



REFERENCES

1. Stordy BJ. Benefit of docosahexaenoic acid supplements to dark adaptation in dyslexics. *Lancet*. 1995;346:385.
2. Jeffrey BG, Weisinger HS, Neuringer M, Mitchell DC. The role of docosahexaenoic acid in retinal function. *Lipids*. 2001;36:859-871.
3. Stordy BJ. Dark adaptation, motor skills, docosahexaenoic acid, and dyslexia. *Am J Clin Nutr*. 2000;71:323-326.
4. McMurchie B, King RSP, Kelly PF, Torrens GE. The importance of dark adaptation for forensic examinations; an evaluation of the Crime-lite Eye™. *Sci Justice*. 2018;59:138-144. <https://doi.org/10.1016/j.scijus.2018.10.006>.
5. Metherel AH, Armstrong JM, Patterson AC, Stark KD. Assessment of blood measures of n-3 polyunsaturated fatty acids with acute fish oil supplementation and washout in men and women. *Prostaglandins Leukot Essent Fat Acids*. 2009;81:23-29.

Longitudinal analysis of cotton wool spots in COVID-19 with high-resolution spectral domain optical coherence tomography and optical coherence tomography angiography

Cotton wool spots (CWS) have been reported in Coronavirus disease 2019 (COVID-19) in cross-sectional studies.¹⁻⁴ Their occurrence in COVID-19 has been proposed as an indicator of a neurological event,¹ an acute vascular event^{3,4} or a biomarker of a systemic vascular disease.² We observed CWS in 5 (5.38%) of 93 patients screened in the convalescent phase of the disease, occasionally accompanied by an intraretinal haemorrhage. We describe their longitudinal follow up with multimodal imaging in a prospective, non-interventional study in a tertiary care referral centre in North India. The study adhered to the principles of the Declaration of Helsinki. Institutional Ethics Committee approval was obtained. Informed consent was obtained from patients.

The patients underwent colour fundus photography, high-resolution spectral domain optical coherence tomography (SD-OCT) using Spectralis HRA + OCT system (Heidelberg Engineering, Heidelberg, Germany) and OCT angiography (OCTA) using swept source OCTA (Topcon DRI OCT Triton plus) (3 × 3 mm or 4.5 × 4.5 mm) centred at CWS, at baseline and subsequent visits.

The CWS were detected in seven eyes (five patients) during fundus screening at a mean of 30 ± 8.72 (median 30; range 22-44) days from the day of COVID-19 diagnosis. One of these patients additionally had an intra-retinal haemorrhage. All lesions were located along the temporal vascular arcades. The mean age was 65.4 ± 8.26 (median 69; range 56-73) years. Systemic comorbidities included hypertension, diabetes mellitus, anaemia, coronary artery disease and chronic kidney disease. None had background features of any retinopathy (diabetic, hypertensive or anaemic retinopathy).

The SD-OCT of CWS demonstrated “hyperreflective sign,” cyst and inner retinal atrophy as they progressed

from the acute to resolved stage (Figures 1 and 2). The OCTA, corresponding to the CWS, showed decorrelation signal in all layers including superficial capillary plexus (SCP), deep capillary plexus (DCP), outer retina (OR) and choriocapillaris (CC). As the CWS resolved, OCTA showed restoration of flow signal in all retinal layers (Figures 1 and 2).

As one patient developed recurring CWS (Figure 1), he was advised to undergo magnetic resonance imaging (T2 weighted, Fluid attenuated inversion recovery (FLAIR) weighted, 3D T1 weighted, diffusion weighted and susceptibility weighted sequences along with 3D-time-of-flight (TOF) magnetic resonance angiography) and magnetic resonance angiography to check for any concomitant cerebral microvascular alteration. There was no discrete ischaemic lesion or vascular narrowing or irregularity.

In diabetic retinopathy (DR), the OCTA showed a decorrelation signal corresponding to the CWS in SCP, along with areas of retinal non-perfusion in their vicinity in SCP and DCP.⁵ The CWS of COVID-19, however, showed only a decorrelation signal on OCTA. The growth of large CWS occurs at the expense of outer retinal layers as seen by their distortion, invasion or compression. A disturbed visualization of the outer retinal layers due to the masking effect of the CWS was reported in 79.3% of cases of CWS in DR.⁵ Although our numbers are small, we found this disturbance in 70% of CWS. Cystic space within the CWS, a possible early sign of retinal ganglion cell degeneration,⁵ was seen in one case (case 4), the significance of which remains unclear.

The blood flow signal in the OR on OCTA may be poor due to interference by the thickened inner retina or due to the shadow effects by the overlying CWS, rather

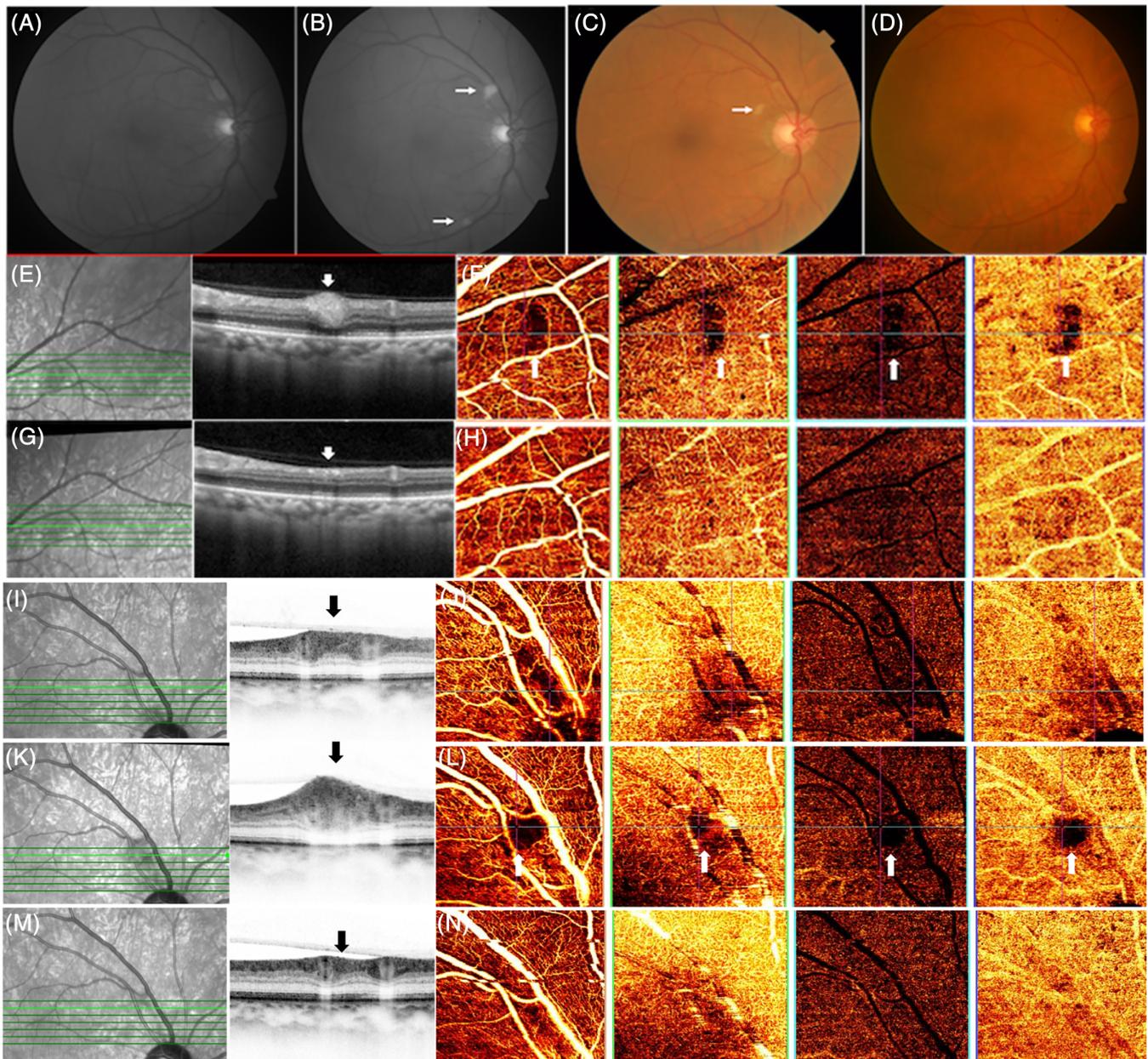


FIGURE 1 Red free fundus photographs of right eye of a 73-year-old male, showing the normal fundus at first visit (A), appearance of two new CWS (arrows) at 2 weeks (B), appearance of a third new CWS (arrow) and resolution of previous two CWS at 9 weeks (C) and complete resolution at 12 weeks (D). In the left eye, the SD-OCT scan showed a hyper-reflectivity (arrow) involving the inner retinal layers, corresponding to the CWS, at first visit (E). The adjacent retinal layers did not show any thickening but appeared mechanically distorted up to the outer nuclear layer. The OCTA (F) showed decorrelation signal (arrows), corresponding to the CWS in all layers, including superficial capillary plexus (first panel) and deep capillary plexus (second panel), outer retina (third panel) and choriocapillaris (fourth panel). As the CWS resolved, the hyper-reflective nodular lesion on SD-OCT decreased both in size and extent, leaving the “hyper-reflective sign” (arrow) at 12 weeks (G), restricted only to the retinal nerve fibre layer and ganglion cell layer, with restoration of other layers (inner nuclear, inner plexiform and outer nuclear layers). The OCTA (H) showed restoration of signals in superficial capillary plexus (first panel) and deep capillary plexus (second panel), outer retina (third panel) and choriocapillaris (fourth panel) as early as 6 weeks. SD-OCT scan of the right eye, along the supero-temporal arcade, at visit 1 (I) showed mild thickening of the inner retinal layers between two retinal blood vessels (artery and vein) along the supero-temporal arcade. OCTA (J) showed a subtle decorrelation signal in the superficial capillary plexus (first panel), with normal DCP (second panel), OR (third panel) and CC (fourth panel). Two weeks later, the SD-OCT (K) showed an increased hyper-reflectivity at the site of appearance of a new CWS along the supero-temporal arcade, and OCTA (L) showed decorrelation signal (arrows), corresponding to the CWS in all layers, including SCP (first panel) and DCP (second panel) plexus, OR (third panel) and CC (fourth panel). As the CWS resolved at 12 weeks, the SD-OCT (M) showed normal inner retinal layers (arrow) at this site. OCTA (N) showed restoration of signals in SCP (first panel) and DCP (second panel), OR (third panel) and CC (fourth panel)

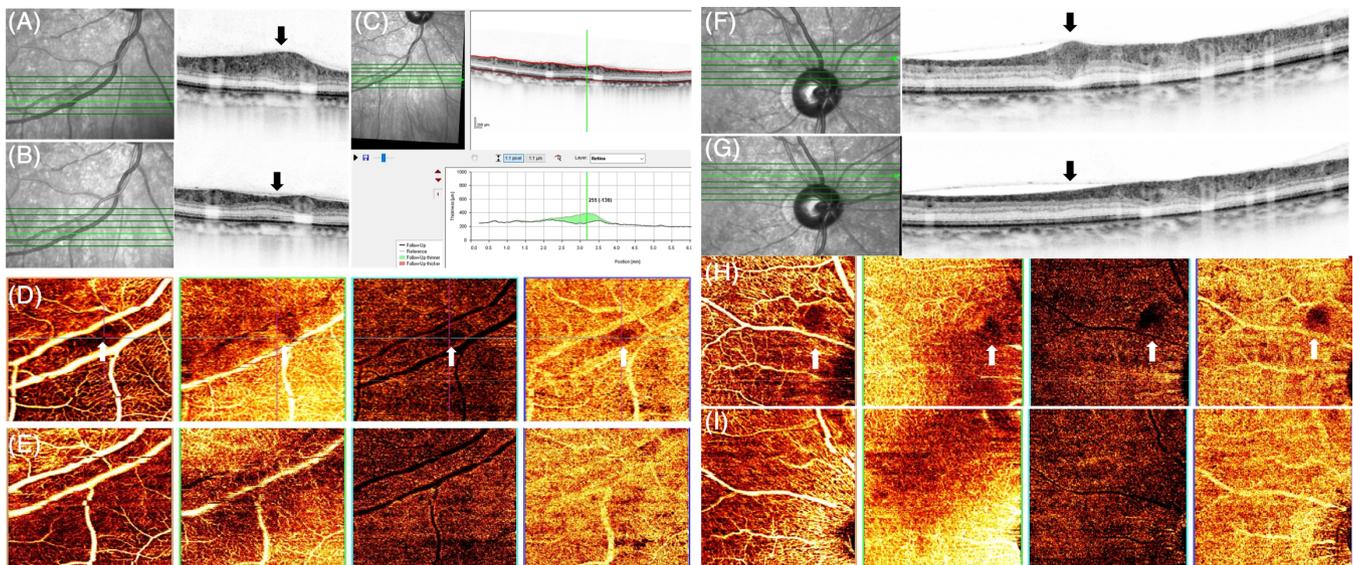


FIGURE 2 SD-OCT scan of the right eye of the same patient (as in Figure 1) along the infero-temporal arcade (A), at visit 2, showing hyper-reflectivity (arrow) corresponding to the new CWS. As the CWS resolved at 10 weeks (B), the SD-OCT showed inner retinal thinning (arrow) compared to the adjacent healthy retina, as seen by green area (C). The OCTA of the CWS (D) showed loss of signal (arrow) in superficial (first panel) and deep (second panel) capillary plexus, outer retina (third panel) and choriocapillaris (fourth panel). The OCTA at 10 weeks (E) showed return of signal in all layers. SD-OCT scan of the right eye of same patient (as in Figure 1) showing a localised hyper-reflectivity (arrow) when a new CWS appeared below the supero-temporal arcade, temporal to the optic disc, at visit 4 (F). At 3 weeks, the retinal layers became normal (G) as the CWS resolved. OCTA of the fresh CWS (H) showed loss of signal (arrow) in superficial (first panel) and deep (second panel) capillary plexus, outer retina (third panel) and choriocapillaris (fourth panel). At 3 weeks, OCTA (I) showed return of signal in all layers

than perfusion defects, as also suggested by the reversibility of decorrelation signal on OCTA. This, however, needs to be explored further, possibly by serial fluorescein angiography.

As all our patients were elderly with systemic comorbidities, we believe that a compromised retinal vasculature predisposed patients to the retinal vasculopathy in these eyes. The primary mechanism of CWS development in COVID-19 still remains a subject of speculation with possibilities of occlusive vasculopathy (as seen in diabetic or hypertensive vascular disease), Angiotensin-converting enzyme 2 (ACE2) down-regulation by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hyper-coagulopathy or an immune-complex deposition (as speculated in human immunodeficiency virus (HIV)) in the vessel walls.

This longitudinal study describes the course of CWS in COVID-19 on SD-OCT and OCTA, which confirmed their previously observed localisation and morphology on SD-OCT with CWS of other diseases. However, the CWS in COVID-19 may be more limited (as seen only in the posterior pole) in terms of incidence, extent, size and number than in other diseases. Although the genesis of CWS in COVID-19 remains unclear, the restoration of the decorrelation signal on OCTA during their clinical resolution may suggest a mechanism (localised, self-limiting and occult) different from that in other retinal vascular

disorders (with widespread and chronic retinal damage) like DR and retinal vein occlusion. In addition, the patient population with CWS in COVID-19 appears different from that with CWS in HIV or DR, being much older and having systemic comorbidities. The possible lack of neurological association of CWS in COVID-19 may also suggest a mechanism different from CWS of HIV retinopathy.

CONFLICT OF INTEREST

None declared.

ETHICS STATEMENT

Approval was obtained by the Institute Ethics Committee, Postgraduate Institute of Medical Education and Research, Chandigarh, India. The approval ID was: INT/IEC/2020/SPL-1383.

Ashish Markan MD DNB¹

Reema Bansal MD PhD¹

Nitin Gautam MSc¹

Chirag Ahuja MD²

Aniruddha Agarwal MD¹

Deeksha Katoch MD¹

Vishali Gupta MD¹

¹Advanced Eye Centre, Post Graduate
Institute of Medical Education and Research,
Chandigarh, India

²Department of Radiodiagnosis and Imaging, Post
Graduate Institute of Medical Education and Research,
Chandigarh, India

Correspondence

Dr Reema Bansal, Additional Professor, Advanced Eye
Center, Post Graduate Institute of Medical Education and
Research, Chandigarh 160012, India.
Email: drreemab@rediffmail.com

ORCID

Ashish Markan  <https://orcid.org/0000-0003-1454-2655>

Reema Bansal  <https://orcid.org/0000-0003-1025-4226>

REFERENCES

1. Marinho PM, Marcos AAA, Romano AC, Nascimento H, Belfort R Jr. Retinal findings in patients with COVID-19. *Lancet*. 2020;395:1610.
2. Landecho MF, Yuste JR, Gandara E, et al. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease. *J Int Med*. 2020;289:116-120. <https://doi.org/10.1111/joim.13156>.
3. Pirraglia MP, Ceccarelli G, Cerini A, et al. Retinal involvement and ocular findings in COVID-19 pneumonia patients. *Sci Rep*. 2020;10:17419. <https://doi.org/10.1038/s41598-020-74446-6>.
4. Pereira LA, Soares LCM, Nascimento PA, et al. Retinal findings in hospitalised patients with severe COVID-19. *Br J Ophthalmol*. 2020. <https://doi.org/10.1136/bjophthalmol-2020-317576>. Epub ahead of print.
5. Mahdjoubi A, Bousnina Y, Barrande G, Bensmaine F, Chahed S, Ghezaz A. Features of cotton wool spots in diabetic retinopathy: a spectral-domain optical coherence tomography angiography study. *Int Ophthalmol*. 2020;40:1625-1640.

Trimethoprim-associated uveitis and retinal vasculitis

Uveitis secondary to sulfonamides is a well-documented adverse effect.¹ The frequent co-administration of sulfonamides with trimethoprim potentially under-recognises trimethoprim as a cause of medication-induced uveitis.¹ We present a case of bilateral uveitis and retinal vasculitis associated with trimethoprim monotherapy. Written consent was obtained from the patient. Ethics approval for this study was obtained from the Human Research Ethics Committee (HREC) of the South Australian Health Institute. The tenets of the Declaration of Helsinki of 1975 were adhered to.

A 74-year-old female presented with 4 weeks of bilateral, painless, blurred vision. She reported cobwebs affecting first her right then both eyes. Past ocular history was significant for left squint surgery in childhood and bilateral cataract extraction 9 months prior with uncomplicated recovery. She had commenced trimethoprim for dysuria 1 week prior to visual decline. A urine microscopy culture and sensitivity was performed at the time which demonstrated growth of *Escherichia coli*. She took perindopril and pravastatin for hypertension and hypercholesterolaemia. She had no known allergies.

On examination, best-corrected visual acuity (BCVA) was 6/7.5 bilaterally and intraocular pressure was 11 and 15 mmHg. Slit lamp revealed 2+ vitreous cells in the right and 1+ in the left, inferotemporal posterior vitreous cellular clumps in the left and peripheral blot haemorrhages bilaterally. Anterior chambers (ACs) were quiet. Ocular coherence

tomography showed normal maculae. Fundus fluorescein angiography revealed retinal vasculitis (Figure 1).

The patient was diagnosed with intermediate uveitis and retinal vasculitis. Investigations for infective and inflammatory aetiologies were normal. White cell count was normal, C-reactive protein <1 and erythrocyte sediment rate 2. Antinuclear and antineutrophil cytoplasmic antibodies were not detected. Immunoglobulin M was negative for infection with herpes simplex (HSV), varicella zoster (VZV), hepatitis B, hepatitis C, cytomegalovirus (CMV), human immunodeficiency virus, human T-cell leukaemia virus, Ross River and West Nile virus and toxoplasmosis. Angiotensin converting enzyme was normal. QuantiFERON was negative. Polymerase chain reaction of vitreous paracentesis was negative for herpes simplex, varicella zoster and cytomegalovirus. MR angiogram brain and orbits was negative for lymphoma. An ASO titre was not performed.

Trimethoprim was stopped. Atropine and chloramphenicol were commenced. The patient's symptoms improved within 2 days without steroid treatment. Ten months later, symptoms had resolved and BCVA improved (6/6 bilaterally). Fundus examination showed inactive vascular sheathing with quiet AC and vitreous.

Six months later, the patient re-presented with similar symptomatology. She had taken one dose of trimethoprim for cystitis. BCVA had reduced to 6/12 bilaterally. Slit lamp revealed 2-3+ cells with flare in the AC, and 2+