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OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY VERSUS DYE ANGIOGRAPHY IN POLYPOIDAL CHOROIDAL VASCULOPATHY

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Introduction :-
Optical coherence tomography angiography (OCTA) could be a valid tool to detect polyps and branching vascular network (BVN) in polypoidal choroidal vasculopathy (PCV) and thus allowing the analysis of the type, the morphology, and the extension of BVN in most of the cases.
Purpose - To determine the sensitivity and specificity of OCTA in detecting polyp and especially BVN, compared to fluorescein angiography (FA) and indocyanine green angiography (ICGA).

Methods - It is a prospective observational study. Patients with suspected PCV were recruited and underwent FFA, ICGA, and OCTA (AngioVue, Optovue, Inc.). Sensitivity and specificity of FA, with ICGA, were assessed and compared with OCTA.

Results – Fifty-four eyes were included clinically consecutively. Out of which, forty-three eyes of 36 patients were studied after confirmation by gold standard ICGA investigation . On ICGA ,21 eyes showed polyp and 16 eyes with polyp with BVN and 6 eyes with BVN only .Sensitivity of OCTA was 88% and specificity was 90%. Concordance between FA/ICGA and OCTA was very good for BVN (0.91; range 0.81–1.00).

Conclusions - OCTA showed high sensitivity and specificity for detection of BVN. Concordance between OCTA and gold-standard dye-based techniques was excellent. OCTA may represent a first-line noninvasive method for the diagnosis of BVN in PCV patients.

Key words - Idiopathic polypoidal choroidal vasculopathy (IPCV), choroidal neovascularization (CNV), Branching venous networks (BVNs), pigment epithelial detachments (PED),

INTRODUCTION

In the past, patients with clinical presentation of choroidal neovascularization (CNV) were usually diagnosed as having age-related macular degeneration (AMD). With the advent of indocyanine green

angiography (ICGA) and optical coherence tomography (OCT), idiopathic polypoidal choroidal vasculopathy (IPCV) has been reported increasingly worldwide. The characteristics of IPCV usually have two compositions; dilated branching venous networks (BVNs) and multiple terminal aneurysmal dilatations at the end of the venous networks.[1] Clinically, the patients usually have recurrent subretinal hemorrhage, subretinal fluid, subretinal lipid and disciform macular scarring, which mimics AMD and other diseases characterized by the presence of CNV.

Although, a typical case presents with recurrent acute submacular haemorrhage or serosanguinous pigment epithelial detachments (PED)[2] , it is now known that many present with features similar to exudative age-related macular degeneration (AMD), namely, submacular exudation, intra-retinal thickening, serous PED,fibrovascular PED, subretinal fluid collection, and disciform scar.[3] Some present with serous sensory retinal detachment, clinically indistinguishable from central serous chorioretinopathy (CSCR).[4] Still others present with patchy areas of retinal pigment epithelial (RPE) atrophy associated with intra-retinal pigmentary disturbance, often associated with visible, orange subretinal nodules.

Previous studies in Caucasians demonstrated that 4%–9.8% of patients presenting with CNV were finally diagnosed as having IPCV.[7–10] Studies in Asians reported a much higher percentage. In cases of suspected PCV, further diagnostic tests should be performed, as fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT). ICGA is also useful in the diagnosis of other specific forms of nAMD, retinal angiomatous proliferation (RAP) and polypoidal choroidal vasculopathy (PCV), characterized by lower incidence, more aggressive natural history, and poorer response to antiangiogenic therapy. ICGA provides anatomical details, detects the grade of activity, and plays a key role in the identification of the PCV. Spectral domain OCT (SD-OCT) is a noninvasive imaging technique, able to visualize structural changes of the neurosensory retina and the retinal pigment epithelium. Recently, OCT angiography (OCTA) has been introduced in the clinical practice. OCTA provides cross-sectional and three-dimensional imaging of the retinal and choroidal vasculature with micrometer-scale depth resolution [5, 6]. The potential role of OCTA in the first noninvasive diagnosis of PCV, combined with or without gold-standard dye angiographic techniques, is still object of debate.

The aim of the present study is to estimate the sensitivity and specificity of OCTA in assessing the presence of PCV, compared to gold-standard techniques (ICGA).

Materials and Methods

This clinical cross-sectional study was conducted on patients attending Retina services provided in our hospital. The study adhered to the tenets of the Declaration of Helsinki and patients signed written consent before being included in the study. We included both treatment & na¨ıve patients and those already treated with PDT. Patients presented clinically with subretinal bleed, subretinal nodule, neuro-sensory detachment in vitreo-retina services were taken and then ICGA was used as a definitive diagnosis of PCV in each patient, based on the presence of polypoidal lesions and branching vascular networks in ICGA which are the characteristic of PCV lesion.

The patients included were based on early sub retinal ICGA hypercyanescence (appearing within the first 5 min of ICG dye injection) and at least one of the following diagnostic criteria:- Nodular appearance of the polyp ,Hypofluorescent halo around the nodule, abnormal vascular channel(s) supplying the polyp ,Orange subretinal nodules corresponding to the hyper fluorescent area on ICGA, massive submacular haemorrhage. Patient who were demonstrating polypoidal changes and neovascular tissue on ICGA were further taken for SD-OCT and OCT-A imaging. Exclusion criteria were any other macular pathologies or comorbid ocular diseases (pathologic myopia), hazy media (e.g. dense cataract) because of the difficulty in acquisition of clear images, along with allergy or medical contraindication to intravenous dyes (fluorescein and indocyanine green) like liver disease, asthmatics, cardiac disease and pregnant women.

After taking informed consent each patient underwent a comprehensive ophthalmologic examination, including measurement of best-corrected visual acuity (BCVA), dilated slit-lamp biomicroscopy, FA and ICGA (Spectralis + HRA; Heidelberg Engineering, Heidelberg,

Germany), SD-OCT, and OCTA (AngioVue, Optovue, Inc.) in the same visit .The OCTA was performed using the AngioVue System, XR Avanti SD-OCT device (Optovue, Inc., Fremont, CA,USA), based on a high-speed SD-OCT platform that operates at 70,000 axial scans per second. Each B-scan in the OCT volume consists of 304 A-scans and is repeated twice at the same retinal location OCTA scan size of 3×3mm was chosen for our purposes; in case of partial visualization of the entire BVN network and polypoidal lesions, a larger (6×6 mm) image was obtained. Scans with low quality (i.e., if the subject blinked, in case of unstable fixation, or if there were many motion artifacts in the data set) were excluded and repeated until good quality was achieved. The AngioVue System offers automatic segmentation of the retinal and choroidal layers; each layer is displayed as the en-face angiogram and co-registered with the cross-sectional OCT B-scans. The software allows manually changing the depth and width of the inner and outer boundary lines, to better visualize PCV plane.

The sensitivity and the specificity of OCTA for neovascular detection (i.e., new diagnostic tool validity assessment) were estimated in comparison to ICGA, considered as the gold standard. To examine the concordance between ICGA and OCTA in assessing the presence CNV, Mc-Nemmar test was used. The analysis was repeated combining FA with ICGA. Statistical analysis, including descriptive statistics for demographics and main clinical records, was performed through The Statistical software namely SPSS 20.0 and MedCalc were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Also Chi-square/ Fisher Exact test were used to find the significance of study parameters on categorical scale between two or more groups. The significant figures suggestive significance (P value: $0.05<P<0.10$), moderately significant (P value:$0.01<P \leq 0.05$) and strongly significant (P value : $P \leq 0.01$)

RESULT :-

We included forty-three eyes affected by PCV were confirmed by ICGA. Forty patients with 54 eyes were suspected clinically for PCV and 36 patients were proven as PCV on ICGA. All patients were Indian with mean age of 69.38±8.389 years and overall ranges between 56-92 years. Out of these 20 (56%) were male and 16(44%) were female. According to ICGA, 6 eyes showed only BVN (14%) and 16 polyp + BVN (37%) and only polyp in 21 eyes (49%). So overall, polyp seen in 37 eyes (86%) out of 43 eyes and BVN in 22 eyes (51.2%) out of 43 eyes by ICGA. Among those with PCV, all patients had previously received anti-VEGF treatment ; 30 patients received PDT and the remaining 6 patients were treatment na¨ıve. No adverse event related to the diagnostic procedures was reported. The general characteristics of population in this study is described in Table1.

Characteristics	**Value**
Minimum age (in years)	52
Maximum age (in years)	87
Mean age (in years)	69.38 ±8.39
BCVA in LogMAR visual acuity range	1.78-0
Mean LOGMAR visual acuity	+0.60454.

Table1- The general characteristics of population in this study with BCVA in LogMAR.

On OCTA, polyp was recognized in polyp lesion in 20 eyes (46.5%) eyes and BVN in 23 eyes 56%. Doubtful polyps were seen in 13 eyes (30.2%) in OCT-A which was due to peripheral locations of PCV lesions or due to the submacular haemorrhage and haemorrhagic PED which obscured the site of lesion. The false negative polyps on OCT-A were 10 eyes and the BVN seen only in 23 eyes (53%) cases. 7 cases were evaluated as false negatives. Thus, sensitivity of OCTA was 88% and the specificity was 90%. BVN appeared on OCTA as either a main feeder vessel with numerous secondary anastomotic vessels or a large central trunk with poorly organized vascular branches. Concordance between OCTA and FA was good, and Cohen's kappa coefficient was 0.88 (0.81–1.00).

Combining ICGA to FA, kappa coefficient was 0.91 (0.81–1.0). Concordance was slightly lower when only polyp was included in the analysis.

The Characteristics of patients with PCV in this study		
Characteristics(Out of total 36 patients presented with PCV in either of eyes)	N	Percentage
1.Gender -Male - Female	 20 16	 56% 44%
2.Laterality -Bilateral -Right Eye - Left Eye	 7 16 13	 20% 44% 36%

Table 2 - Characteristics patients with PCV, N= Number of patients

Discussion

Our study aimed to investigate the capability of the noninvasive dye-less OCTA technique in detecting PCV lesions, compared to traditional dye angiography (FA and ICGA). In our study, OCTA demonstrated high ability to identify and visualize the polypoidal lesions, in accordance with FA whereas it is reverse in case of demonstration of BVN.

The polypoidal lesion were not seen in 10 eyes by OCT-A which were also not seen on FFA. On the contrary, OCTA did not provide any evidence of polypoidal lesions, depicted on FA, in 7% of eyes.Out of 20 eyes with confirmed polyps on OCT-A, only 4 eyes showed polypoidal lesion on FFA (11.6%) with p value = 0.079. On the contrary, OCTA did not provide any evidence of BVN in 22%of eyes (11 eyes) which were depicted on FA. Whereas all doubtful 6 eyes with BVN on OCT-A were clearly seen on FFA. Thus showing OCT-A clearly picked up the polyps comparing to FFA , which is reverse in case of BVN. Hence proving FFA detected the BVN more than OCT-A ($p < 0.001$).

False negatives presented a high serous-hemorrhagic PED, which limited the penetration of the OCTA signal under the RPE. In addition, the distortion of the retinal architecture caused by the RPE elevation creates difficulty in identifying the underlying neovascular complex, even after manual adjustment of the segmentation lines. True negative cases (10 eyes, 26%) featured haemorrhagic or serous PED without any associated BVN. A small number of cases in our series (two eyes, 3%) were evaluated as false positives, as the OCTA demonstrated the presence of a neovascular complex in the choriocapillaris layer, despite negative FA and ICGA. In the second case, we can speculate that traditional angiography imaging would have been flawed by some masking artifacts, hiding the presence of a neovascular network visualized instead on OCTA.

The sensitivity and specificity of OCTA in detecting PCV have been investigated in different studies. No article showed the sensitivity and specificity of OCTA till of our knowledge. At first, Inoue et al demonstrated the ability of OCTA to detect and quantify PCV in 7 subjects who have evaluated the spectrum of PCV by using OCTA and the polyps are visualized in only three of seven cases (42.9%) by OCTA[7]. Another study, Kim et al[8] mentioned that only 50% polyps were hyperreflective lesions on the outer retinal reference on OCTA. According to the authors, OCTA provided better visualization of the neovascular network with respect to ICGA, as images were not obscured by subretinal hemorrhage or other artifacts. Our results were partially in discordance with Kim's conclusions, as serous-hemorrhagic PED limited the penetration of the OCTA signal in our study population

Upon review of their false negatives, 3 out of 4 cases had a large subretinal hemorrhage. Differently, the authors concluded that OCTA does not perfectly detect the extent of CNV in cases or large subretinal hemorrhages. A study conducted by Kuehlewein et al.[9] on occult neovascular

membranes in nAMD concluded that OCTA identified the vascular complex in 75% of cases. Recently, Souedan [10] and his group evaluated the diagnostic accuracy of OCTA in detecting CNV compared to FA only and FA coupled to SD-OCT, graded independently by ophthalmologists with varying expertise levels[11]. In this study, OCTA was more sensitive than FA alone. However, when FA was combined with SD-OCT it remained more sensitive and specific (sensitivity of 92.72% and specificity of 90.91%) than OCTA alone (sensitivity of 85.62% and specificity of 81.51%). Our findings demonstrate that OCTA is able to detect the neovascular complex in most of the cases of nAMD, allowing the analysis of the morphology of the CNV in every single patient. According to the most recent literature, new vascular proliferation is usually characterized by well-defined complexes, with a main feeder vessel and numerous tiny anastomotic capillaries with thin walls and small diameter.

On the contrary, inveterate neovascular lesions, already treated with antiangiogenic therapy, show a thick central trunk with large anastomotic vessels, probably due to an arteriogenesis process during vessel branches expansion 11 Our findings substantially agree with this features of CNV. We can speculate that OCTA would display worse sensitivity in na¨ıve CNV, due to undetectable flow inside the small peripheral branches of the neovascular complex; further studies, specifically addressing na¨ıve nAMD, are warranted. The main novelty of the study is the calculation of agreement between OCTA and FA combined with ICGA, which was excellent in all the cases. A sub analysis, including only patients featuring type I CNV, showed a slightly worse correlation between the OCTA and the gold-standard. We can speculate that this is due to the presence of PED or RPE abnormalities in occult CNVs, which limited the correct visualization of the CNV under the RPE.

Limitations of the study are the small size of the sample and the heterogeneity of the included population. In fact, we considered patients with different types of CNV—most were type I CNV—and both na¨ıve and treated patients. It would be interesting to repeat the same analysis by dividing the patients into separate groups.

Conclusion

Our findings demonstrated that OCTA is a valid tool to detect the neovascular complex in PCV. In detail, OCTA allowed the diagnosis of polypoidal lesions in most of the cases analyzed, with the important exception of cases presenting subretinal hemorrhages or high serous-hemorrhagic PEDs. In routine practice, OCTA is still coupled with angiography for the diagnosis and the follow-up of PCV. Further studies are necessary to understand the possibility of noninvasive OCTA to completely replace conventional dye tests, avoiding their unpredictable side effects.

Conflicts of Interest

The authors have no proprietary, funding, or conflicts of interest to disclose.

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