 2). SDD constitute an independent risk factor for the progression of ARMD towards advanced stages.

The hard drusen do not have the same pathological relevance of other types of deposits and are considered to be some sort of physiological processes associated to aging. Their usually small size and yellowish appearance with well-defined edges make them easy to distinguish. Histologically, they are characterized by a nodular appearance and a lobulated smooth surface. They are made up of hyaline material which presents positive staining with Schiff periodic acid.

In turn, soft drusen are an ophthalmoscopic sign most frequently associated to advanced ARMD stages. They are easily recognizable due to their size, larger than 124 μm (about the diameter of a retinal vein when it exits the papilla) and due to their yellowish-grayish appearance with poorly defined edges. At the histological level, they are characterized by poorly defined edges and a tendency to group together. On the other hand, the thickening of the internal surface of Bruch’s membrane is typical, with the membrane being separated from the baseline RPE membrane. This hydrophobic space is potentially and lethally adequate for the subsequent development of CNV. The behavior of the drusen is dynamic and evolutionary with time. Accordingly, hard drusen can form clusters in the foveal region which produce alterations in the subfoveal RPE profile (Fig. 3). Chronic inflammation of said clusters can induce changes in the environment of the chorio-foveal interface which promotes the progression towards more advanced stages of ARMD. Therefore, the number and location of hard drusen must be considered and analyzed by means of SD-OCT.

On the other hand, soft drusen exhibit a clear tendency to group together in their growth, producing coalescent drusen or RPE drusenoid detachments. The difference between both entities lies in the size of the RPE area distorted by the deposit located under it. When this area exceeds a diameter of 1000 μm, it becomes an RPE drusenoid detachment (Fig. 4). The clinical behavior and the high risk of evolution to advanced ARMD stages associated to this disease (5 years after diagnostic, 19% develop geographical atrophy and 23% develop CNV) make it necessary to identify this type of injury. When the coalescence area does not exceed said 1000 μm diameter, these are coalescent drusen. As in the case of hard drusen, although ophthalmoscopically and even angiographically there are no signs of risk beyond the deposits, chronic severe alterations induced by these on HRB together with the tangential traction component upon RPE can produce an accumulation of fluid in the subretinal and intraretinal space. Here again, SD-OCT is essential in the evaluation of cases with coalescence of soft drusen, either in the form of coalescent drusen or RPE drusenoid detachment.

It seems evident that SD-OCT supplies much more information than that shown in the clinical classification of ARMD, not only in the neovascular form but also in the dry form. CNV are no longer classic or hidden but tomographic type I or tomographic type II. Classifying a case of ARMD with RPE drusenoid detachments or coalescent drusen with subretinal fluid as an intermediate stage does not seem very coherent because it would equal in relevance the existence of a single soft drusen isolated in the macula.
Fig. 3 – Coalescence of hard drusen (cluster). Tomographic section in color and grayscale corresponding to the horizontal image centered in the fovea, showing the changes induced in the external retina (red arrow tips) corresponding to the clustering of hard drusen evidenced in the retinograph.

Fig. 4 – Drusenoid detachment of the retina pigment epithelium. Retinographs and tomographic sections (horizontal in the central row, vertical in the lower row) evidence the confluence of soft drusen that make up a retina pigment epithelium drusenoid detachment of virtually the entire macula. Angiographic tests discarded the association of neovascularization. The fourth tomographic image showing the heterogeneous nature of the contents of the retina pigment epithelium detachment.
An additional hypothesis that could be formulated is related to the convenience of carrying out prophylactic treatment with regular antiangiogenic intravitreal injections. Knowing that the endothelial vascular growth factor (VEGF) is the main stimulating factor for the progression of ARMD towards advanced stages, it is not unreasonable to consider the possibility of inhibiting its expression to prevent said progression. Without a doubt, this requires going beyond the merely theoretical possibility because performing intraocular surgery in a presumably healthy eye borders on the unethical.

In summary, dry ARMD presents a range of tomographic signs that additionally involve risk of progression towards advanced stages of the disease. With SD-OCT we are able to visualize more than what can be classified according to the current stratification system. Accordingly, international consensus is required to advance and treat in the best possible way all patients comprised within ARMD, not only in its exudative form but also in its dry form.

Conflict of interests

No conflict of interests has been declared by the authors.

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