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Non leaking Cystoid Macular Edema

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Abstract

Purpose;

The current study was conducted to report the discrepancy in findings between Spectral Domain-Optical Coherence Tomography (SD-OCT) & Fundus Fluorescein Angiography (FFA) examinations of the macular area regarding Cystoid Macular Edema (CME) in patients with diabetic retinopathy (DR) or retinal vein occlusion (RVO).

Patients &Methods;

This was a retrospective observational case study, involved 205 eyes of 179 patients. Eyes with diabetic retinopathy or retinal vein occlusion those underwent SD-OCT & FFAwere included in the study. All eyes had SD-OCT detected CME.

Results;

In the current study, SD-OCT detected CME was associated with diabetic retinopathy in 56.1% of eyes & with retinal vein occlusion in 43.9 % of eyes. CME associated with DR or RVO was undetected on FFA examination in 12.2% and 7.3 % of eyes, respectively.

Conclusion;

Both SD-OCT & FFA were complementary to each other in the detection of CME in eyes with DR or RVO. The use of both SD-OCT & FFA aided in the diagnosis, the choice of the treatment option &the final visual outcome.

Keywords: Cystoid, edema

Introduction

The term cystoid macular edema (CME) applies when there is evidence by slit-lamp biomicroscopy, fundus fluorescein angiography (FFA), and/or optical coherence tomography (OCT) of fluid accumulation into multiple cyst-like spaces within the macula. [1]

It is the final common pathway of several intraocular and systemic diseases. [2]

Common causes of CME are postsurgical (cataract, glaucoma and laser surgeries), intraocular inflammatory diseases, medications, diabetic retinopathy and retinal vein occlusions. Treatments of CME vary from observation, medical and surgical. The visual outcomes are basically related to retinal structural changes of the macula especially in the longstanding cases.[3]

On FFA, the appearance of CME is relatively well-defined as a petalloid, or honeycomb-like, pattern of hyper-fluorescence as a result of dye pooling in the cystoid spaces.[4]

CME could be easily detected by OCT independent of the angiographic degree of leakage, and OCT is at least as sensitive as FFA for identifying macular edema. [5]

Both FFA and OCT are highly sensitive in detection of macular edema (ME) of various etiologies, with OCT superior to FFA according to certain parameters. The noninvasive character of OCT compared with FFA makes it a much more popular option among patients and among some clinicians. With the extensive use of OCT for the diagnosis of ME, there is a tendency toward the less frequent use of FFA, especially during frequent follow-up visits.[6]

The current study was conducted to report the discrepancy in findings between both OCT & FFA examinations of the macular area as regard CME in patients with diabetic retinopathy (DR) or retinal vein occlusion (RVO).

Methods

This was a retrospective observational case study, where the presence of CME was evaluated on both FFA &Spectral Domain-OCT (SD-OCT) examinations in patients with diabetic retinopathy or retinal vein occlusion (branch or central). This study involved 205 eyes of 179 patients, 115 eyes had diabetic retinopathy & 90 eyes had retinal vein occlusion. **Inclusion criteria included;** eyes

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with diabetic retinopathy or retinal vein occlusion & CME detected on SD-OCT examinations with either diabetic retinopathy or retinal vein occlusion. **Exclusion criteria included;** opaque media hindering the performance of FFA or SD-OCT, the presence of extensive pre-retinal or intra-retinal hemorrhage at the macula area shadowing the underlying retinal structures on SD-OCT examinations, history of previous ocular surgeries or laser procedures, the presence of vitreo-macular traction or epiretinal membranes, the presence of other retinal pathologies apart from DR or RVO and the presence of positive history of drugs known to cause angiographically silent CME. **Spectralis OCT** (Heidelberg Engineering, Heidelberg, Germany) was used to provide cross-sectional images of the macular area with high resolution; scans were done on horizontal multiple line scans, vertical multiple line scans and radial line scans through the centre of the fovea.FFA was performed using **Topcon TRC-50EX** (Topcon Corporation, Tokyo, Japan) machine with the final print out included 4 images; one was the colored fundus photograph, an image in the early phase, one in the middle phase & the last was an image of the late phase of the angiogram(up to 10 minutes after intravenous injection). SD-OCT was performed on the same day or the next day to FFA.The presence of CME on FFA images (accumulation of the dye in a petalloid or honeycomb- like appearance within the macular area in the late phases of the angiogram) was evaluated &the outcome was **"CME present"** or **"CME absent".**Statistical analysis was performed using commercial software package [Statistical Package for Social Science (SPSS)] (SPSS Inc., version 16; SPSS, Chicago, IL).

Results

This study involved 205 eyes of 179 patients, 105 of them were females (58.66%). On SD-OCT, cystoid macular edema appeared as increase of the retinal thickness within the central macular area with loss of the normal foveal contour & the presence of rounded or ovoid intra-retinal hypo-reflective cystic spaces involved the central area of the scan.Of the 205 eyes with CME detected on SD-OCT examination, 115 eyes were diabetic CME (56.1%) & 90 eyes (43.9%) were CME associated with retinal vein occlusion (65 eyes (31.7%) withbranch retinal vein occlusion [BRVO]& 25 eyes (12.2%)withcentral retinal vein occlusion [CRVO]) **(Table 1)**.

Evaluation of their FFA pictures revealed the presence of the typical petalloid or honeycomb-like appearance of CME on the angiogram **"CME present"** in 165 eyes **(80.5%),** while 40 eyes **(19.5%)** had absent petalloid or honeycomb-like appearance of CME on the angiogram **"CME absent"** (no leakage of fluorescein in the known patterns of CME till the late phase of the angiogram) although their SD-OCT pictures revealed the typical cystoid appearance **(Figure 1)**.

This non-leaking CME on FFA was reported in 25 eyes with diabetic retinopathy **(12.2%)**&15 eyes**(7.3%)** withretinal vein occlusion (10eyes with BRVO & 5 eyes withCRVO).So, of the 205 eyes; 165 eyes **(80.5%)** had CME detected on both SD-OCT & FFA examinations **"OCT present& FFA present",** while 40 eyes (19.5%) had CME detected only on SD-OCT examinations & failed to be detected on FFA**"OCT present& FFA absent"**. Of these 40 eyes **(19.5%)** with non leaking CME, 25 eyes (12.2%) were Diabetic CME, while 15 eyes (7.3%) had CME associated with retinal vein occlusion (10 eyes (4.9%) with BRVO & 5 eyes (2.4%) with CRVO**) (Table 2& Figure 2)**.OCT was able to detect the cystoid appearance of the macular edema (CME) which was missing on FFA in 19.5% of eyes.

Table 1. Causes of the OCT- detected CME.

OCT- detected CME	Number of eyes	%
With DR	**115**	**56.1**
With BRVO	**65**	**31.7**
With CRVO	**25**	**12.2**
Total	**205**	**100 %**

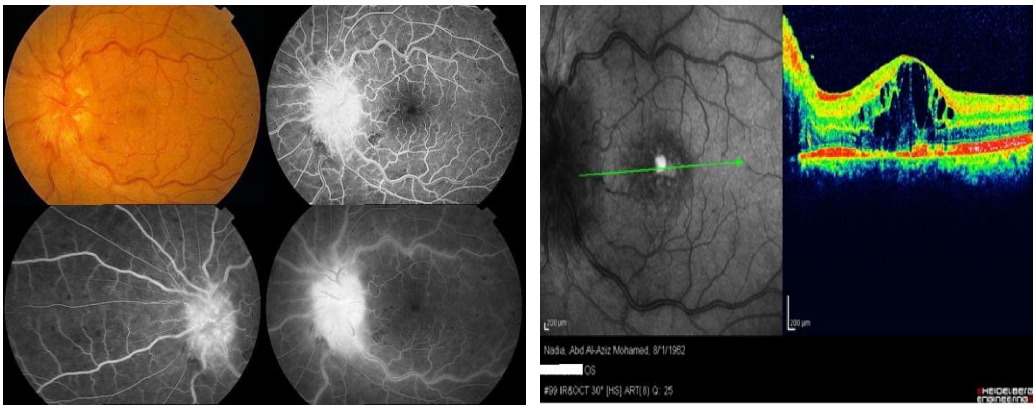

Figure 1.CRVO with angiographically silent CME which was detected on OCT exam.

Table 2. FFA & OCT findings regarding CME among included eyes.

CME detection	Number of Eyes	%
FFA present &OCT present	165	80.5%
FFA absent & OCT present with DR	25	12.2%
FFA absent& OCT present with BRVO	10	4.9%
FFA absent &OCT present with CRVO	5	2.4%
Total	205	100.0%

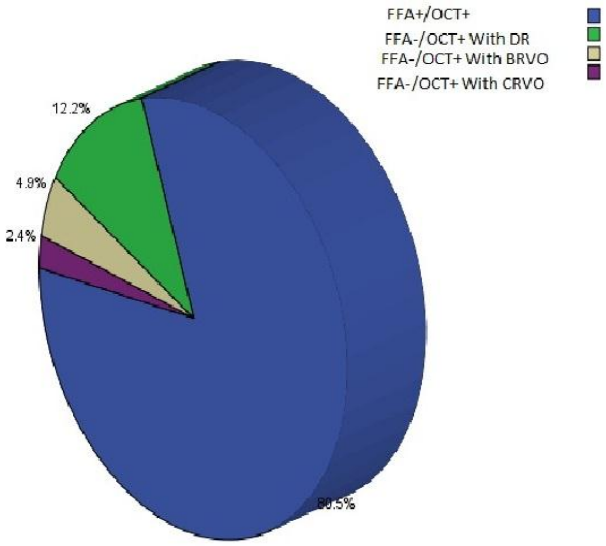

Figure 2.FFA & OCT findings regarding CME among included eyes.

Discussion

CME is a cause of severe visual loss that occurs in a variety of pathologic conditions, such as age-related macular degeneration (AMD), diabetic retinopathy (DR), branch or central retinal vein occlusion (BRVO/CRVO), and epiretinal membrane or vitreo-macular traction (ERM/VMT), and as a complication of intraocular surgery. In CME, two primary pathologic events occur: abnormal fluid accumulation and cystoid degeneration.[4]

Although the classic pathology of CME consists of large cystoid spaces in the outer plexiform layer of Henle, such fluid-filled spaces can be seen in various layers of the retina depending in part on the underlying etiology.[1]

CME is thought to result from disruption of the normal blood-retinal barrier. Leakage from parafoveal capillaries is demonstrated on fluorescein angiograms in a classic petalloid pattern in typical CME. Expansion of the intracellular fluid space may also lead to CME. Accumulation of fluid in the intracellular space may lead to CME without evidence of leakage on fluorescein angiograms.[7]

The ability to characterize the existence of CME is important in providing early treatment and knowing when to stop the treatment. This is critical in prevention of structural damages in long-standing CME that takes effect on the patient final visual outcomes. The conventional standard tool for the diagnosis of CME is fluorescein angiography, which is an invasive contrast-assisted modality.[3]

OCT has gained widespread popularity in detection of macular changes in various diseases. It is a safe, noninvasive, and rapid technology that provides objective documentation of foveal and retinal morphology. In some practices, it is an alternative to FFA in the follow-up of changes in retinal thickness. However, it does not provide information about the perfusion state of the retina and occasionally can miss foveal changes.[6]

OCT has provided useful information on the morphologic changes associated with macular edema. It provides cross-sectional images of the retina, which mimic the histological sections of light microscopy.[8]

Spectral-domain OCT (SD-OCT) is the latest generation of the technique and can provide images with high axial resolution and fewer motion artifacts. It allows identification of individual retinal layers approaching histological details with significant clinico-pathological information in several retinal conditions.[3]

There were discrepancies in the findings between OCT and FFA in detection of macular edema. There were cases in which FFA showed obvious patterns of macular leakage but lacked any corresponding changes in retinal thickness by OCT. The reverse phenomenon had been seen that in some cases FFA can miss intra-retinal fluid and, especially, sub-retinal fluid apparent by OCT. [6]

It has been reported that certain conditions may demonstrate significant intra-retinal cystoid spaces on OCT without leakage on FFA. Conversely, cases of CME had also been described that appear only on FFA and not on OCT.[4]

In the current study, SD-OCT revealed the characteristic appearance of CME in all included eyes while FFA revealed the petalloid or honeycomb-like appearance of CME in 80.5% of examined eyes while 19.5% showed absent petalloid or honeycomb-like appearance of CME on FFA till the late phase of the angiogram (angiographically silent or non-leaking CME on FFA of the OCT- detected CME).

In their study, **Ouyang et al.** [4] found that Three-Dimensional-OCT (3D-OCT) was more sensitive and reproducible than FFA for the detection of CME. Cystoid spaces were more frequently identified on 3D-OCT compared with FFA, regardless of underlying disease etiology. So, CME can be present in the absence of leakage into cystoid spaces on FFA.

Expansion of the intracellular fluid space may lead to CME, and accumulation of fluid in the intracellular space may lead to CME without evidence of leakage by FFA.[6]

Also, fluid accumulation may occur without obvious hyper-fluorescence if the source of leakage is very small and the fluorescein molecules leak slowly and disperse quickly into the space. For this reason, FFA may fail to demonstrate CME. [4]

In the present study, there were discrepancies between SD-OCT & FFA findings regarding detection of CME with DR or RVO (whether branch or central). The typical appearance of CME associated with DR or RVO could be detected in all included eyes (205 eyes) on SD-OCT examination of the macular area in contrast to angiographically silent CME on FFA examination till the late phase **"CME absent"**(40 eyes/205 eyes). This CME missed on FFA (19.5% of eyes) included eyes with diabetic retinopathy (12.2%), eyes with branch retinal vein occlusion (4.9 %) & eyes with central retinal vein occlusion (2.4%).

Jittpoonkuson et al. [3]found that SD-OCT was more sensitive than FFA in detecting CME structural changes and in characterizing complications of long-standing CME. CME was most commonly missed by FFA in patients with retinal vein occlusion and diabetic retinopathy in 18.52% and 33.33% of their cases, respectively.

Ozdeket al. [9] reported CME with diabetic retinopathy that was detected with OCT in 15.4% of eyes in their study (30/195 eyes), 63.3% of which (19/30 eyes) was not evident in FFA.

In the current study, eyes with vitreo-macular traction or epiretinal membrane were excluded from the study to exclude the tractional CME with angiographically silent macular edema associated with vitreo-macular traction syndrome.

Tractional CME is a subtle variant of the vitreo-macular traction syndrome with important clinical clues to the tractional etiology of this disorder may include metamorphopsia, subtle asymmetry of the cystoid foveal thickening, and the absence of leakage on fluorescein angiography. [10]

In the current study, eyes with retinal pathologies apart from diabetic retinopathy and retinal vein occlusion& patients with positive history of drugs known to cause angiographically silent CME were excluded.

CME without leakage on fluorescein angiography has been reported in cases of juvenile retinoschisis, Goldman-Favre disease and retinitis pigmentosa where cystic macular changes are noted on ophthalmoscopic examination but demonstrable normal permeability of the perifoveal capillaries is present.[11]

Angiographically negative macular edema also has been seen in drug toxicity.[6]

A subcategory of CME not associated with leakage on FFA and therefore abnormal capillary permeability has been described and is associated with toxicity to niacin.[11]

The lipid-lowering agent niacin may cause typical CME with no vascular leakage is seen on fluorescein angiography. The clinical appearance most likely represents intracellular fluid accumulation, as opposed to true edema (extracellular fluid).[12]

CME without capillary leakage is associated with the taxane drugs; docetaxel and paclitaxel.[13] Paclitaxel and docetaxel are members of the taxane family of microtubule stabilizing agents that has demonstrated clinical efficacy in multiple human malignancies.[14] Toxicity to Muller cells with subsequent intracellular fluid accumulation and subclinical leakage of extracellular fluid had been proposed.[7]

Ossewaarde-van Norelet al. [15] reported discrepant results of FFA and OCT in eyes with inflammatorymacular edema in 46% of eyes (51eyes/112eyes) and were present predominantly in mild degrees of macular edema. The FFA negative /OCT positive discrepancy occurred in 17 (15%) of 112 eyes. The FFA negative /OCT positive discrepancy may be explained by the initial accumulation of fluid in the intracellular spaces or in the sub-retinal space, leading to retinal thickening but no evident leakage.

FFA continues to be the criterion standard for studying macular pathological conditions because it provides anatomic structural diagnosis, vascular perfusion dynamics and evidence of blood-retinal barrier breakdown.[3] OCT is an important tool for detecting foveal changes that are not evident in eyes angiographically. [9]

Discrepancies between the FFA and OCT findings occurred because these two investigations revealed different ME characteristics, specifically morphologic and functional features. The ophthalmologists caring for the patients with ME should be aware of

possible pitfalls using only one of these imaging methods. [16]

In the present study, SD-OCT was more able to detect CME with DR&RVO than FFA. The use of both SD-OCT & FFA to detect macular edema is recommended.They were complementary to each other in detection of CME in eyes with DR&RVO. The use of both SD-OCT & FFA aided in diagnosis, choice treatment option & final visual outcome.

Conclusion

Both FFA and OCT are essential tools for examining patients with macular edema; they are complementary to each other.In the current study, the presence of CME on SD-OCT examination &its absence on FFA examination were noticed in some eyes.So, the use of both OCT & FFA helped in the diagnosis and consequently in treatment of the underlying pathology. If either of them was performed alone, the diagnosis of macular edema could be missed which could affect treatment options& final visual outcome.

References

1. **Johnson MW (2009):** Etiology and treatment of macular edema. Am J Ophthalmol., 147(1):11-21.
2. **Nagpal M, Nagpal K & Nagpal PN (2001):** Post cataract cystoid macular edema. Ophthalmol Clin North Am., 14(4):651-9, ix.
3. **Jittpoonkuson T, Garcia P M & Rosen R B (2010):** Correlation between fluorescein angiography and spectral-domain optical coherence tomography in the diagnosis of cystoid macular edema. Br J Ophthalmol., 94(9): 1197-1200.
4. **Ouyang Y, Keane PA, Sadda SR &Walsh AC (2010):** Detection of Cystoid Macular Edema with Three-Dimensional Optical Coherence Tomography versus Fluorescein Angiography. Invest Ophthalmol Vis Sci., 51(10): 5213-5218.
5. **Hajali M & Fishman GA (2009):** The prevalence of cystoid macular edema on optical coherence tomography in retinitis pigmentosa patients without cystic changes on fundus examination. Eye, 23(4): 915–919.
6. **Kozak I, Morrison VL, Clark TM, Bartsch DU, Lee RB, Falkenstein I, Tammewar A M, Mojana F &Freeman W R (2008):**Discrepancy between fluorescein angiography and optical coherence tomography in detection of macular disease. Retina, 28(4): 538–544.
7. **Joshi MM & Garretson BR (2007):** Paclitaxel Maculopathy. Arch Ophthalmol., 125(5):709-710.
8. **Catier A, Tadayoni R, Paques M, Erginay A, Haouchine B, Gaudric A &Massin P (2005):** Characterization of macular edema from various etiologies by Optical Coherence Tomography. Am J Ophthalmol., 140(2):200–206.
9. **Ozdek SC, Erdinç MA, Gürelik G, Aydin B, Bahçeci U& Hasanreisoğlu B (2005):** Optical coherence tomographic assessment of diabetic macular edema: comparison with fluorescein angiographic and clinical findings. Ophthalmologica, 219(2):86–92.
10. **Johnson MW (2005):** Tractional cystoid macular edema: A subtle variant of the vitreomacular traction syndrome. Am J Ophthalmol., 140(2):184–192.
11. **Teitelbaum BA & Tresley DJ (2003):** Cystic maculopathy with normal capillary permeability secondary to Docetaxel. Optom Vis Sci., 80(4):277–279.
12. **Schwartz SG & Mieler WF (2002):** Medications and retinal toxicity. Ophthalmol Clin North Am., 15 (4): 517– 528.
13. **Smith SV, Benz MS & Brown DM (2008):** Cystoid Macular Edema Secondary to Albumin-Bound Paclitaxel Therapy. Arch Ophthalmol., 126 (11):1605-1606.
14. **Murphy CG, Walsh JB, Hudis CA, Lake D, & Theodoulou M (2010):** Cystoid Macular Edema Secondary to nab-Paclitaxel Therapy. J Clin Oncol., 28(33): e684-e687.
15. **Ossewaarde-van Norel J, Camfferman LP& Rothova A (2012):** Discrepancies between fluorescein angiography and optical coherence tomography in macular edema in uveitis. Am J Ophthalmol., 154(2):233-239.
16. **Ossewaarde-van Norel J & Rothova A (2013):** Reply: To PMID 22541651. Am J Ophthalmol. , 155(3):609-10.