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Optical Coherence Tomography Angiography in Exudative Age-related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is one of the leading causes of visual impairment in the aging population, with an estimated incidence of 6.8% in the population age of 40 years and older. Fundus fluorescein angiography (FFA) remains the classic and gold-standard test for the diagnosis of NAMD. The widespread use of optical coherence tomography (OCT) in recognizing and following up eyes with NAMD has been reported in the recent years. Combining OCT with color fundus photographs was shown to attain comparable sensitivity to FFA in detecting NAMD. OCT angiography (OCT-A) is a non-invasive, evolving technology that provides depth-resolved images of blood flow within both the choroid and retina to an extent that surpasses all previous modalities. While FFA can only effectively assess blood flow in the superficial vascular layers of the retina. The best choice for imaging NAMD has remained a subject of debate. Most authors agree that multimodal imaging provide superior accuracy than a single test alone.

Keywords: Optical Coherence Tomography Angiography, Age-related Macular Degeneration, Fundus fluorescein angiography

Full-length article **Corresponding Author, e-mail: mahmoud.hassan.eg@gmail.com*

1. Introduction

OCT angiography (OCT-A) is a non-invasive, evolving technology that provides depth-resolved images of blood flow within both the choroid and retina to an extent that surpasses all previous modalities. While FFA can only effectively assess blood flow in the superficial vascular layers of the retina, OCT- A provides valuable information about blood flow in the deeper layers; this makes it of value in detection and follow-up of deep vascular lesions, such as CNV [1]. Consequently, the best choice for imaging NAMD has remained a subject of debate [2]. Most authors agree that multimodal imaging provide superior accuracy than a single test alone, but the availability of different modalities and the extra financial burden on both insurance and out-of-pocket systems limit the ability to perform multimodal imaging [3]. The aim of this study was to determine the specificity and sensitivity of OCT-A in detecting CNV lesions in eyes with suspected NAMD.

2. Age-related macular degeneration

Age-related macular degeneration (AMD) is a degenerative disease of the outer retinal layers, including the photoreceptors and retinal pigment epithelium (RPE), that occurs in the elderly population [4]. The disease is more common in the developed world, with an estimated incidence of 1.4 per 1,000 individuals in the European Union population [5].

3. Epidemiology

Epidemiological studies have shown that AMD is the third leading cause of visual impairment globally, only preceded by uncorrected refractive errors and cataract [6]. The condition has been increasing in incidence in the recent years, owing at least in part to an ageing population [5]. The number of people that will be living with AMD globally by the year 2040 is estimated at 300 million [4]. The prevalence of early or intermediate AMD in the European population aged 60 years and older was estimated at 25.3%, while late AMD was estimated to occur in 2.4% of the same population [5].

4. Risk factors

Multiple risk factors have been reported to collectively contribute to the development of AMD (multifactorial) [7].

4.1. Non-modifiable Risk Factors

Older age is by far the most important non-modifiable risk factor for the development of AMD, Genetic factors also seem to play an integral role in the development of AMD [4].

4.2. Modifiable Risk Factors

Higher dietary intake of vitamins (namely vitamin A, vitamin B6, vitamin C, leutin, β- carotene, and zeaxanthin), minerals (copper and magnesium), and saturated fatty acids was associated with a lower risk of developing AMD and Previous cataract surgery [8,9].

4.3. Pathophysiology

The pathogenesis of AMD entails four major processes. These processes are namely lipofuscin formation, drusen formation, local inflammation and neovascularization [10]. The initial stages of AMD consist of deposition of lipid material between the RPE and Bruch's membrane. When these materials coalesce, the focal accumulations are clinically visible and are termed drusen. The size of the drusen is important for disease staging. Small-sized drusen are those whose diameter is ≤ 63 μm, intermediate-sized drusen range in size between 63 μm and 125 μm, while large drusen are those whose diameter exceeds 125 μm [4]. Possible mechanisms of its development include disturbed autophagic pathways responsible for recycling proteins, immune dysregulation resulting in an inflammatory process, metabolic imbalance caused by genetic predisposition unmasked by environmental exposures, or a mixture of all the aforementioned factors [11,12].

CNV is responsible for approximately 90% of severe vision loss in eyes that develop AMD, although it represents only about 10% of the cases. Choroidal neovascularization (CNV) causes exudation of blood and/ or fluid into its layers with an end-result of a destructive macular scar and central blindness [13]. The vessels constituting the CNV are different from normal choroidal vasculature. They are fenestrated and leaky, allowing the egress of blood constituents (blood cells and serum) resulting in subretinal or intraretinal edema and/or subretinal or intraretinal hemorrhage. The fluid that leaks into the retina results in disturbance in the photoreceptor alignment resulting in disturbed vision, while the hemosiderin in the blood cells results in retinal toxicity. The end result is scar formation [14].

5. Classification

Several classification systems have been proposed for AMD, which reflects the variation between the clinical and research approaches towards the disorder [4].For neovascular AMD (NAMD), the classification systems have tremendously evolved over the years. The initially utilized angiographic classification of choroidal neovascularization (CNV) associated with AMD was based on fundus fluorescein angiography (FFA) to determine which subset of eyes would benefit from thermal laser photocoagulation to eradicate the entire neovascular lesion.

The term ''classic CNV" (also known as "well-demarcated CNV") was used for areas of early well-demarcated choroidal hyperfluorescence with later leakage and pooling into the subretinal space that obscures the boundaries of the CNV. Occult (or poorly-defined CNV) compromised fibrovascular pigment epithelial detachment (PED) and ''late- phase leakage of undetermined source'' [15].With the widespread use of optical coherence tomography (OCT) and the development of therapeutic options for NAMD (namely anti-vascular endothelial growth factors, anti-VEGF), the angiographic classification fell out of favor. Current classification schemes are based on OCT findings and include: Type 1 CNV: the neovascularization is completely below the level of the RPE (sub-RPE), Type 2 CNV: the neovascularization is partly or completely above the level of the RPE (subretinal) and Type 3 CNV: retinal angiomatous proliferation (RAP). Newer classification schemes attempt to employ the new technology of OCT-angiography (OCT-A) in classifying CNV lesions associated with AMD according to vascularity and blood flow density [16-18].

6. Clinical Picture

The clinical presentation of AMD depends on the type and stage of the disease. Dry AMD may be asymptomatic in the early stages until GA ensues and involves the central photoreceptors resulting in decreased visual acuity (particularly in near tasks), disturbed color recognition, and central scotomata. The nAMD type may also be asymptomatic if the CNV develops outside the foveal region or if minimal leakage occurs. Symptoms may occur abruptly if hemorrhage occurs or insidiously due to slow leakage; symptoms often include diminution of vision and/or metamorphosia. On examination, visual acuity is often impaired to a variable degree, but may not be affected on rare instances. Color vision testing may reveal subtle defects, and contrast sensitivity may be an early marker for the disease [19]. Fundus examination often reveals drusen in both types of AMD. GA is characterized by sharply demarcated hyperpigmented or depigmented areas within the macula. CNV often appears as pinkish orange lesion, with possible overlying exudation, subretinal or intraretinal fluid, and/or hemorrhage [1]

7. Management

It depends on the type and severity of the disease. Early stages of dry AMD may benefit from lifestyle modifications to slow down the disease process, including smoking cessation and adoption of a healthy diet [4]. There is no treatment available for late stages with GA. Trials are underway and future options may include stem cell transplantation and/or gene therapy [20]. Options for treating nAMD include intravitreal injection of anti-VEGF agents and verteporfin photodynamic therapy [4].

8. Diagnostic imaging in NAMD

Multimodal imaging has become indispensable in the management of cases with nAMD. The imaging modalities help with the diagnosis, selection of the optimum treatment modality, follow-up, assessment of response to treatment, detection of recurrence, and providing specific prognostic implications for each eye with the disease [21].
The gold standard method for diagnosis of dry AMD is color fundus photography, while that for diagnosis of NAMD is FFA. There is no gold standard method for assessment of activity of the CNV associated with NAMD, but the most widely accepted method is through the use of OCT [22].

8.1. Fundus Fluorescein Angiography (FFA)

For over 5 decades, FFA has been the method of choice for evaluating the vascular and capillary bed in eyes with suspected NAMD. Generally, FFA is warranted in AMD cases in the following situations: To determine the location,

size, and extend of the CNV, to guide treatment, to determine persistent or recurrent CNV or other retinal diseases following treatment and to investigate visual loss that is not explained by the clinical examination [23].

The classical angiographic classification of CNV depends on the pattern of leakage of CNV. An occult CNV appears as poorly defined, mottled, and patchy hyperfluorescence in early- phase angiogram, with leakage at the later phase of angiogram, forming larger hyperfluorescence dots [24]. The occult CNV is further classified based on its leakage characteristics found upon FFA examinations into two types [25]. Occult CNV type 1 is rather a fibrovascular PED and is often described in FFA imaging as stippled hyperfluorescence in early phases followed by poorly defined progressive leakage upon late-phase angiogram.Occult CNV type II is often described as late leakage from undetermined source and is described as CNV that does not appear as frank hyperfluorescence during early phase but shows speckled hyperfluorescence upon mid- to late-phase angiogram. The other type of CNV seen angiographically is the classical type. A third, more-recently recognized type of CNV is RAP lesions, also known as type 3 CNV. This type represents retinal capillary proliferation that is associated with a telangiectatic response. Features on FFA include intra- and sub-retinal leakage with indistinct margins, simulating an occult CNV. Focal intraretinal staining surrounded by retinal edema is suspicious of RAP. Occasionally, a clear retinal-retinal anastomosis, or retinal-choroidal anastomosis may be seen [24, 26]. According to location, CNV is classified as foveal (sub- foveal), juxta-foveal, or extra-foveal [1]. According to location, CNV is classified as foveal (sub- foveal), juxta-foveal, or extra-foveal [1]. With the widespread use of anti-VEGF for treating NAMD, the role of FFA in follow-up has declined significantly [22].

8.1.1. Disadvantages of FFA

Disadvantages of FFA in imaging NAMD include impairment in imaging the radial peripapillary or the deep capillary networks well [22].

8.2. Fundus Photography

Although color fundus photographs are more useful in dry AMD, they may be helpful in cases with NAMD as well. They help in finding landmarks, assessing serous detachments of the neurosensory retina and RPE, and in detection of the etiology of blocked fluorescence [25].

8.3. Optical Coherence Tomography (OCT)

OCT has become an indispensable and the most widely utilized modality in the assessment and follow-up of cases with NAMD. This is probably owing to their non-invasive nature, short capturing duration, and availability [27]. The sensitivity of OCT for detection of NAMD activity (85%) is higher when compared to FFA (71%).

Furthermore, the frequent (monthly) use of FFA is not recommended, since the modality is limited by its higher risk of adverse events [28]. OCT also has the advantage of quantitative assessment of the volumes of choroidal and retinal tissues, subretinal fluid (SRF) or intraretinal fluid, subretinal tissue, and/or PED volumes [29].

8.3.1. Prognostic Value of OCT in NAMD

OCT has allowed for the characterization of biomarkers that predict response to treatment and long-term prognosis. This has even recently allowed for the development of artificial intelligence- based technology to automatically identify patients with active disease and predict response to treatment [30]. Biomarkers can be majorly classified into retinal and choroidal, fluid biomarkers, and structural alterations biomarkers. Negative prognostic biomarkers include IRF, SHRM, outer retinal tubulations (ORT), photoreceptor layer integrity affection, and RPE tears [31].

8.3.2. Other imaging modalities for NAMD

ICGA allows visualization of the chorioretinal vasculature, in particular the choroidal circulation. It was demonstrated useful in the assessment of specific forms of AMD, namely polypoidal choroidal vasculopathy (PCV) [32]. PCV was first described early in the 1990s as characteristic subretinal nodular polypoidal vascular lesions on ICGA that often resulted in recurrent hemorrhages and exudation within or beneath the retina. ICGA reveals two basic vascular features: branching vascular intertwining below the Bruch's membrane, and aneurysmal dilations within the border regions [33].

8.3.3. Optical coherence tomography angiography

OCT-A allows the capturing of a clear, depth-resolved image of the retinal and choroidal microvasculature. It is based on the detection of the flow of blood cells within a static fundus and, through consecutive B-scans at the same section, creates a contrast output between static and non-static tissue [34]. OCT-A is a non-invasive diagnostic tool that does not need dye injection, thus it is theoretically free of adverse effects [35].

8.3.4. Operational Principle (How OCT-A Works)

While conventional OCT scans form an image cube through successive B-scans at different retinal locations, to detect motion the OCT-A must repeatedly image the exact retinal location multiple times. Repeated B-scans are utilized in the same location (row L1, N1 to N3) and the structural images are compared on a pixel-by-pixel basis in order to detect signal changes caused by the flowing red blood cells. These changesare displayed as a motion contrast image (rows L2 and L3). Comparisons can be made in pairwise fashion or in various combinations using algorithms to obtain a motion contrast image (row L3).

8.4. Limitations of OCT-A

Multiple limitations hinder the output of OCT-A. Image artefacts are the major ones. The following is a brief discussion of the major artefacts seen with OCT-A [37-38].

8.4.1. Shadow-graphic flow projection artifact

These are a result of fluctuating shadows cast by flowing blood in a superficial vascular layer that result in variation of the OCT signal in deeper, highly reflective layers.

8.4.2. Motion Artifact

This is due to difference in B-scans taken in the same region to detect flow. This difference is due to breathing, heartbeats, and patient motion.

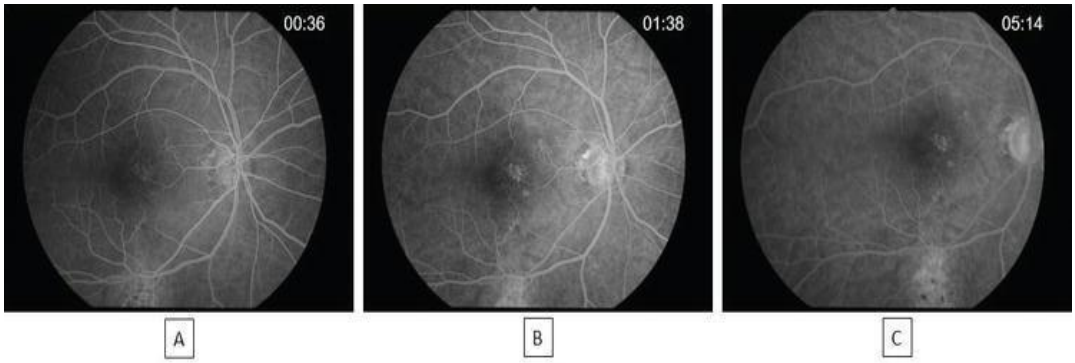

Figure 1. FFA characteristics of type 1 occult CNV (fibrovascular PED type). The early phase (A) shows a stippled hyperfluorescence followed by progressive increase of hyperfluorescence at mid-phase (B) and late-phase angiogram (C) [25].

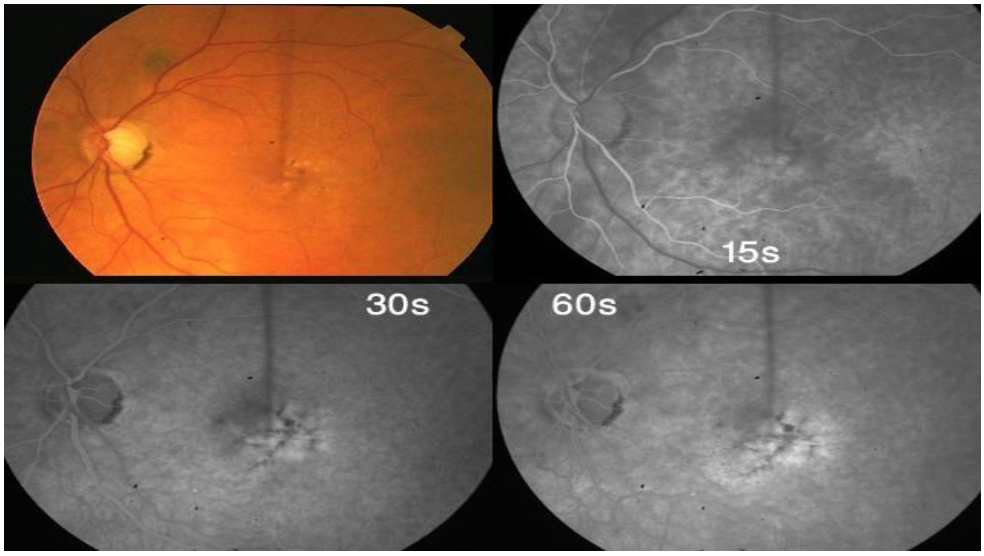

Figure 2. Color fundus photography and FFA images of type 2 occult CNV.

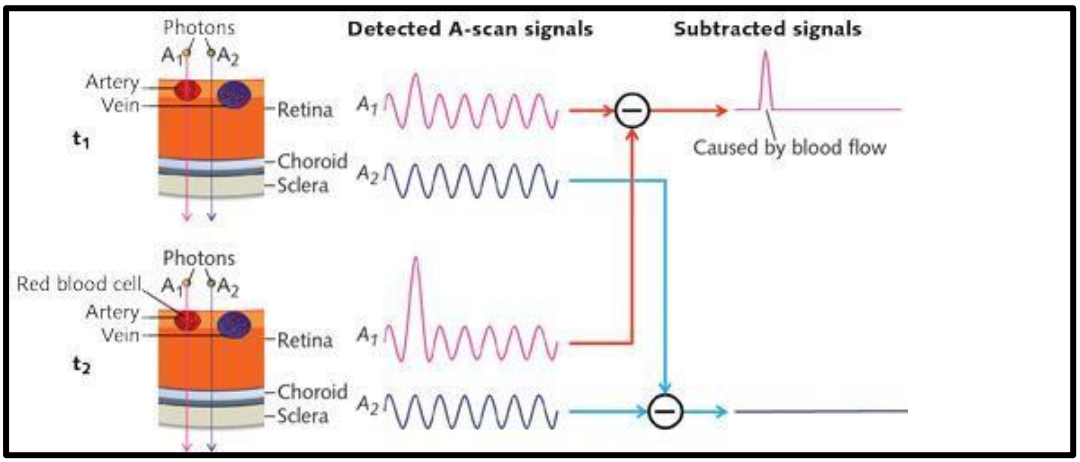

Figure 3. Schematic representation of how an OCT-A works [36]

Image Acquisition

Each assessment comprises two different sets of imaging, each consists of two raster volumetric patterns (one vertical and one horizontal) covering areas of 2 × 2 mm, 3 × 3 mm, 6 × 6 mm, or 8 × 8 mm [36].

Segmentation and Perfusion Indices of OCT- Angiography Image.

Segmentation of the retina into exact layers allows en- face visualization of the corresponding vascular supply for that layer. In-built software processes the image-information producing sets of perfusion indices (vessel density and flow index) for four en-face sections of the retina [36].

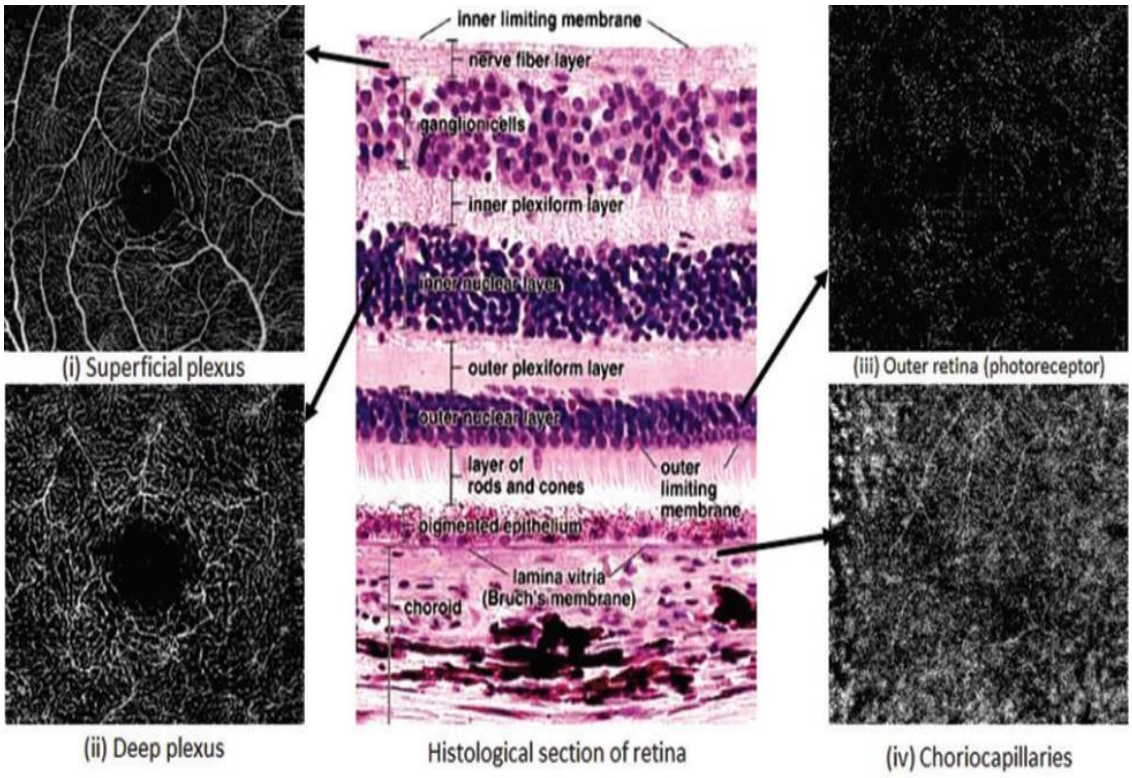

Figure 4. The different en-face zones obtained by OCT-A in relation to histology of the human retina [36].

8.4.3. Projection Artefact

These occur due to backscattering of residual OCT signals not reflected by moving RBCs from underlying tissues giving the appearance of ghost vessels of the superficial plexus.

8.4.4. Other artefacts

Banding: bands of increased intensity with bands of low intensity, segmentation artifacts: errors in automatic adjusting of slabs at the correct position, masking: shadowing of the superficial lesion obscuring deeper structures, unmasking: increased reflectivity of the deeper structures due to RPE atrophy**,** blink: A black zone within the image due to patient blinking and doubling and stretching of blood vessels.

9. OCT-A in NAMD

OCT-A alone provided 95% concordance with multimodal imaging (FFA, ICGA, and OCT combined) and that there was significant inter- observer agreement on OCT-A image analysis regarding the treatment decision. The features of nAMD on OCT-A can be classified into qualitative and quantitative ones [39-40].

9.1. Qualitative Features of NAMD on OCT-A

Shape, "Medusa" or "sea fan" or "glomelular" pattern, "Long linear vessels" or "filamentous pattern" and Indistinct network" pattern.

9.2. Other morphological variables: those include

Tiny branching capillaries, in contrast to rare large mature vessels, anastomotic loops and peripheral arcades versus the "dead- tree" pattern seen with inactive lesions and Perilesional hypointense halo [41].

9.3. Quantitative Features of NAMD on OCT-A

En-face OCT-A can be used for analysis of quantitative features of CNV, such as CNV area, vessel density, vessel length, number of CNV junctions, and lacunarity, using a validated, semi-automated software (Angiotool); these variables were recently demonstrated to correlate to response to treatment [42].

9.4. Types & Patterns of NAMD on OCT-A

Type 1 refers to sub-RPE lesions; type 2 refers to chorioretinal anastomosis, mixed type 1 & 2 with features of a fibrovascular PED and SHRM and type 3 or RAP lesion which are typically inner retinal lesions that expand outwards.

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