Assessing Deep Retinal Capillary Ischemia in Paracentral Acute Middle Maculopathy by Optical Coherence Tomography Angiography

JULIA NEMIROFF, LAURA KUEHLEWEIN, EHSAN RAHIMY, IRENA TSUI, RISHI DOSHI, ALAIN GAUDRIC, MICHAEL B. GORIN, SRINIVAS SADDA, AND DAVID SARRAF

• PURPOSE: To assess microvascular blood flow of the deep retinal capillary plexus in eyes with paracentral acute middle maculopathy using optical coherence tomography (OCT) angiography.

• DESIGN: Retrospective, multicenter observational case series.

• METHODS: Clinical and multimodal imaging findings from 8 patients with paracentral acute middle maculopathy were reviewed and analyzed. OCT angiography scans were analyzed and processed, and vessel density was calculated.

• RESULTS: Eight patients (7 male, 1 female, aged 9–82 years) were included. OCT angiography was obtained at either the acute (4 cases) or old stage (4 cases). Scans of the deep capillary plexus showed preservation of perfusion in acute lesions and capillary attenuation in old cases. Cases of central retinal artery occlusion showed marked loss of the deep capillary plexus. The mean vessel density of the superficial capillary plexus in normal fellow eyes was 12.8 ± 1.8 mm^{-1} vs 12.1 ± 1.9 mm^{-1} in eyes with paracentral acute middle maculopathy (reduction −6.0%, $P = .08$). The mean vessel density of the deep capillary plexus in normal fellow eyes was 17.5 ± 1.4 mm^{-1} vs 14.7 ± 3.5 mm^{-1} in eyes with paracentral acute middle maculopathy (reduction −19.4%, $P = .04$). This significant difference was representative of the eyes with old lesions.

• CONCLUSION: Paracentral acute middle maculopathy lesions correspond to preservation of perfusion in focal acute lesions and to pruning of the plexus in old cases. Cases of central retinal artery occlusion demonstrate marked hypoperfusion of the deep capillary plexus. Our study further supports an ischemic pathogenesis of this retinal vasculopathy. (Am J Ophthalmol 2016;162:121–132. Published by Elsevier Inc.)

Accepted for publication Oct 29, 2015.

From the Stein Eye Institute, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, California (J.N., I.T., M.B.G., D.S.); Institute for Ophthalmic Research, Center for Ophthalmology, Eberhard Karls University Tübingen, Tübingen, Germany (L.K., S.S.); Retina Service, Wills Eye Hospital, Philadelphia, Pennsylvania (E.R.); Kaiser Permanante, Tustin, California (R.D.); Ophtalmologie, Hopital Lariboisiere, AP-HP, Université Paris 7 – Sorbonne Paris Cité, Paris, France (A.G.); and Greater Los Angeles Veterans Affairs Healthcare Center, Los Angeles, California (D.S.).

Inquiries to David Sarraf, Retinal Disorders and Ophthalmic Genetics Division, Stein Eye Institute, David Geffen School of Medicine at UCLA, 100 Stein Plaza, Los Angeles, California 90095; e-mail: dsarraf@ucla.edu

PARACENTRAL ACUTE MIDDLE MACULOPATHY IS A recently described entity in patients presenting with an acute-onset paracentral scotoma. Spectral-domain optical coherence tomography (OCT) reveals hyperreflective band-like lesions at the level of the inner nuclear layer. Although these lesions resolve, patients are left with atrophy of the inner nuclear layer, resulting in a permanent paracentral visual field defect. Paracentral acute middle maculopathy can be idiopathic, or it can be secondary to local retinal vascular or systemic disease.

Deep retinal capillary ischemia has been proposed as a causative factor in the development of these lesions, as the intermediate and deep retinal capillary plexuses flank the inner and outer boundaries of the inner nuclear layer, respectively.[1–3] Fluorescein angiography, the reference standard for visualizing the retinal vasculature, has limited depth resolution.[4] With OCT angiography, it is possible to obtain high-resolution, depth-resolved en face images of the retinal microvasculature by calculating motion contrast in OCT B-scans acquired repeatedly at the same location. OCT angiograms are co-registered with OCT B-scans from the same location, allowing simultaneous visualization of structure and blood flow.[5–8] We used OCT angiography to study the retinal capillary microvasculature at different levels of the retina in 8 cases of paracentral acute middle maculopathy occurring in various clinical scenarios.

METHODS

APPROVAL FOR THIS STUDY WAS OBTAINED FROM THE UNIversity of California Los Angeles (UCLA) Institutional Review Board committee. Research adhered to the tenets of the Declaration of Helsinki and was conducted in accord with regulations set forth by the Health Insurance Portability and Accountability Act.

We retrospectively identified 8 patients from 3 tertiary referral centers. All were evaluated between August 2014

TABLE 1. Clinical Characteristics and Associated Pathology in Patients Presenting With Paracentral Acute Middle Maculopathy

Case	Sex	Age (y)	Affected Eye	BCVA	Ophthalmologic Diagnosis	Systemic Disease
1	Male	66	OD	20/50	CRAO	HTN; type II DM; hypothyroidism
2	Male	72	OD	$20/20^{-1}$	BRAO	HTN; atrial fibrillation; mitral valve repair; pacemaker
3	Male	31	OS	$20/20^{-1}$	BRAO	Transposition of the great vessels (status post repair); head trauma 2 days prior
4	Male	63	OS	20/30	CRAO	Left middle cerebral artery infarction; HTN
5	Female	57	OS	20/300	CRAO	Internal carotid artery dissection; cerebral vascular occlusion coinciding with ocular event; meningioma; hyperlipidemia
6	Male	82	OS	CF at 4 ft	CRAO, NPDR	HTN; type II DM
7	Male	16	OU	20/20	SCR	Sickle cell disease (hemoglobin type SC)
8	Male	9	OD	$20/20^{-1}$	Trauma	Alpha-thalassemia trait

BCVA = best-corrected visual acuity; BRAO = branch retinal artery occlusion; CF = count fingers; CRAO = central retinal artery occlusion; DM = diabetes mellitus; HTN = hypertension; NPDR = nonproliferative diabetic retinopathy; SCR = sickle cell retinopathy.

and July 2015 and diagnosed with paracentral acute middle maculopathy. Written informed consent was obtained for each patient. We reviewed the clinical and multimodal imaging data for each patient and obtained OCT angiography analysis. The diagnostic criteria of paracentral acute middle maculopathy included a history of acute-onset paracentral scotoma with or without decline in visual acuity and a nonprogressive course. All patients demonstrated characteristic abnormalities with spectral-domain OCT, including either the acute finding of hyperreflective, plaque-like bands within the inner nuclear layer or old lesions demonstrating thinning of the inner nuclear layer. High-resolution digital color imaging, red-free photography, spectral-domain OCT, and OCT angiography were performed at the time of presentation for each patient. Fluorescein angiography was obtained in 7 of the 8 cases.

The AngioVue OCT angiography system (Optovue, Inc, Fremont, California, USA) operates at 70, 000 A-scans per second to acquire OCT angiography volumes consisting of 304 × 304 A-scans in approximately 2.6 seconds. It uses a split-spectrum amplitude decorrelation angiography software algorithm and orthogonal registration and merging of 2 consecutive scan volumes to obtain 3 × 3 mm and 6 × 6 mm OCT angiography volumes of both eyes of each patient. OCT angiograms were co-registered with OCT B-scans, to allow visualization of both retinal vasculature and structure, and were performed in both the normal and affected eyes of each patient.

The OCT angiography software was used to segment the superficial capillary plexus and deep capillary plexus in 3 × 3 mm scans. Consistently in each patient, the superficial capillary plexus slab was taken from the internal limiting membrane (offset 3 μm) to the inner plexiform layer (offset 15 μm). The deep capillary plexus slab was taken from the inner plexiform layer (offset 15 μm) to the outer plexiform layer (offset 70 μm). In cases where thinning of the inner nuclear layer caused failure of automatic segmentation, a thinner 30 μm band was manually adjusted to include the deep capillary plexus. OCT angiography analysis of the superficial and deep capillary plexus was performed independently by a trained reader to assess for capillary attenuation and pruning involving either plexus.

Quantitative analyses were performed using the publicly available software Fiji ImageJ 2.0.0-rc-29/1.49q (http://fiji.sc/Fiji)[9] and GNU Image Manipulation Program GIMP 2.8.14 (http://gimp.org). Fiji was used to binarize and skeletonize the en face image of the superficial and deep retinal capillary plexus, showing the blood vessels as a 1-pixel-wide line. GIMP was used to count the number of black pixels and total pixels. Vessel density was then calculated as [(pixels of vessels) (3/304)]/(area in mm^2) in mm^{-1}.[10,11] In cases of partial or complete projection artifact from the superficial capillary plexus, Fiji was used to binarize the superficial and deep capillary plexus images. GIMP was then used to subtract the black pixels of the superficial capillary plexus from the deep capillary plexus image. The resulting deep capillary plexus was skeletonized using Fiji software, and pixels were calculated using GIMP. Vessel density calculation was then repeated in the manner described above.

RESULTS

NINE EYES WITH PARACENTRAL ACUTE MIDDLE MACULOPathy (8 patients: 7 male, 1 female) were identified and enrolled in this study. Clinical characteristics are summarized in Table 1. Patient ages ranged from 9 to 82 years (mean 49.5 years, median 60). Isolated band-like hyperreflective lesions in the middle retinal layers consistent with acute paracentral middle maculopathy lesions were observed with spectral-domain OCT imaging in 5 patients at baseline. Three patients presented with patchy