Validation of multicolor imaging signatures of central serous chorioretinopathy lesions vis-a-vis conventional color fundus photographs

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Purpose: The current study compares the ability of multicolor imaging (MCI) to detect the lesions of central serous chorioretinopathy against conventional color fundus photographs (CFP). Methods: It was a retrospective, observational case series of 93 eyes of 58 patients of central serous chorioretinopathy who underwent MCI and CFP. MCI and spectral-domain optical coherence tomography (SD-OCT) were performed using Spectralis SD-OCT system (HRA + OCT). CFP was obtained using FF 450 Plus fundus camera (Carl Zeiss Meditec, Jena, Germany). SD-OCT was considered gold standard for subretinal fluid (SRF) and retinal pigment epithelium detachment (PED). CFP was considered confirmatory investigation for fibrin and blue autofluorescence image (BAF) was considered gold standard to detect retinal pigment epithelium atrophy (RPE) atrophy. Results: CFP could detect SRF in 41 (44.1%) eyes. MCI detected SRF in 43 (46.2%) eyes. The sensitivity and specificity of MCI to detect SRF were 70.7% and 94.3%, respectively. PED was detected by CFP in 21 (22.6%) eyes and MCI in 27 (29%) eyes. The sensitivity and specificity of MCI to detect PED were 70% and 97.7%, respectively. CFP could pick RPE atrophy in 52 (55.9%) eyes whereas MCI was picked it in 78 (83.9%) of eyes. Conclusion: Both MCI and CFP were inferior to a gold standard in identifying the SRF, PED, and RPE atrophy. However, MCI was better than CFP in comparison with gold standard for these clinical findings in CSC. Thus, MCI seems to be a more valuable imaging tool compared to CFP.

Key words: Autofluorescence imaging, central serous chorioretinopathy, color fundus photo, infrared autofluorescence, multicolor imaging, reflectance imaging

Central serous chorioretinopathy (CSC) is characterized by serous retinal detachment and retinal pigment epithelium detachment involving macula. It predominantly involves young middle-aged males.¹ Since its first description in 1866 by Albrecht von Graefe as central recurrent retinitis, the knowledge about CSC has evolved a great length.[3] A significant proportion of patients with CSC have a self-limiting course with good recovery of vision. However it may become a recurrent disease resulting in permanent visual disability.[3] Though it is predominantly a choroidal pathology that involves retinal pigment epithelium and causes subretinal serous fluid, its etiology can vary from idiopathic to endogenous or exogenous corticosteroid, type A behavioral pattern and drug adverse effects such as phosphodiesterase-5 inhibitors.[4-7]

The diagnosis of CSC is mainly based on clinical examination along with optical coherence tomography and fluorescein angiography. Fundus autofluorescence and optical coherence tomography angiography have further been added to the multimodal imaging armamentarium for CSC.[8] Indocyanine green angiography is vital for the differentiation of CSC from polypoidal choroidal vasculopathy. In spite of astute clinical judgment and meticulous investigations, CSC is still considered as a great mimicker.[8] Various unrelated clinical conditions can mimic CSC, and CSC can mimic several unrelated retinochoroidal disease entities. For example, it is not uncommon for CSC with fibrin being referred as choroiditis and circumscribed or diffuse choroidal hemangioma being initially diagnosed as CSC.[9-11]

Multicolor imaging (MCI) is a novel, noninvasive retinal imaging technique available on Spectralis spectral-domain optical coherence tomography (SD-OCT) system (Heidelberg Engineering, Heidelberg, Germany).[12] Instead of white light used for conventional color fundus photography (CFP), MCI uses three laser lights to image the retinal layers. MCI has shown promising imaging capabilities in various retinochoroidal diseases such as epiretinal membrane, age-related macular degeneration, and optic disc changes.[11,13] MCI was better in delineating epiretinal membrane than conventional color fundus photography.[13] It was better in identifying various lesions of posterior segments such as geographic atrophy and optic disc swelling compared to CFP.[13,14] MCI imaging characteristics of CSC is meagerly

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Received: 22-Jun-2019  Revision: 12-Sep-2019  Accepted: 19-Nov-2019  Published: 20-Apr-2020

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Cite this article as: Saurabh K, Roy R, Goel S, Garg B, Mishra S. Validation of multicolor imaging signatures of central serous chorioretinopathy lesions vis-a-vis conventional color fundus photographs. Indian J Ophthalmol 2020;68:861-6.
reported in literature. He et al. from China have reported that MCI was superior in delineating area of subretinal fluid (SRF) compared to CFP. In a series of 25 eyes with CSC, Govindahari et al. from India have reported that MCI detected various lesions of CSC and pachyvessels better than CFP. Venkatesh et al. have compared MCI with CFP and fluorescein angiography and report that MCI was similar to fluorescein angiography in identifying focal leaks. They also report that MCI was able to detect retinal pigment epithelium detachment and trophy. We herein present the MCI signatures from a larger series of CSC, explaining the appearance of individual CSC lesions on MCI. We also aim to compare the ability of MCI to detect CSC lesions in comparison to CFP, SDOCT, and autofluorescence.

Methods
The study was carried between December 2018 and May 2019 in the retina clinic in eye hospital in eastern India. It was a retrospective study that included consecutive patients of CSC visiting the clinic. Eyes with active CSC defined by SRF and eyes with resolved CSC defined by PED and RPE atrophy in absence of SRF but with documented history of active CSC were included in the study. The study was approved by institutional review board and adhered to the tenets of Declaration of Helsinki. Demographic data such as age and gender were captured from the electronic medical records. All patients underwent comprehensive ophthalmic examination which included visual acuity assessment, anterior segment examination with slit-lamp and dilated fundus evaluation with indirect ophthalmoscope. Patients with media opacity due to cataract, vitreous floaters or hemorrhage, pre- or coexisting macular pathology, and inadequate image quality were excluded.

After pupillary dilatation, CFP was obtained with FF 450 Plus fundus camera (Carl Zeiss Meditec, Jena, Germany). CFP was viewed on the same machine with highest image setting. MCI and SDOCT were performed using Spectralis SD-OCT system (HRA + OCT) with mydriasis on same day. Multicolor and SD-OCT images were viewed using Heidelberg Eye Explorer software (version 1.7.1.0). The grading of images was performed independently by fellowship-trained retina specialists (RR and KS) who were blinded to each other's grading. In case of conflict the decision of a third-grader, senior retina specialist, was taken as final. Inter-observer agreement was high (kappa = 0.89). Four clinical features of CSC such as SRF, retinal pigment epithelium detachment (PED), fibrin, and retinal pigment epithelium atrophy (RPE atrophy) were studied. Each lesion was studied using CFP, MCI, SD-OCT, blue reflectance (BR), green reflectance (GR), infrared reflectance (IR), short wave or blue autofluorescence (BAF), and near-infrared autofluorescence (IRAF). Data were analyzed using SPSS software (version 20.0, SPSS, IBM, Chicago, IL).

Results
A total of 93 eyes of 58 patients (53 male and 5 female) of CSC were included in the study [Table 1]. The mean age of patients was 44.13 ± 8.85 years (range 29–76 years). All eyes were phakic. Out of 93 eyes, 58 (62.4%) eyes had active CSC defined by the presence of SRF whereas remaining 35 (37.6%) had resolved CSC defined by PED and RPE atrophy and documented history of active CSC without current SRF.

| Parameters                      | Value |
|---------------------------------|-------|
| Number of eyes/patients         | 93/58 |
| Mean age (years)                | 44.13±8.85 |
| Male                            | 53 (91.4%) |
| Female                          | 5 (8.6%) |
| Mean duration of CSC (months)   | 9.11±13.32 |
| History of focal laser treatment| 21 (22.6%) |

**SDOCT was considered confirmatory imaging modality to detect SRF and it detected SRF in all 58 (62.4%) eyes with active CSC. CFP could detect SRF in 41 (44.1%) eyes whereas MCI detected SRF in 43 (46.2%) eyes [Fig. 1]. Among MCI color channels, SRF was picked up most in GR (44; 47.3%). BAF detected SRF more than IRAF (23; 24.7% vs 20; 21.5%) [Table 2]. SRF was seen better on MCI compared to CFP and GR compared to BR and IR [Tables 3 and 4]. The sensitivity and specificity of CFP to detect SRF compared to SDOCT was 67.2% and 94.3%, respectively. For MCI, the sensitivity and specificity were 70.7% and 94.3%, respectively.**

The confirmatory imaging for fibrin was CFP which detected it in 7 (7.5%) eyes. MCI detected fibrin in five (5.4%) eyes. MCI color channels BR and GR picked up fibrin in a maximum of five (5.4%) eyes each [Fig. 2]. Among two autofluorescence imaging modalities BAF (5; 5.4%) picked fibrin more than IRAF (3; 3.2%). Fibrin was seen most distinctly on CFP compared to MCI and GR and IR compared to BR.

For the detection of PED, SDOCT was considered a confirmatory imaging technique. PED was detected on SDOCT in 50 (53.8%) eyes. It was detected by CFP in lesser number (21; 22.6%) of eyes compared to MCI which detected PED in 27 (29%) eyes [Fig. 3]. Further, IR was able to pick up PED in most numbers (27; 29%) of eyes. Both BAF and IRAF detected PED in equal number (22; 23.7%) of eyes. PED was seen better on MCI compared to CFP and IR compared to BR and GR. The sensitivity and specificity of CFP to detect PED compared to SDOCT was 54% and 100%, respectively. For MCI, sensitivity and specificity were 70% and 97.7%, respectively.

BAF was taken as a confirmatory imaging modality to detect RPE atrophy. CFP could pick RPE atrophy in 52 (55.9%) eyes whereas MCI was able to do so in 78 (83.9%) of eyes [Fig. 4]. Among MCI color channels, RPE atrophy was picked up most by IR (79; 84.9%) eyes. Compared to BAF (71; 76.3%), IRAF was able to pick RPE atrophy in more number of eyes (79; 84.9%). RPE atrophy was seen more distinctly on MCI compared to CFP and IR compared to BR and GR images. The sensitivity and specificity of CFP to detect SRF compared to BAF was 69% and 86.4%, respectively. For MCI the sensitivity and specificity were 98.6% and 63.6%, respectively.

Discussion
MCI has been used to image both superficial and deep retinal and choroidal pathologies. Muftuoglu et al. have studied epiretinal membrane with MCI and have concluded that it was visualized better on MCI compared to CFP. GR image was best suited to image epiretinal membrane among the three
Figure 1: (a) Color fundus photo (CFP) of the left eye shows subretinal fluid (SRF) marked with white arrows as a bleb at the center of macula. (b) SRF is seen more distinctly in multicolor image (MCI). The greenish hue over the SRF is due to retinal elevation. Margins of SRF (white arrow) are better delineated than CFP. Not the orange-pink coloration of retinal pigment epithelium atrophy (RPE atrophy) near the inferior margin of SRF (blank arrow) (c) Blue reflectance (BR) image shows the SRF as bleb. (d) Green reflectance (GR) image shows SRF better than BR. The temporal margin (white arrow) is better demarcated than BR image. (e) SRF is seen less distinctly than BR and GR images and is detected as hyperreflectivity at the site of bleb of SRF. Note the hyperreflective RPE atrophy (blank arrow) coinciding with same seen on MCI in (b). (f) On blue autofluorescence (BAF) image the foveal zone of normal hypoautofluorescence is reduced and hyperautofluorescence is seen inferonasal to fovea (white arrow) which coincides with zone of greenish hue seen on MCI. (g) The normal hyperautofluorescence at foveal due to maximum melanin content in infrared autofluorescence (IRAF) image is replaced by hypoautofluorescence due to the presence of SRF. Note the inferonasal hypoautofluorescence (white arrow) denoting RPE atrophy which is not seen on BAF and coincides with orange-pink discoloration seen on MCI in (b). (h) SD-OCT scan through fovea shows the SRF

Figure 2: (a) CFP of the right eye shows fibrin as light yellow lesion (white arrow) super temporal to fovea. Note the PED (blank arrow) superior to fovea. (b) Fibrin is seen as greenish hue (white arrow) superior to fovea. It is seen less distinctly than CFP. Note the PED (blank arrow) which is seen better than CFP. (c) Fibrin is seen as hyperreflective zone (white arrow) super temporal to fovea. (d) The hyperreflectivity of fibrin (white arrow) is seen more distinctly in GR image compared to BR. Note the PED (blank arrow) as hyperreflectivity superior to fovea. (e) IR image shows fibrin as irregular zones of hyperreflectivity (white arrow). PED (blank arrow) is seen more distinctly. (f) BAF shows fibrin as hyperautofluorescence (white arrow). (g) Fibrin is silent on IRAF image in this case. (h) Fibrin is seen as hyperreflective material (black arrow) in the subretinal space along with adjacent serous PED
reflectance images. Graham et al. have done a comparative analysis of MCI with CFP in age-related macular degeneration and report the sensitivity of 100% to detect atrophy, hypopigmentation, and fibrosis.[14] MCI aids in differentiation between true and pseudo optic disc edema by showing greenish hue extending well beyond optic disc margin in former.[15]

He et al. and Govindahari et al. have recently reported the MCI findings of CSCR.[16,17] They have found MCI to be useful in the diagnosis and monitoring of the disease. They have studied SRF, PED, RPE atrophy, and pachyvessels which is similar to our study. Our study includes a larger number of CSCR eyes and also reads CFP and MCI characteristics of fibrin along with other lesions of CSCR. The present study has assessed the ability of MCI to detect four distinctive CSC lesions; SRF, fibrin, PED, and RPE atrophy. SRF was seen as greenish hue over the retina on MCI. Keeping SDOCT as gold standard, MCI was able to pick SRF in more number of eyes than CFP. We believe that the green pseudocolor rendering of composite MCI assigned to elevated retinal contour helps in detecting SRF in CSC. Such greenish hue has also been reported in cases of retinal elevation due to macular pucker.[13]

On the other hand, detection of SRF on CFP is mainly based on difference in contrast between SRF and adjacent normal retina. This leads to a possibility of showing no SRF on CFP if the fluid layer was thin or retina adjacent to SRF too had poor contrast due to atrophy or pigmentary changes commonly seen in CSC. Among three reflectance images SRF was best seen on GR. Shallow SRF does not lift the retina to the extent it would be best picked by blue laser channel responsible for imaging vitreoretinal interface. Similarly, IR is not the best modality to pick SRF because it images retinal pigment epithelium and

| Table 2: Totals for each feature of central serous chorioretinopathy (CSC) across each imaging modality |
| --- |
| Lesion | CFP n (%) | MCI n (%) | BR n (%) | GR n (%) | IR n (%) | BAF n (%) | IRAF n (%) |
| SRF | 41 (44.1) | 43 (46.2) | 41 (44.1) | 44 (47.3) | 25 (26.9) | 23 (24.7) | 20 (21.5) |
| Fibrin | 7 (7.5) | 5 (5.4) | 5 (5.4) | 5 (5.4) | 4 (4.3) | 5 (5.4) | 3 (3.2) |
| PED | 21 (22.6) | 27 (29) | 21 (22.6) | 23 (24.7) | 27 (29) | 22 (23.7) | 22 (23.7) |
| RPE atrophy | 52 (55.9) | 78 (83.9) | 21 (22.6) | 27 (29) | 79 (84.9) | 71 (76.3) | 79 (84.9) |

SRF: Subretinal fluid, PED: Pigment epithelial detachment, RPE: Retinal pigment epithelium, CFP: Color fundus photograph, MCI: Multicolor image, BR: Blue reflectance, GR: Green reflectance, IR: Infrared reflectance, BAF: Blue autofluorescence, IRAF: Infrared autofluorescence

| Table 3: Comparison of visibility of various lesions of CSC between CFP and MCI |
| --- |
| Lesion | Image modality in which lesion is seen most distinctly |
| |
| CFP n (%) | MCI n (%) |
| SRF | 2 (2.2) | 44 (47.3) |
| Fibrin | 7 (7.5) | 0 (0) |
| PED | 0 (0) | 27 (29) |
| RPE atrophy | 0 (0) | 79 (84.9) |

Figure 3: (a) CFP or left eye shows PED as round elevation (white arrow). (b) MCI shows PED as a greenish lesion with pink ring surrounding it (white arrow). PED is seen more distinctly on MCI than CFP. (c) BR image shows PED as circumscribed zone of central hyperreflectivity at peak flanked by zone of hyperreflectivity (blank arrow). (d) GR image shows similar pattern as BR (blank arrow). (e) PED appears as hyporeflective lesion (blank arrow) surrounded by rim of hyperreflectivity on IR image. (f) BAF shows stippled hyperautofluorescence (blank arrow) at the site of PED. (g) PED appears as central hyperreflectivity (blank arrow) surrounded by hyperautofluorescent rim on IRAF image. (h) SDOCT line scan shows serous PED
beyond. This leaves GR as the most suited among component reflectance images to detect SRF.

PED is a deep lesion and an integral feature of CSC. In our series, MCI was superior in detecting PED in comparison to CFP. PED in CSC is serous and like SRF it is seen on CFP by the virtue of difference in contrast to adjacent normal retina. However, MCI detects PED as an elevation of retinal contour and renders it greenish hue which is darker than SRF because PED is present at deeper level than SRF. Smaller well-circumscribed size and surrounding pink ring differentiate PED from SRF on MCI. Among the reflectance images, PED was best detected on IR image due to its deeper location. On BAF image, PED appeared as area of stippled hyperautofluorescence with hyperautofluorescent rim. IRAF showed it as hypoautofluorescent center with hyperautofluorescent rim. Hyperautofluorescence on BAF may be due to RPE stress causing increased production of lipofuscin. IRAF shows PED atrophy as dark hypoautofluorescent patch due to depletion of melanin content in the RPE. Though MCI had high sensitivity to detect PED, it had a low specificity (63.6%) meaning it may overestimate RPE atrophy.

Our study has a few limitations. It is retrospective with limited number of eyes. We have not studied the fluorescein leakage patterns or tried to identify site of leak in our study which can be considered a drawback.

**Conclusion**

This is the first report of MCI signatures of fundus lesions of CSC. MCI had higher sensitivity and lower specificity compared to CFP in picking up RPE atrophy. Serous PED was detected better on MCI compared to CFP whereas MCI and CFP were similar in their ability to detect SRF. The findings of present study may have a role for MCI in multimodal imaging techniques for CSC. A study undertaken prospectively with larger number of CSC eyes will further validate the findings of our pilot study.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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