Imaging of choroidal neovascular membrane by optical coherence tomography Angiography

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Background: Optical coherence tomography angiography (OCTA) is a new safe imaging technique that uses motion contrast imaging to high-resolution volumetric blood stream information to produce angiographic pictures in a matter of seconds.
Objectives: We aimed to identify different patterns and types of CNV by OCTA and the relationship between these patterns and activity of CNV.
Patients and Methods: Fifty eyes of 50 patients presented with CNV had a regular diagnostic evaluation that included FA and/or OCT. Suspected cases with CNV underwent scanning by OCTA in this study. Patients with media opacity or bad image quality had been excluded.
Results: In 80% of patients, there is a statistically significant correlation between the patterns of CNV and its activity (P-value =0.0001).
Conclusion: OCTA is a critical technique for better characterizing the various forms and patterns of CNV, as well as the link between these patterns and CNV activity.
Keywords: Choroidal neovascular membrane; Multimodal imaging; Fluorescein angiography; Optical coherence tomography; Optical coherence tomography angiography.

DOI: 10.21608/svuijm.2022.141294.1319
*Correspondence: hanybhai@yahoo.com
Received: 28 May,2022.
Revised: 4 July,2022.
Accepted: 8 July,2022
Cite this article as: Somaya Ramadan Ali, Alaa F Elsayed, Ahmed Hassan Aldghaimy, Mohamed Sharaf (2022). Imaging of choroidal neovascular membrane by optical coherence tomography Angiography. *SVU-International Journal of Medical Sciences*. Vol.5, Issue 2, pp: 394-400.

Introduction

OCTA (optical coherence tomography angiography) is a safe imaging technique that utilizes motion contrast imaging to provide angiographic pictures in a matter of seconds. In order to generate an outline of the blood stream, The decorrelation signal (intensity or amplitude differences within the backscattered OCT signal) is compared with subsequent OCT b-scans obtained at the same cross-section using OCTA.

Because axial bulk movement from the patient is excluded, the movement of RBCs in the retinal blood vessels is represented by points of motion between several OCT B-scans (**Spaide et al., 2015**).

OCTA necessitates faster imaging speeds than the majority of currently available OCT frameworks. Traditional OCT imaging slow velocity causes small field, bad image resolution so more time is needed for scanning.Both fluorescein angiogram (FA) and indocyanine green angiogram (ICGA) are invasive procedures that need injection of a dye intravenously. Other disadvantages of FA and ICGA may restrict their widespread application; they are not ideal tactics to use regularly since they are intrusive, often costly, and time-consuming. Despite the fact that they are deemed safe, the dyes can cause nausea, unfavorable allergic responses and rare incidences of anaphylaxis. Besides allergic reactions, indocyanine green dye is not permitted to be used during pregnancy or in severely deteriorated renal patients. (**Kaylor et al., 2013**).

OCTA, on the other hand, could be a non-invasive way to get radiological data without dye injection. It takes about six seconds to get a three-dimensional scan. By scrolling the en-face pictures (OCT angiograms); the detailed vascular anatomy can be viewed.OCTA provides information about blood flow. If the comparative OCT b-scans are co-registered with the OCT angiograms, the examiner can move within this OCT angiogram like a cube scan so the exact location of pathology may be detected. OCTA can image the minute vascular anatomy of both retina and choroid, whereas FA can only image the retinal blood vessels and ICGA can only image the choroid.

Patients and Methods

Patients: This is an observational prospective study that includes patients who diagnosed with any type of CNV. Patients were chosen from Ophthalmology Department; Qena Faculty of Medicine and private clinics from 2018 to 2020.

a. Inclusion criteria: Any patients diagnosed with CNV by FA and/or OCT.

b. Exclusion criteria:

1. Patients who declined to participate in the research.
2. Patients with media opacity such as dense cataract and corneal edema.
3. Bad image quality.

Methodology

Participants were subjected to the following:

Clinical examination: the patients were already diagnosed with CNV, had been evaluated by F/A and/or OCT.

Imaging study: The DRI Triton SS-OCTA from Topcon was used to investigate the patients. The images were captured with a DRI Triton OCT device with a wavelength of 1050 nm and a scan speed of 100,000 A-scans per second, providing images with high resolution . These images were obtained from the central 3 × 3 mm of the fovea. The OCTA program detected movement between two OCT pictures. OCTA pictures were captured many times at the same site. After that, a registration technique was used to link these photos together. The automated layer segmentation boundaries on the en face projection angiography images were manually changed to better visualize the neovascular complex (**Yeo et al., 2019**). The device also contains an active eye tracker that reduces motion artifacts and collects several scans per second. All collected scans were captured with the (low eye-tracker) mode to save time during the assessment. According to the CNV localization, Topcon's OCTA analysis software was utilized to change the associated automated OCT segmentation lines for superficial inner retinal plexus, deep inner

retinal plexus, outer retina, and choriocapillaris. Resegmentation was done manually in the case of significant segmentation artifacts. For projection artifacts, the technology includes an automated artifact removal option **(Ahmed et al., 2018).**

Statistical analysis

The statistical methods used as follow:

A) Descriptive Statistics

A- Frequencies, percentages and data displays in order to enumerate and classify the data of the study variables.

B - Mean: to determine the average age of the patients in the study sample.

C- Standard deviation: It is used to determine the extent of dispersion of patients' ages around the mean.

B) Analytical statistics

1- Chi-square test in cross tables: to establish the correlation relationships between the study variables.

2- Significance level: It is used to determine the extent of the statistical significance of the relationship between the study variables according to the result of the chi-square test .

Ethical approval: All patients gave their informed consent. Only scientifically certified persons conducted the research. All patients' information was kept private.

Results

This study includes 50 patients with their mean ages were 49.70±12.97; (46%) were males, (54%) were females **(Table.1).** (56%) of patients were diagnosed as AMD, (36%) myopic CNV, (6%) inflammatory and (2%) Best disease **(Table.2).** (80%) active CNV, (20%) inactive CNV **(Table.3)**. (68%) sub-RPE, (20%) sub-retinal and (12%) mixed type **(Table.4)**. All choroidal neovascular membranes included in the study are subfoveal.

Choroidal neovascular membrane patterns were (6%) sea fan shape, (10%) caput medusa shape, (28%) indistinct pattern, (12%) dead tree inactive pattern, (8%) disorganized vascular loop pattern of myopic CNV, (28%) organized interlacing pattern. (2%) ring shaped vascular pattern of BEST disease and (6%) is the inflammatory pattern **(Table.5).**

Relationship between pattern of CNV and its activity: The relationship between disease pattern and its activity can be determined through the **(Table. 6).**

Table 1. details of patient gender

Variables	No	%
Males	23	46
Females	27	54
Total	50	100

Table 2. Details of CNV causes and their percentages in sample size

Variables	No	%
AMD	28	56
Myopic	18	36
inflammatory	3	6
BEST	1	2
Total	50	100

Table 3. Details of CNV activity

Variables	No	%
Active	40	80
Inactive	10	20
Total	50	100

Table 4. Details of CNV location

Variables	No	%
Sub-RPE (type1)	34	68
Sub-retinal (type2)	10	20
Mixed	6	12
Total	50	100

Table 5. Details of CNV patterns

Variables	No	%
Sea-fan	3	6
Caput medusa	5	10
Indistinct pattern	14	28
Dead tree	6	12
Disorganized vascular loop	4	8
Organized interlacing pattern	14	28
Ring shaped	1	2
Inflammatory	3	6
Total	50	100

It is clear from the table that there is a relationship between both CNVM pattern and its activity, where the value of X2 is 50 and the corresponding level of significance level is less than 0.01. Accordingly, there is a statistically significant correlation between the disease pattern, and the activity of the disease, whether it is active or inactive.

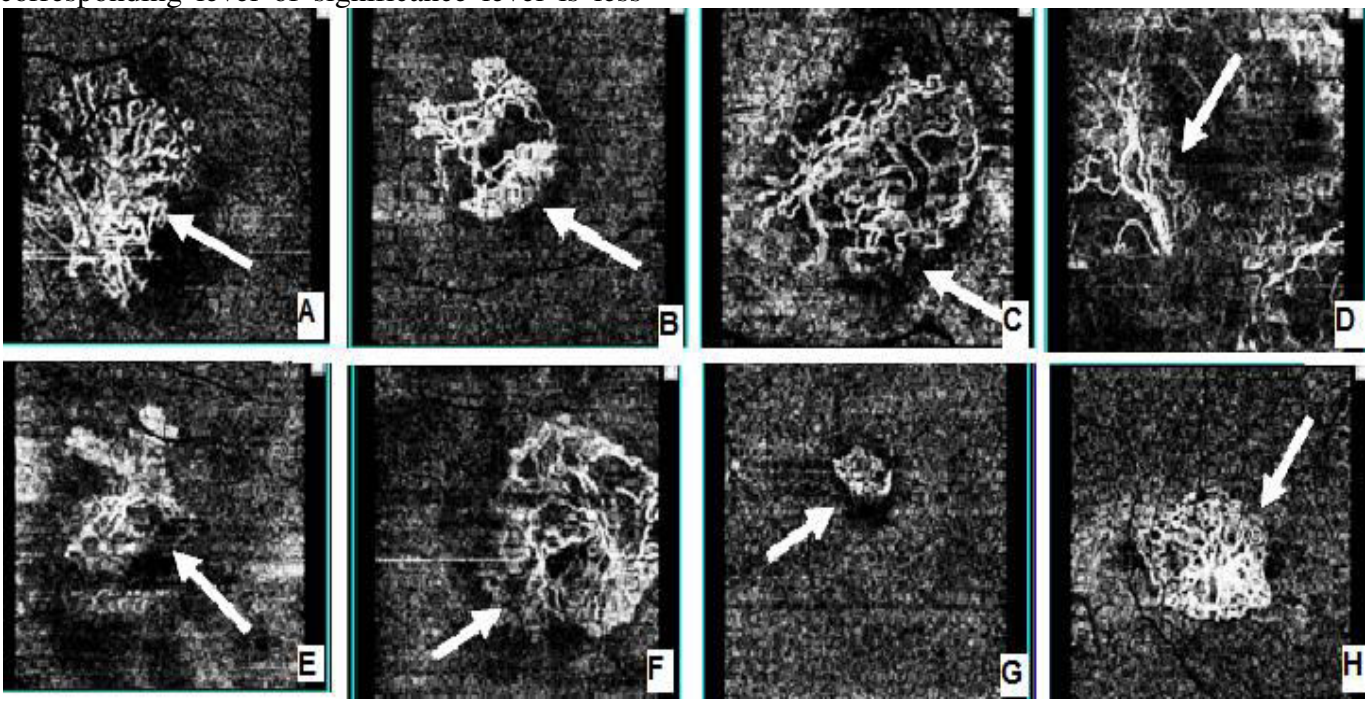

Fig.1. En face OCT angiography 3x3 outer retinal slabs are showing different patterns of CNV by OCTA by order from upper left to right: (A) Sea-fan pattern, (B, C) caput-medusa pattern, (D) dead tree pattern, (E, F) myopic CNV, (G) CNV due to BVM, (H) the inflammatory pattern (white arrows)**.**

Table 6. Relationship between CNVM pattern and its activity

Variables			CNVM activity		Total	X^2	df	P-value
			Active	Inactive				
CNVM pattern	**(sea-fan)**	**Count**	3	0	3	50	7	0.0001
		% of Total	6.0%	0.0%	6.0%			

	(caput-Medusa)	**Count**	5	0	5			
		% of Total	10.0%	0.0%	10.0%			
	Indistinct pattern	**Count**	14	0	14			
		% of Total	28.0%	0.0%	28.0%			
	Dead tree	**Count**	0	6	6			
		% of Total	0.0%	12.0%	12.0%			
	Disorganized vascular loop	**Count**	0	4	4			
		% of Total	0.0%	8.0%	8.0%			
	Organized interlacing pattern	**Count**	14	0	14			
		% of Total	28.0%	0.0%	28.0%			
	Ring shaped vascular loop	**Count**	1	0	1			
		% of Total	2.0%	0.0%	2.0%			
	Inflammatory pattern	**Count**	3	0	3			
		% of Total	6.0%	0.0%	6.0%			
Total		**Count**	40	10	50			
		% of Total	80.0%	20.0%	100.0%			

Discussion

OCTA is a non-invasive way to check for CNV. FA has an advantage (it does not exist in OCTA) which is that the individual photos can be captured within a second, whereas OCTA needs patients ' fixation for several seconds with no movement. Other characteristics like retinal vascular leak, peripheral ischemia, and retinal periphery assessment can also be evaluated using FA.

Many characteristics of the choroidal neovascular membrane have been studied. The medusa and the sea-fan shape, as well as the vague morphology which has no apparent pattern and without any details, are three kinds of CNV caused by age-related macular degeneration **(Kuehlewein et al., 2015).** A new classification for wet AMD: Pattern with fine vessels with high branching index, well-defined vessel pattern with less branching index, and another pattern without neovascular vessels detectable were identified **(Sulzbacher et al., 2017).** Miere et al found different types of the vascular tuft within a fibrotic scar: pruned vascular tree, tangled network, and/or vascular loop **(Miere et al., 2015).** Membranes were classified in the current research as: medusa in five eyes, sea-fan in three eyes, indistinct pattern in fourteen eyes and dead tree pattern in six eyes. Eyes with clinically active CNV had well-defined patterns (caput medusa and sea fan). While eyes with clinically inactive CNV had ill-defined vessel patterns (dead tree).

The long filamentous vessel patterns were observed in two different categories (the dead tree and the indistinct regressing type). The assessment of vascular tufts' patterns and their relationship to the activity is important in exudative AMD. Previous studies have looked at this relationship **(Coscas et al., 2015, Al-Sheikh et al., 2018, Karacorlu et al., 2019**).

If choroidal neovascularization appeared as a distinct lesion consisting of sea-fan shaped vessels, it was classified as well circumscribed; if it appeared as long-filamentous vessels without smaller vessels filling the spaces in between, it was classified as poorly circumscribed. OCTA plays an important role in myopic CNV detection. In this current study 18 of 50 eyes have high flow

vascular tufts, obviously visible using a 30 mm manual segmentation below Bruch's membrane. We identified two subtypes of myopic CNV: well defined interlacing pattern and ill defined disorganized one. Because of the manually segmented space underneath Bruch's membrane, tiny CNV identification is become easier with more image quality. It is difficult to identify myopic CNV in the choriocapillaris due to chorioretinal atrophy, posterior staphyloma, and choriocapillaris layer thinning. Thus 30 mm manual segmentation underneath Bruch membrane is an important step so the myopic choroidal neovascular membranes become more visualized. Although automatic segmentation has been calibrated in emmetropic eyes, when architectural changes are present, alterations and errors are likely. Aside from the OCTA-observed location of myopic CNV, segmentation errors were a continuous and difficult artifact for patients with high myopia **(Spaide et al., 2015).**

To obtain a correct connection between the B-scan depth imaging and the OCTA, this artifact was overcome by manual adjustment. CNV does not show the same way in people with posterior uveitis as it does in other retinal illnesses. It can be difficult to tell the difference between CNV and isolated inflammatory lesions due to pigmentary retinal changes induced by underlying inflammation or prior CNV formation. On OCT, the characteristic appearance of active CNV such as intra-retinal and sub-retinal fluids is unreliable in the case of inflammatory CNV. FA isn't always reliable, and distinguishing inflammatory lesions' staining and leaking from CNV leakage can be problematic. The pigmentary alterations might make the look of the FA and OCT harder to comprehend **(Levison et al., 2016).** Channa et al. presented the varied OCT findings in people with Punctate inner choroidopathy diagnosed to have isolated inflammatory lesions with no CNV below. When comparing the lesions described in the previous study to lesions that resulted in RPE elevation and photoreceptor loss in our patients, it's plausible that those patients had underlying CNV that wasn't obvious on FA (**Channa et al., 2012).**

In our study, inflammatory CNV represent only 6% of the study sample and appears as hyper reflective vessels at the level of the choroid which may extend to the outer retina. On OCTA, the underlying inflammatory CNV maybe masked by sub retinal/outer retinal hyper reflective alterations and indistinct RPE demarcation.

In the presence of vitelliform lesions, worsened by CNV, our study investigates the varied findings in the different layers of the retina in patients with BEST vitelliform macular dystrophy. Lipofuscin, a consequence of RPE breakdown, causes the 'egg-yolk' deposit found in patients' retinas **(Blodi and Stone., 1990)**. The retinal tissue and vasculature are both affected by this deposit. In the current research and according to OCTA, the patients had an abnormal FAZ and patchy vascularity loss in the superficial and deep layers of the retina, as well as a hypo-reflective centre in the choriocapillary layer due to shadowing from hyper-reflective vitelliform material.

Capillary dropout may be caused by the pressure applied by the lesion on the surrounding veins, which explains the patchy vascularity loss and hypo-reflective centre. Thus patients with CNV in BVMD have a hypo-reflective centre in the CC layer with hyperreflective material within this center surrounded by halo in the outer retinal layer as well as abnormal FAZ and patchy vascularity loss in the superficial and deep layers of the retina (ring shaped pattern).

Conclusion

OCTA represents a very important key technology in detecting different types and shapes of active and inactive choroidal noevascular membranes.

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