Optical coherence tomography angiography (OCTA) of retinal vasculature in patients with post fever retinitis: a qualitative and quantitative analysis

Srinivasan Sanjay1, Santosh Gopi Krishna Gadde1, Sameeksha Agrawal1, Padmamalini Mahendradas1, Nivedhitha Govindaswamy1, Ankush Kawali1, Chaitra Jayadev2, Sajjan Sangai2, Abhijit Sinha Roy3 & Rohit Shetty4

Post fever retinitis is a heterogenous entity that is seen 2–4 weeks after a systemic febrile illness in an immunocompetent individual. It may occur following bacterial, viral, or protozoal infection. Optical coherence angiography (OCTA) is a newer non-invasive modality that is an alternative to fundus fluorescein angiography to image the retinal microvasculature. We hereby describe the vascular changes during the acute phase of post fever retinitis on OCTA. Imaging on OCTA was done for all patients with post fever retinitis at presentation with 3 × 3 mm and 8 × 8 mm scans centred on the macula and corresponding enface optical coherence tomography (OCT) scans obtained. A qualitative and quantitative analysis was done for all images. 46 eyes of 33 patients were included in the study. Salient features noted were changes in the superficial (SCP) and deep capillary plexus (DCP) with capillary rarefaction and irregularity of larger vessels in the SCP. The DCP had more capillary rarefaction when compared to the SCP. The foveal avascular zone (FAZ) was altered with an irregular perifoveal network. Our series of post fever retinitis describes the salient vascular features on OCTA. Although the presumed aetiology was different in all our patients, they developed similar changes on OCTA. While OCTA is not useful if there is gross macular oedema, the altered FAZ can be indicative of macular ischemia.

Post fever retinitis is seen 2–4 weeks after a systemic febrile illness caused by either bacteria, viruses, or protozoa, in an immunocompetent individual1. Uveo-retinal manifestations include solitary or multifocal patches of retinitis, localised or generalised involvement of the retinal vessels in the form of beading of the vessel wall, tortuosity, and perivascular sheathing, and macular serous detachment or oedema, and optic nerve involvement1,2. Optical coherence tomography angiography (OCTA) is a recent advancement which is a non-invasive alternative to fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) to assess the retinal and choroidal microvasculature3,4. Dye-based angiography has been found to be useful in assessing retinal vascular involvement and in detecting occlusive complications in retinitis5. Extensive leakage of the dye may obscure adequate visualisation of microvasculature in eyes with retinitis. Compared with FFA and Indocyanine green angiography (ICGA), which are the current retinal/choroidal angiographic gold standards, OCTA acquires volumetric scans that can be segmented to specific depths, uses motion contrast instead of intravenous dye, can

1Department of Uveitis and Ocular Immunology, Narayana Nethralaya, 121/C, Chord Road, Bangalore, Karnataka 560010, India. 2Department of Retina, Narayana Nethralaya, 121/C, Chord Road, Bangalore, Karnataka 560010, India. 3Imaging Bio Mechanics and Mathematical Solutions Lab, Narayana Nethralaya Foundation, #258/A Hosur Road, Bommasandra, Bangalore, Karnataka 560099, India. 4Department of Cornea and Refractive Surgery, Narayana Nethralaya, 121/C. Chord Road, Bangalore, Karnataka 560010, India. s email: sanjaygroup24@gmail.com
especially with vascular pathology. It provides good delineation of the pathology along with volumetric data for the detection of pathophysiology, early diagnosis, treatment and determination of the progression in patients, especially with vascular diseases. FAZ and capillary density can be measured at both the SCP and DCP. Despite the imaging and evaluation of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) in several studies, OCTA, being rapid, non-invasive and repeatable, is performed both by automated and manual techniques, especially in case of gross oedema or poor scan features. Automated vessel flow density was used to measure the blood vessel measurement was used to measure automated vessel flow density. Segmentation was performed both by automated and manual techniques, especially in case of gross oedema or poor scan features. Local fractal dimension was used to represent the presence of vessels in OCTA scans. Calculation of the ratio of local fractal dimension of each pixel in an OCTA image to the maximum fractal dimension was done as described in earlier studies. Coloured contour, normalised ratio to provide a pictorial representation of an apparent probability index of the presence of vessel was done. Visual comparison of the normalized ratio map with the OCTA image was used to develop a scoring system. The vessel density was computed as a percentage, by counting all the pixels with a normalized ratio between 0.7 and 1.0 and then dividing by the total number of pixels in the OCTA image. Capillary dropouts is a significant parameter to distinguish between normal and diseased eyes. In this study, capillary dropouts were labeled as "spacing between large vessels" and "spacing between small vessels". Spacing between or around the large vessels with a normalized ratio between 0.0 and 0.3 were considered. Pixels in regions around closely packed small vessels, which may be branching out from a large vessel or surrounding small vessels, with a normalized ratio between 0.3 and 0.7 were termed as "spacing between small vessels".

Gadde et al. have described local fractal dimension to calculate vessel density and FAZ area in a normal healthy Asian Indian population. Quantification of vascular parameters can be affected by projection artefacts (PAs) in the DCP. Govindaswamy et al. have described the methodology to reduce the PAs. The inbuilt software from the instrument allows the users to choose flow and non-flow area on a selected layer. OCTA indices from local fractal analysis differentiate the large and small vessel regions of the non-flow area. Thus we used custom OCTA metrics rather than using inbuilt software of the machine for the quantitative analysis.

Deep capillary plexus was found to be the affected initially in most of the retinal vascular disorders. We have previously reported that a significant vascular loss in different grades of diabetic retinopathy at the level of deep vascular plexus after removal of projection artefacts. Before the removal of projection artefacts, this was not apparent with the presence of projection artefacts. Our approach is software-based where a normalized...
cross-correlation between superficial and deep layer was estimated as a scaling factor to subtract the projection artifact. Hence, it can be presumed that irrespective of the instrument used to obtain and the algorithm used to re-construct angio images, the software-based approach would provide comparable results.

**Conference presentation.** Oral presentation at a meeting: Preliminary data at 35th Singapore-Malaysia Joint Meeting in Ophthalmology in conjunction with the 1st Asia–Pacific Ocular Imaging Society Meeting, held from 17 to 19 January 2020 at the Academia, Singapore General Hospital Campus.

**Informed consent.** Written Informed consent was obtained from all study subjects.

**Results**

Thirty-three consecutive patients with post fever retinitis (46 eyes, 13 bilateral) in the age 18–73 years (median age 40 years) who underwent OCTA between August 2018 and July 2020 were included in the study (Male:Female—17:16). The presumed etiologies for the post fever retinitis were dengue, rickettsia and typhoid fever based on the serology as illustrated in Table 1. The predominant clinical picture was of multifocal retinitis with macular oedema.

**Quantitative analysis.** Figure 1 shows the pre and post removal of projection artefact (PAs). In the SCP, the large vessel spacing was increased with small vessel spacing similar to a normative data. The DCP was more affected in terms of small and large vessel spacing and the vessel density was also significantly lower.

The FAZ was not affected during the acute stage in both the SCP and DCP. Figure 2 shows the fractal analysis after removal of the artefacts. The vascular parameters of small and large vessels in the superficial capillary and deep capillary layers are shown in Table 2.

**Qualitative analysis.** Salient features of active retinitis on OCTA included changes in both SCP and DCP with capillary rarefaction and irregularity of larger vessels in SCP. Pruning of the vessels was noted in SCP and DCP. The FAZ was altered with a broken perifoveal network suggestive of macular ischaemia on 3 x 3 mm scans in patients with active retinitis and areas of retinal thinning on OCT. Capillary rarefaction was better appreciated in the DCP than SCP. Bright hyper-reflective material on OCT was seen corresponding to the areas of capillary rarefaction and artefacts at DCP. The choriocapillaris (CC) layer had a loss of the normal coarse architecture corresponding to areas of retinal oedema on OCT and on the enface image. Both intra retinal and sub retinal oedema had a shadowing effect on the DCP, outer retina (OR) and CC layer causing artefacts thus impeding an accurate measurement of the vascular density and confirmation of the dropout areas. Middle retinal thickening, highly reflective spots (HRS) and hard exudates were seen as bright areas in the DCP and CC and in the OR in some scans. These areas of HRS with middle retinal oedema causing radial striations in the Henle’s layer were more apparent in the CC layer, which may reverse with disease resolution. Inner retinal thickening and middle retinal thickening corresponded with capillary rarefaction in the SCP and DCP, respectively. FAZ enlargement could not be accurately documented in all patients as many presented with macular edema during the acute phase. Figures 3 and 4 show an OCTA 3X3mm scan in mild and severe intra retinal edema, respectively. Figure 5 shows CC layer with enface projection of active retinitis. Figure 6 shows an 8X8 mm scan which is useful to detect the extent of retinitis, but has poorer vascular resolution compared to 3X3 scans.

**Discussion**

OCTA has the ability to non-invasively provide details of retinal and choroidal vasculature, which helps us better understand the microvascular changes in eyes with retinitis, which cannot be delineated well on FFA due to the vascular leakage in inflammatory conditions. Few studies in post fever retinitis have described changes in the SCP/DCP following dengue and chikungunya retinitis. Agarwal et al. reported that there were flow void areas in the SCP, DCP and choriocapillaris slabs in chikungunya retinitis. Aggarwal et al. have also described the OCTA features in acute macular neuro-retinopathy post dengue fever showing disruption of both the SCP and DCP, flow deficit in the foveal region and an increase in the FAZ. They propose that the presence of hairpin loop configuration of the adjacent retinal capillaries is suggestive of retinal capillary ischaemia, which persisted even at their last follow up. Khatri et al. noted a broken FAZ in only the SCP of OCTA in a case of dengue maculopathy and these changes persisted at follow-up visits. Kahloun et al. described hypointense areas in the SCP/DCP but larger hypointense areas in the DCP/OR/CC on their swept source (SS) OCTA in a patient with rickettsial retinitis. On follow up six weeks later the hypointense greyish areas of retinal capillary nonperfusion persisted in both SCP/DCP.

Khatri et al. have described microaneurysms (MA) on OCTA based on their signals. MAs were classified as high flow MAs and low flow MAs. High Flow MAs show a signal on OCTA. Due to pericyte loss however these high flow MAs are prone to thickening of macula due to leakage and are often are located in the DCP. Nearly three quarters of them were located adjoining cystoid spaces.
| Serial.no | Age | Sex | Eye | Serology          | OCT                                      | CMT (in µ) | OCTA                                                                 |
|-----------|-----|-----|-----|-------------------|------------------------------------------|-----------|-----------------------------------------------------------------------|
| 1         | 28  | M   | LE  | WFT               | SRF + middle retinal band like HR along OPL | 361       | Capillary rarefaction in DCP > SCP                                     |
|           |     |     |     |                   |                                           |           | Gross vessel dropouts in DCP                                          |
|           |     |     |     |                   |                                           |           | FAZ enlarged on DCP                                                    |
|           |     |     |     |                   |                                           |           | Darker areas peripapillary corresponding to the                       |
|           |     |     |     |                   |                                           |           | disc edema in all the layers, more pronounced in                      |
|           |     |     |     |                   |                                           |           | OR and CC                                                             |
|           |     |     |     |                   |                                           |           | Radial lines/streaks along PMB apparent on the                       |
|           |     |     |     |                   |                                           |           | CC layer                                                              |
|           |     |     |     |                   |                                           |           | Coarse architecture of CC layer maintained otherwise                   |
| 2         | 20  | F   | RE  | Dengue IgG WFT     | Middle retinal HR + spongy edema          | 216       | SCP grossly normal                                                     |
|           |     |     |     |                   |                                           |           | DCP shows darker areas corresponding to the                         |
|           |     |     |     |                   |                                           |           | retinal edema superiorly along ST arcade                            |
|           |     |     |     |                   |                                           |           | FAZ maintained                                                        |
|           |     |     |     |                   |                                           |           | Diffuse changes in coarse architecture of CC                          |
|           |     |     |     |                   |                                           |           | Capillary rarefaction in SCP and DCP                                 |
|           |     |     |     |                   |                                           |           | Enlarged and broken FAZ- vessel loss more appreciable along PMB      |
|           |     |     |     |                   |                                           |           | OR has areas of shadowing and dark patches                           |
|           |     |     |     |                   |                                           |           | CC layer shows a better extent of the involved area                   |
|           |     |     |     |                   |                                           |           | with radial streaks of alternating darker and lighter areas           |
| 3         | 41  | F   | LE  | WFT               | LE IRF + gross SRF with HRS               | 618       | Capillary rarefaction beyond macular area, more prominent in DCP     |
|           |     |     |     |                   |                                           |           | large patches of darker areas corresponding to the areas of IRF      |
|           |     |     |     |                   |                                           |           | FAZ enlarged and altered in SCP and not seen                          |
|           |     |     |     |                   |                                           |           | totally in DCP                                                       |
|           |     |     |     |                   |                                           |           | Darker areas more prominent again in OR and CC layers                 |
|           |     |     |     |                   |                                           |           | PMB and ST arcade involved more                                      |
| 4         | 39  | M   | RE  | WFT               | SRF + inner and middle retinal edema- HRS middle retina | 371       | Extensive capillary rarefaction DCP >> SCP                            |
|           |     |     |     |                   |                                           |           | FAZ landmarks obliterated                                             |
|           |     |     |     |                   |                                           |           | Radial streaks seen in OR and CC layer- noted on even on enface OCT  |
| 5         | 49  | F   | RE  | Dengue IgG WFT     | ↓ CFT OR atrophy                          | 143       | Enlarged FAZ- due to CFT                                              |
|           |     |     |     |                   |                                           |           | Patchy capillary rarefaction both in SCP and DCP                     |
|           |     |     |     |                   |                                           |           | Prominent choroidal vasculature in OR and CC                         |
|           |     |     |     |                   |                                           |           | Patchy areas of rarefaction in SCP > DCP                             |
|           |     |     |     |                   |                                           |           | Enlarged FAZ in both SCP and DCP                                     |
|           |     |     |     |                   |                                           |           | No FAZ seen in DCP                                                    |
|           |     |     |     |                   |                                           |           | Radial streaks noted in DCP and more prominent in CC                  |
|           |     |     |     |                   |                                           |           | Shadowing of areas in OR                                              |
| 6         | 29  | M   | LE  | WFT               | SRF + middle retinal HE SRHRM more inferiorly | 468       | Inferior capillary rarefaction beyond perimacular area                 |
|           |     |     |     |                   |                                           |           | Enlarged FAZ on DCP                                                   |
|           |     |     |     |                   |                                           |           | Artefacts on OR                                                       |
|           |     |     |     |                   |                                           |           | Prominent radial streaks inferiorly with wider bulb                   |
|           |     |     |     |                   |                                           |           | like dilatations-cystoid spaces in the CC layer                      |
| 7         | 23  | F   | RE  | WFT               | SRF + middle retinal and SR HRS           | 200       | SCP normal                                                            |
|           |     |     |     |                   |                                           |           | DCP radial streaks seen nasally continuing into                     |
|           |     |     |     |                   |                                           |           | OR and more prominent in the CC Prominent                            |
|           |     |     |     |                   |                                           |           | vasculature on DCP                                                   |
|           |     |     |     |                   |                                           |           | FAZ normal                                                            |
| 8         |     |     | LE  | WIDAL             | SR scar + taut posterior hyaloids face + traction + inner and middle retinal thickening | 402       | Prominent perimacular network in DCP                                 |
|           |     |     |     |                   |                                           |           | Grossly normal FAZ                                                    |
|           |     |     |     |                   |                                           |           | Change in coarse architecture in CC                                  |
|           |     |     |     |                   |                                           |           | OR Normal                                                             |
| 9         | 34  | M   | RE  | WIDAL             | RE SRF + SR HRM -middle retinal HR         | 415       | Prominent perimacular vasculature in DCP > SCP                       |
|           |     |     |     |                   |                                           |           | Enlarged FAZ in DCP                                                   |
|           |     |     |     |                   |                                           |           | NV complex nasally in OR and CC                                      |
|           |     |     |     |                   |                                           |           | Coarse architecture in CC                                             |
| 10        |     |     | LE  | WFT               | SRF + HR middle retina and SRHRM          | 373       | Rarefaction at DCP                                                    |
|           |     |     |     |                   |                                           |           | Increased FAZ, shadow on OR corresponding to                           |
|           |     |     |     |                   |                                           |           | edema                                                                 |
|           |     |     |     |                   |                                           |           | Radial streaks in OR and more prominent in CC                         |

Continued
| Serial.no | Age  | Sex | Eye | Serology      | OCT                        | CMT (µ) | OCTA                                                                                                                                 |
|----------|------|-----|-----|---------------|----------------------------|---------|---------------------------------------------------------------------------------------------------------------------------------------|
| 11       | 26   | M   | RE  | WIDAL         | SRF with SRHRM             | 393     | Grossly Normal SCP  
DCP showed capillary rarefaction nasally  
FAZ normal  
Prominent perimacular vasculature on DCP |
|          |      |     | LE  | SRF with SRHRM |                            | 481     | Grossly normal SCP  
DCP shows capillary rarefaction nasally more in LE  
Radial streaks seen in CC layer  
FAZ normal  
Prominent perimacular vasculature on DCP |
| 12       | 24   | M   | LE  | Dengue IgG    | SRF + inner and middle retinal thickening + HRS | 763     | Images poor quality-  
complete distortion of vasculature, CNP  
OR and CC not clearly visualised |
| 13       | 59   | F   | RE  | WFT           | SRF + HRS middle retina, inner thickening     | 495     | Gross rarefaction in SCP and DCP |
|          |      |     | LE  | Minimal SRF and spongy thickening   |                            | 312     | Patchy areas of rarefaction SCP and DCP |
| 14       | 18   | M   | RE  | WIDAL         | SRF – HR SR                  | 322     | Prominent perimacular vasculature DCP  
OR and CC altered texture |
|          |      |     | LE  | Inner and middle retinal thickening |                            | 217     | Rarefaction more in SCP > DCP  
Shadowing in DCP, OR and CC |
| 15       | 56   | M   | RE  | Dengue IgG    | SRF + IRF Inner retinal thickening             | 707     | Gross capillary rarefaction DCP >> SCP  
Distorted and enlarged FAZ artefacts seen inferiorly  
Brighter shadows inferiorly in CC layer |
|          |      |     | LE  | SRF + IRF Inner retinal thickening |                            | 657     | Gross capillary rarefaction DCP >> SCP more inferiorly  
Enlarged and distorted FAZ  
Shadows of IRF on OR and CC |
| 16       | 60   | M   | RE  | WFT           | SRF + IRF —inner and middle retinal thickening | 915     | RAREFACTION IN DCP >> SCP  
FAZ maintained in SCP, enlarged in DCP  
Irregular shadows and artefacts In OR and CC  
Shadows of IRF and SRF on OR and CC |
| 17       | 68   | M   | LE  | Dengue IgG    | SRF + middle retinal HRS       | 649     | Rarefaction in both SCP and DCP  
FAZ normal in SCP and DCP |
| 18       | 18   | F   | RE  | WFT           | Intraretinal HRS              | 831     | Normal SCP  
Generalised and non specific rarefaction at DCP, more inferonasally  
Shadows of IRF and SRF on OR and CC |
| 19       | 73   | M   | LE  | Negative      | SRF + IRF, inner retinal thickening along PMB | 297     | Generalised capillary rarefaction in both SCP and DCP  
Darkers areas corresponding to IRF on all the layers |
| 20       | 18   | F   | RE  | Negative      | SRF + inner retinal thickening—middle retinal HR-SR precipitates | 233     | Generalised extra macular capillary rarefaction in DCP >> SCP  
Enlarged FAZ on DCP  
Brighter areas on OR And CC layers  
Darkers areas inferiorly corresponding to SRF |
|          |      |     | LE  | SRF + inner retinal thickening—middle retinal HRS SRHRM |                            | 370     | Generalised extra macular capillary rarefaction in DCP >> SCP  
Enlarged FAZ on DCP  
Brighter areas on OR And CC layers  
Darkers areas inferiorly corresponding to SRF |
| 21       | 23   | F   | RE  | Dengue IgG    | Middle retinal thickening       | 258     | Minimal capillary rarefaction in DCP  
FAZ normal in SCP and DCP |
|          |      |     | LE  | SRF + inner and middle retinal thickening |                            | 690     | Gross capillary rarefaction SCP and DCP  
Distorted FAZ, DCP >> SCP  
Darkers areas in DCP, OR and CC corresponding to intraretinal edema |
| 22       | 26   | M   | RE  | Dengue Ig G   | WNL                           | 215     | Capillary rarefaction temporal to the disc both at SCP and DCP  
Rest of macula normal |
|          |      |     | LE  | WNL           |                            | 196     | Capillary rarefaction temporal to the disc both at SCP and DCP  
Rest of macula normal |
| 23       | 20   | M   | RE  | Serology Negative | SRF + middle retinal HR SRHRM | 496     | Capillary rarefaction DCP >> SCP  
Enlarged FAZ in DCP >> SCP  
Shadowing in OR and diffuse radial streaks in CC layer |
|          |      |     | LE  | SRF + middle retinal HR SRHRM |                            | 486     | Rarefaction in SCP >> DCP  
Shadowing in OR  
Radial streaks in CC layer |
| 24       | 55   | F   | RE  | Serology Negative | SRF + middle retinal HR | 385     | SCP is normal  
DCP shows diffuse non specific capillary rarefaction  
with artefacts of striations with enlarged FAZ  
CC has prominent striations with brighter areas  
corresponding to the middle retinal HR |

Continued
Table 1. Shows demographic, aetiological and descriptive characteristics in patients with post fever retinitis. 
M Male, F Female, RE Right eye, LE Left eye, WFT Weil Felix Test, OCT Optical Coherence Tomography, 
CMT Central macular thickness, HR Hyper-reflective, HRS Hyper-reflective spots, SRHRM Subretinal 
Hyper-reflective material, CFT Central Foveal thickness, SCP Superficial capillary plexus, DCP Deep capillary 
plexus, FAZ Foveal avascular zone, SRF Subretinal fluid, HE HE Hard exudates, CC Choriocapillaries, OR Outer retina, PMB Papillomacular bundle, PRL Photoreceptor loss, OPL Outer plexiform 
layer, CNP Capillary non-perfusion, ST Superotemporal, SR Subretinal

| Serial.no | Age | Sex | Eye | Serology | OCT | CMT (in µ) | OCTA |
|-----------|-----|-----|-----|----------|-----|------------|------|
| 25        | 73  | F   | LE  | WFT      | Inner and middle retinal thickening nasal to the fovea along PMB | 233 | Capillary rarefaction both in SCP and DCP—more nasally | |
| 26        | 21  | M   | RE  | Dengue   | Focal PRL loss | 221 | Focal rarefaction in DCP | |
| 27        | 53  | F   | RE  | Dengue IgM—Positive | RE cilioretinal A occlusion | 228 | RE gross CNP in SCP and DCP—poor fixation | |
| 28        | 38  | M   | RE  | WFT      | SRF + inner retinal thickening | 249 | Rarefaction in DCP > SCP | |
| 29        | 56  | M   | LE  | Dengue IgG | Serology negative | 413 | Patchy rarefaction in SCP and DCP Alter Capillary non-perfusion in SCP and DCP | |
| 30        | 23  | F   | LE  | Dengue IgG | HRM- middle and OR HR SRF, SRHRM | 426 | Rarefaction DCP Gross shadowing in OR and CC and DCP FAZ minimally altered | |
| 31        | 40  | M   | LE  | Dengue IgG | ↓ CFT | 229 | CNPs inferiorly with breach in FAZ inferiorly in DCP Corresponding shadowing in OR | |
| 32        | 42  | F   | LE  | Dengue IgG | SRF + IRF + Middle retinal HRS | 532 | Rarefaction in DCP > SCP | |
| 33        | 35  | F   | RE  | Dengue IgG | SRF + inner retinal thick + HRS + large SRHRM | 618 | Rarefaction in DCP > SCP | |
| 34        |     |     |     |           |                 | 642 | Rarefaction in SCP/DCP over PMB | |

Low Flow MAs do not appear on OCTA, they may however be visible on fundus photo or other enhanced techniques.

Schreur et al. in their study of retinal MA in patients with diabetic macular edema (DME) by OCTA found that MA with focal leakage and located in a thickened retinal area were more likely to be detected on OCTA. In their study MAs were located in intermediate and deep plexus.

In our series of post fever retinitis, microvascular abnormalities were noted in the SCP and DCP with quantifiable changes in both the smaller and larger vessels. Capillary rarefaction areas corresponding to retinitis patches and pruning of vessels was seen in the active phase. The DCP showed profound capillary rarefaction when compared to the SCP due to the involvement of the middle retinal layers. Our series did not show any individual MAs on OCTA. The CC slabs showed signal void areas which can be attributed to shadowing caused by the overlying retinitis patch similar that reported by Shanmugam et al. The regular vascular pattern or the “angi-architecture” in SCP and DCP was lost in active retinitis, the intraretinal edema and exudation causing an impression of vessel drop out. The flow void areas in the choriocapillaris layer are due to the shadow effect of the superficial edema on to the choroid resulting in loss of the regular coarse architecture. These changes are reversible in non-ischemic retinas once the active inflammation subsides.

In a patient with post typhoid fever neuroretinitis, OCTA showed macular thickening and neuro sensory detachment. Choroidal imaging showed abnormal “patchy” flow voids in the choriocapillaris-like highly suggestive of a sluggish blood flow or ischemia. Deep range imaging (DRI) of the choroid revealed increased choroidal thickness and dilated choroidal vasculature, indicating a concurrent choroidal inflammation.

In our series choroidal imaging had artifacts in acute stages due to intraretinal fluid. In cases where choroidal imaging was possible, we noted altered choroidal architecture with darker areas. We will be, in a future study of these patients analyse the choroidal architecture during the follow up of our patients.

A study of OCTA in a patient with varicella retinal vasculopathy showed loss of capillary plexus in both SCP and DCP. OCTA has also been useful in choroidal imaging as described in a case of sympathetic ophthalmia. OCTA of the choroidal vascular revealed flow void pockets initially at inflammatory stage, and this normalized over time into typical granular pattern after initiation of the treatment.
Figure 1. OCTA image of deep layer (3 × 3 mm). (a) Original image exported from OptoVue. (b) Deep layer after removal of projection artefacts from the superficial layer. OCTA Optical coherence tomography angiography.

Figure 2. Optical coherence tomography angiography (OCTA) image of superficial (a) and deep layer after removal of projection artifacts (b). (c, d) are the respective images after fractal analysis. Regions in red pixels correspond to vessels, blue corresponds to large vessel spacing, and yellow corresponds to small vessel spacing.
Table 2. Showing the vascular variable parameters of small and large vessels in superficial capillary and deep capillary layers of our series against age matched normal. Normal age group: 20–67 years. Our series: 18–72 years.

| Vascular parameters                  | Normative data[^24] | Post fever retinitis median with 2 SD included | 95% CI   |
|--------------------------------------|----------------------|-----------------------------------------------|----------|
| FAZ area (superficial)               | 0.42 ± 0.01          | 0.431                                         | 0.393–0.502 |
| Small vessels spacings (superficial) | 36.97 ± 0.32         | 40.190                                        | 39.078–41.403 |
| Large vessels spacings (superficial) | 14.85 ± 0.46         | 25.718                                        | 23.239–29.503 |
| Vessel density (superficial)         | 48.17 ± 0.69         | 31.436                                        | 29.382–35.085 |
| FAZ area (deep)                      | 0.42 ± 0.01          | 0.407                                         | 0.363–0.452 |
| Small vessels SPACINGS (DEEP)        | 34.03 ± 0.39         | 42.744                                        | 42.170–43.381 |
| Large vessels spacings (deep)        | 12.19 ± 0.33         | 24.623                                        | 21.824–26.866 |
| Vessel density (deep)                | 53.77 ± 0.64         | 32.284                                        | 29.715–35.004 |

Figure 3. (Patient 24) OCTA: 3 mm × 3 mm section. SCP—Capillary rarefaction seen between larger vessels. FAZ maintained. Beading and aneurysmal dilatation of perifoveal vasculature (yellow arrow). DCP—Diffuse capillary rarefaction seen as radial darker stripes (green arrow) corresponding to retinal oedema in Henle’s layer. Areas of pruning noted in the smaller network of vessels. OR—Projection artifacts with darker radial lines continuing in the avascular layer. CC—Loss of the regular coarse architecture. A better appreciation of the darker radial striations corresponding to oedema in the Henle's layer (green arrow). OCT showing mild intraretinal oedema and HRS and SRF with subretinal hyperreflectivity. OCTA Optical coherence tomography angiography. SCP Superficial capillary plexus, DCP Deep capillary plexus, OR Outer retina, CC Choriocapillaries, OCT Optical coherence tomography, FAZ Foveal avascular zone, HRS Hyperreflective spots.
Despite the advantages of being non-invasive and repeatable, OCTA has certain limitations in active retinitis. Its interpretation can be challenging due to projection and motion artifacts and retinal edema due to active retinitis causing an impression of vessel drop out and a loss of the regular “angio-architecture” due to vessel displacements, pruning effects and non-flow areas in edematous areas. The interpretation of OCTA and particularly the FAZ is difficult in patients with gross macular edema and will need longitudinal follow up to assess for enlargement, distortion and possible ischemia.

Other limitations include a relatively small field of view, inability to show leakage, and proclivity for image artifact due to patient eye movement/blinking. Manual segmentation can be tedious and time consuming. The variations in capillary density or vascular thickness are influenced by the type of segmentation. We overcame this limitation by having two observers performing the manual segmentation, comparing the findings and taking the average of the two readings.

**Conclusion**
Ours is the largest series of OCTA of retinal vasculature findings in post fever retinitis. Although the presumed etiology was different in our patients, they developed similar changes on OCTA. Quantitative analysis confirmed that the insult was more in the DCP. Serial follow up of these patients will help unravel the vascular changes on the road to recovery.
Figure 5. (Patient 24) A 3 mm × 3 mm scan showing CC layer (left image) with Enface projection (right image) of active retinitis. A well demarcated alternating bands of dark and lighter radial striations corresponding to areas of retinal edema in Henle’s layer. CC Choriocapillaris.
Figure 6. (Patient 24) OCTA 8 mm × 8 mm scan: Larger scan sections show the extent of retinal involvement in active retinitis. Larger vessels in SCP can be seen. Finer vasculature in SCP and DCP are poorly appreciated due to lesser resolution in larger scans. The macular involvement can be estimated from DCP onwards. A CC section shows the radial striations with brighter signals corresponding to the intraretinal HRS. A corresponding OCT B scan shows the severity and retinal involvement. OCTA Optical coherence tomography angiography, SCP Superficial capillary plexus, DCP Deep capillary plexus, OR Outer retina, CC Choriocapillaries, OCT Optical coherence tomography, FAZ Foveal avascular zone, HRS Hyperreflective spots.
17. Bajgai, P., Singh, R. & Kapil, A. Progression of dengue maculopathy on OCT-angiography and fundus photography. *Ophthalmology* **124**, 1816 (2017).
18. Kahloun, R. *et al.* Swept-source optical coherence tomography angiography in *Rickettsial retinitis*. *Retin. Cases Brief Rep.* **13**, 348–351 (2019).
19. Khatri, A. *et al.* Detection, localization, and characterization of vision-threatening features of microaneurysms using optical coherence tomography angiography in diabetic maculopathy. *Eur. J. Ophthalmol.* https://doi.org/10.1177/1120672120924669 (2020).
20. Khatri, A., Bai Kumar, C., Kharel, M., Ashma, K. C. & Pradhan, E. Analysis of microaneurysms and capillary density quantified by OCT-angiography and its relation to macular edema and macular ischemia in diabetic maculopathy. *Eye* **35**(6), 1777–1779. https://doi.org/10.1038/s41433-020-1060-4 (2021).
21. Schreur, V. *et al.* Morphological and topographical appearance of microaneurysms on optical coherence tomography angiography. *Br. J. Ophthalmol.* https://doi.org/10.1136/bjophthalmol-2018-312258 (2018).
22. Shanmugam, M. *et al.* Optical coherence tomography angiography features of retinitis post-*rickettsia* fever. *Indian J. Ophthalmol.* **67**, 297–300 (2019).
23. Khatri, A. *et al.* Post typhoid fever neuroretinitis with serous retinal detachment and choroidal involvement: A case report. *Am. J. Ophthalmol. Case Rep.* **21**, 101025. https://doi.org/10.1016/j.ajoc.2021.101025 (2021).
24. Khatri, A., Timalsena, S., Gautam, S. & Kharel, M. Varicella retinal vasculopathy: Unilateral cilioretinal artery occlusion despite acyclovir therapy caught using optical coherence tomography-angiography (OCTA). *Case Rep. Ophthalmol. Med.* **2019**, 5752180. https://doi.org/10.1155/2019/5752180 (2019).
25. Khatri, A. *et al.* A rare entity: Sympathetic ophthalmia presumably after blunt trauma to the phthisical eye and optical coherence tomography angiography metrics to monitor response to treatment. *Clin. Case Rep.* **8**, 149–154. https://doi.org/10.1002/ccr3.2597 (2019).

**Author contributions**
S.S.: Design, Acquisition of data, Analysis and interpretation, Manuscript writing, Manuscript editing, Intellectual content. S.G.K.G.: Design, Acquisition of data, Analysis and interpretation, Manuscript editing, Intellectual content. S.A.: Acquisition of data, Manuscript writing, Manuscript editing. P.M.: Design, Analysis and interpretation, Manuscript writing, Manuscript editing. N.G.: Acquisition of data, Analysis and interpretation, Intellectual content. A.K.: Analysis and interpretation, Manuscript writing, Manuscript editing. C.J.: Analysis and interpretation, Manuscript writing, Manuscript editing. S.S.: Acquisition of data, Analysis and interpretation, Manuscript writing, Manuscript editing. A.S.R.: Acquisition of data, Analysis and interpretation, Manuscript writing. R.S.: Design, Manuscript writing, Intellectual content. Figures: S.G.K.G., S.A. and S.S. All authors approved the final manuscript.

**Competing interests**
The authors declare no competing interests.

**Additional information**
Correspondence and requests for materials should be addressed to S.S.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2021