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Retinal Vascular and Neural Remodeling Secondary to Optic Nerve Axonal Degeneration

A Study Using OCT Angiography

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Purpose: To investigate the pathophysiologic interrelations between retinal neural and vascular changes, detected by spectral-domain OCT (SD-OCT) and OCT angiography (OCTA), resulting from optic nerve axonal degeneration.

Design: Institutional, observational, case-control study with prospective enrollment.

Participants: Twenty-six patients affected by optic nerve axonal degeneration secondary to posterior optic pathway glioma (OPG) involving the chiasma, the postchiasmatic visual pathway, or both (but not involving optic nerves) and 24 gender- and age-matched healthy participants were included consecutively.

Methods: Best-corrected visual acuity (Early Treatment Diabetic Retinopathy Study score) was measured and SD-OCT (Heidelberg Engineering, Heidelberg, Germany) and OCTA (Nidek RS-3000 Advance device; Nidek, Gamagori, Japan) were performed.

Main Outcome Measures: Peripapillary retinal nerve fiber layer (pRNFL), macular ganglion cell complex (GCC), and inner nuclear layer (INL) were analyzed using SD-OCT. The radial peripapillary capillary plexus, full-thickness peripapillary retina vascularization, and the macular superficial plexus (SCP) and deep capillary plexus (DCP) were analyzed using OCTA.

Results: Peripapillary retinal nerve fiber layer and GCC thickness were reduced in eyes affected by OPG ($P < 0.0001$). Radial peripapillary capillary plexus perfusion also was reduced, as well as full-thickness peripapillary retina vascularization ($P < 0.01$ and $P < 0.05$, respectively). Macular DCP perfusion was reduced in eyes affected by OPG, whereas macular SCP perfusion did not differ between the 2 groups ($P < 0.05$ and $P > 0.05$, respectively). Global pRNFL thickness reduction correlated with the reduction of peripapillary perfusion ($P < 0.01$). Macular GCC thickness reduction did not correlate with SCP reduction ($P > 0.05$). The reduction of macular DCP perfusion did not correlate with inner nuclear layer thickness ($P > 0.05$).

Conclusions: Retinal neural remodeling secondary to optic nerve axonal degeneration resulting from OPG located at or posterior to the chiasm is accompanied by a secondary retinal vascular remodeling involving not only the peripapillary area, but also the macular area (DCP). *Ophthalmology Retina 2017;■:1–9 © 2017 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology*

Optic neuropathies are a relatively frequent cause of vision loss and can be secondary to demyelinating diseases, inflammation, ischemic diseases, neoplastic infiltration, or compression or secondary to hereditary, toxic, or nutritional causes.[1] Optic atrophy is the final morphologic end point caused by axonal degeneration in the retinogeniculate pathway.[1] The loss of axons and neurons in the human retina can be assessed easily in vivo using spectral-domain (SD) OCT to measure retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness.[2–4] Although axonal degeneration is considered the main cause of vision loss, a concomitant role of optic nerve head microvascular direct damage by the primitive disease is supposed (glaucomatous optic neuropathy and optic neuritis) or proven (anterior ischemic optic neuropathy) in different diseases.[5–7] The recent introduction of OCT angiography (OCTA) has confirmed in vivo, in a noninvasive way, the presence of optic nerve head vascular remodeling with reduction of optic nerve head perfusion in different optic neuropathies.[5–7] Unfortunately, the proportion of vascular remodeling that may be considered primitive (disease related) and the proportion that is secondary to the axonal degeneration itself remains unknown.[1,5–7]

Compressive optic neuropathies result from mechanical compression secondary to tumors and nonneoplastic lesions, which impinge on intraorbital or intracranial structures of

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the visual pathway.[1–4] A concomitant microvascular direct damage to the optic nerve head microcirculation theoretically may concur in the pathogenesis of vision loss when compression occurs in the anterior visual pathway (optic nerve). Conversely, neural and vascular retinal remodeling secondary to posterior (chiasmatic and postchiasmatic) compressive optic neuropathies may be considered as a purely secondary result of axonal degeneration.

Optic pathway glioma (OPG) is a relatively rare neoplasm in the general population, but it is the most common (15%) tumor in patients affected by neurofibromatosis type 1 (NF1).[8] Magnetic resonance imaging (MRI) has proved to be able to identify OPGs in patients with subclinical disease, presymptomatic patients, or both.[9] This tumor may occur in any part of the visual pathway, but in NF1 patients, a consistent proportion of lesions occur in the posterior visual pathway.[8,10] Therefore, OPG secondary to NF1 is a promising model to analyze retinal vascular and neural remodeling purely as a consequence of optic nerve axonal degeneration. The aim of the present study was to investigate the pathophysiologic interrelations between retinal neural and vascular changes detected by SD-OCT and OCTA using OPG as a model of retinal vascular and neural remodeling secondary to optic nerve axonal degeneration.

Methods

Patients, Setting, and Design

This was an institutional, observational, case-control study with prospective enrolment. Institutional review board approval was obtained from the University of Padova and G.B. Bietti Foundation, IRCCS. The study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from each enrolled participant. Patients were recruited consecutively from those referred to our departments between December 2016 and March 2017. Inclusion criteria were: patients between 7 and 32 years of age affected by posterior OPGs (OPGs involving the chiasma, the postchiasmatic visual pathway, or both, but not involving the optic nerve) confirmed by orbital and brain MRI. Exclusion criteria were patients affected by OPGs involving the optic nerve or with anterior extension of a posterior OPG, identified at the MRI as an enlargement of the optic nerve, anterior to the chiasm; lack of cooperation in visual acuity assessment; lack of SD-OCT and OCTA imaging; inability to fix the internal fixation target (e.g., nystagmus); and history of any other ophthalmologic or neurologic diseases that could affect visual function or retinal or optic nerve vasculature, function, or aspect. Twenty-six eyes of 26 gender- and age-matched healthy participants also were enrolled as a healthy control group. Inclusion criteria for the control group were healthy persons with normal visual acuity (best-corrected visual acuity of 20/20 or better) and spherical equivalent less than 3 diopters. Exclusion criteria were any history or clinical evidence of ocular or systemic diseases, or both; any previous ocular surgery or laser treatment; and media opacities precluding adequate fundus imaging. Each enrolled patient and each age-matched healthy participant contributed only 1 study eye, chosen by a random number generator.

Data Acquisition

Ophthalmologic evaluation included visual acuity assessment using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts and fundus examination using indirect ophthalmoscopy. Posterior OPGs were defined using the modified Dodge classification.[11] Peripapillary RNFL (pRNFL) analysis was performed by SD-OCT (Heidelberg Engineering, Heidelberg, Germany). Each patient underwent pRNFL assessment as previously reported.[1,12] Briefly, pRNFL thickness measurements were calculated automatically by SD-OCT software, providing global average thickness of pRNFL (circle scan size, 3.5 mm).

OCT angiography was performed using a Nidek RS-3000 Advance device (Nidek, Gamagori, Japan). OCT angiography software was used for acquisition of a 3 × 3-mm optic disc map and a 3 × 3-mm macular map. The inbuilt automatic image intensity score was seated at 0 for the macula and +5 for the optic disc map. The peripapillary area was segmented automatically into multiple layers by the inbuilt software, allowing generation of multiple en face OCTA slabs. The radial peripapillary capillary plexus (RPCP) network (located in the RNFL) and the entire peripapillary capillary bed detected in the full-thickness retina were selected automatically. Automatic segmentation defined the RPCP network as the retinal vasculature detected in the first 102 μm of retina, starting from the internal limiting membrane. The full-thickness peripapillary retina vascularization was detected from the internal limiting membrane to the interface between the retinal pigment epithelium and Bruch's membrane. Macular scans were segmented automatically into multiple layers by the inbuilt software. Superficial capillary plexus (SCP) and deep capillary plexus (DCP) networks were analyzed for each patient. The en face image of the SCP was defined as the retinal vasculature detected from the internal limiting membrane to 8 μm below the inner boundary of the inner nuclear layer (INL), as identified by automated segmentation. The en face image of the DCP was defined as the retinal vasculature detected from 12 to 86 μm below the inner boundary of the INL. We also separately analyzed the portion of SCP included in the GCC to differentiate it from the entire SCP, including the vascularization located inside the RNFL. The foveal avascular zone (FAZ) for both the SCP and the DCP was measured using the inbuilt automatic area measurement editor, after manual selection of the edge points along the center line of the vessels. The GCC also was segmented automatically by the inbuilt software, reporting the corresponding mean thickness, as well as the INL, that was individuated automatically by the software as a sole layer with the outer plexiform layer. The presence of macular microcystic degeneration located in the INL also was analyzed. All SD-OCT and OCTA images were reviewed to confirm accurate segmentation by the automated instrument software and presence of artifacts. No manual adjustment was necessary. OCT angiography images with evident artifacts, signal strength index lower than 7/10, or signal quality index lower than 4/5 were excluded.

Data Elaboration

Quantitative analysis of the OCTA images was performed using open-source available ImageJ software (National Institutes of Health, Bethesda, MD). To quantify each bidimensional en face image, 3 quantitative parameters were analyzed: vessel area density (VAD), vessel length fraction (VLF), and vessel density index (VDI).[13,14] Briefly, OCTA images were converted automatically into a binary image. Vessel area density was obtained by dividing the number of black pixels counted by the software in the binary image by the total number of image pixels (868 pixels × 868 pixels = 753 424 pixels).[13] A skeletonized image then was elaborated automatically from the binary image by iteratively deleting in the outer boundary of the binary image until a single pixel remains for each vessel segment. Vessel length fraction was obtained dividing the number of vessel pixels obtained by the software in the skeletonized image by the total number of