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The Evolution of Outer Retinal Tubulation, a Neurodegeneration and Gliosis Prominent in Macular Diseases

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Purpose: To document outer retinal tubulation (ORT) formation in advanced retinal disorders.

Design: Retrospective, observational study.

Participants: Consecutive cases with retinal diseases showing outer retinal disruption and atrophy of the retinal pigment epithelium (RPE) associated with ORT on spectral-domain (SD) optical coherence tomography (OCT) at the final available visit.

Methods: Cross-sectional SD OCT scans showing ORT at the last available visit were compared with eye-tracked baseline scans. Only patients showing the formation of ORT over time with absence of ORT at baseline were analyzed.

Main Outcome Measures: Steps in ORT formation based on shapes of the external limiting membrane (ELM) descent (flat, curved, reflected, and scrolled) at the border of outer retinal and RPE atrophy, ORT characteristics (open, closed), and time between steps through a long-term follow-up.

Results: From 170 eyes of 86 patients with ORT, 38 eyes of 30 patients (11 men, 19 women) with a mean age of 78.87 years (range, 56–96 years) met inclusion criteria. Of these 38 eyes, 23 (60%) had geographic atrophy secondary to age-related macular degeneration (AMD) and 2 eyes (5%) had geographic atrophy secondary to pattern dystrophy. Twelve eyes (32%) had neovascular AMD and 1 eye (3%) had neovascularization secondary to pseudoxanthoma elasticum, all showing similar ORT formative steps. Seventy-three different retinal areas (1434 cross-sectional images) were analyzed over a mean follow-up of 69.5 months (range, 21–93 months). At 73 borders, grading of eye-tracked follow-up SD OCT line scans showed a flat ELM descent at least once at 34 borders (47%), a curved ELM at 47 borders (64%), a reflected ELM at 37 borders (51%), and a scrolled ELM at 24 borders (33%). Of 81 ORTs, 73 (90%) were closed and 8 (10%) were open. The mean time for ORT formation was 14.9 months (range, 1.4–71.3 months).

Conclusions: We propose progressive steps in the development of ORT and analyze the time of progression between these steps. Analyzing the borders of atrophy to determine the origin of ORT provides new insights into the pathophysiology of advanced retinal disease highlighting a role for Müller cells and may inform future therapeutic strategies. *Ophthalmology 2017;■:1–15 © 2017 by the American Academy of Ophthalmology*

Outer retinal tubulation (ORT) is a degenerative process of outer retinal reorganization located primarily in eyes where the macula is disrupted and there is absent retinal pigment epithelium (RPE). The advent of high-resolution spectral-domain (SD) optical coherence tomography (OCT)[1] enabled the recognition of ORT as a circular or ovoid hyperreflective band around a hyporeflective core always located in the outer nuclear layer in eyes with advanced outer retinal diseases.[1] Independently, histologic analysis had revealed interconnecting tubes of surviving cone photoreceptors interleaved with and enclosed by processes of Müller glia, overlying disciform scars associated with age-related macular degeneration (AMD).[2,3] Outer retinal tubulation has been described in numerous retinal disorders showing macular atrophy involving the RPE, including AMD,[1] retinal dystrophies,[4–7] and mitochondrial diseases,[4] with the highest prevalence in AMD. The appearance of ORT also has been described in cases of macular neovascularization resulting from diseases including AMD,[1,8–13] multifocal choroiditis,[1] pseudoxanthoma elasticum,[1] enhanced S-cone syndrome,[14] and choroidal nevus.[15] The clinical significance of ORT lies in its prognostic value, because it arises in cases of advanced disruption of the outer retina, and its presence suggests poor visual function. In eyes with neovascularization, the hyporeflective ORT lumen may be misdiagnosed as intraretinal or subretinal fluid. Thus, the recognition of ORT as a process separate from exudation may avoid unnecessary treatment.[1,3,16] Because ORT tends to change slowly over time, it is unlikely to be related to an active inflammatory or exudative process.[16]

The correlation of structural SD OCT images and histologic features has increased our understanding of ORT as neurodegenerative and gliotic processes involving the outer retina.[17–19] The hyperreflective border of ORT seen in SD OCT

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scans has been correlated histologically with the presence of both an external limiting membrane (ELM) delimiting the ORT lumen and mitochondria translocating from the inner segments to the cell bodies of degenerating cone photoreceptors.[3,17,18] The term *hyperreflective band* thus may be preferable to *hyperreflective border* because the hyperreflectivity corresponds with 2 anatomic structures (ELM and mitochondria).[19] The main histologic characteristics of ORT include: (1) location at the level of the outer nuclear layer, (2) presence of an ELM delimiting all or part of the lumen, (3) presence of surrounding radially oriented photoreceptors pointing into the lumen, and (4) degeneration or absence of the underlying RPE.[3] The presence of degenerating inner and outer segments of cones radially oriented into the lumen of ORT varies over the process.[3] Initially, both the inner and outer segments of the cones are present (nascent phase), losing gradually the outer segments (mature phase) with retraction and atrophy of the inner segments (degenerate phase), and finally, complete absence of photoreceptors with only remaining ELM (end stage).[3,17] Outer retinal tubulation-participating photoreceptors were confirmed histochemically as long- and middle-wavelength sensitive cones.[2] Because rods predominate in the extrafoveal macula,[20,21] the demonstration of only cones at the end stage of ORT shows that the rod loss begun in aging[22] continues throughout AMD. We previously hypothesized that the macular predilection of ORT suggested a requirement for photoreceptors and Müller cells with long Henle fibers.[3]

Detailed analysis of cross-sectional SD OCT images has provided information on different shapes of ORT: closed, open, forming, and branching.[3,17–19] A branching or pseudodendritic pattern is observed mainly in association with neovascularization, whereas a singular tube may line the border of geographic atrophy (GA; perilesional ORT).[23] Interestingly, analysis of ORT over time has shown fluctuations in ORT volume in cross-sectional SD OCT scans,[1] even while the ORT footprint seen with en face imaging remains constant.[16] Some studies have shown that ORT can occupy a greater area over time.[9] However, longitudinal studies to date have used either single or widely spaced time points, thus potentially overlooking the origin and dynamic nature of ORT.[16,19]

Previous authors hypothesized that ORT may originate in relation to a free edge of ELM that can scroll.[3,24] The ELM descends towards Bruch's membrane, along with subsidence of the outer nuclear layer,[25] to delimit the area of outer retinal degeneration in AMD.[26] The ELM descent has been described and classified in a recent histologic analysis of donor eyes with GA and macular atrophy secondary to neovascularization.[24,26] Shapes of the ELM descent were termed *flat*, *curved*, and *reflected*,[24,26] with the latter plausibly representing proximate steps in the formation of ORT. Informed by these histologic findings, we evaluated ORT precursors and proposed progressive steps in the origin of ORT, providing valuable information on this dynamic neurodegenerative and gliotic process of the human macula. Early detection of ORT precursors may inform the prognosis of patients with macular diseases and the selection of appropriate patients in trials of neuroprotective therapies.

Methods

This study was approved by the Western Institutional Review Board (Olympia, WA), adhered to the tenets of the Declaration of Helsinki, and complied with the Health Insurance Portability and Accountability Act of 1996. This was an observational retrospective study based on medical records and multimodal imaging data for consecutive cases seen by a single doctor (K.B.F.) at the Vitreous Retina Macula Consultants of New York and diagnosed with different advanced retinal diseases with ORT present at the last available visit. At least 12 months of follow-up with 6 visits of consecutive eye-tracked structural SD OCT volumes were required. From each volume scan, the best-quality single-line scans showing the ORT origin were selected for evaluation after a careful review of all the scans. Those scans that crossed the atrophy border perpendicularly (as confirmed in en face imaging) were the most informative. Those scans with poor visualization of the outer retina resulting from media opacities, poor patient fixation, or poor illumination were excluded. A literature review was performed reviewing all the articles containing the description or analysis of ORT and reviewing the methodology used in each published manuscript.

Imaging Protocol and Data Analysis

All eyes in the present study were scanned using Spectralis HRA+OCT (Heidelberg Engineering GmbH, Dossenheim, Germany). Because of the retrospective nature of the study, the area of analysis and the spacing between scans of structural SD OCT were not uniform across the study cohort. The analyzed area ranged from 20°×10° to 30°×25°. Line spacing ranged from 11 to 242 μm among participants, but was constant within each individual patient.

For the analysis of ORT formation, the best-quality cross-sectional SD OCT scans showing ORT at the last available visit were selected and compared with eye-tracked baseline scans. Only retinal areas lacking ORT at baseline were included in the final analysis. For the selected cross-sections, all consecutive eye-tracked scans between baseline and the last available visit were extracted and included in the analysis.

All eyes underwent high-resolution digital color fundus photography (Topcon TRC 50IX fundus camera; Topcon Medical Systems, Tokyo, Japan) and near-infrared reflectance imaging (Spectralis Heidelberg Spectralis HRA+OCT). Many eyes also were imaged with fluorescein angiography (Topcon TRC 501X fundus camera or Spectralis Heidelberg Spectralis HRA+OCT) and fundus autofluorescence (Topcon TRC 50IX fundus camera or Spectralis Heidelberg Spectralis HRA+OCT).

Demographic and clinical data collected for each patient included age, gender, affected eye, and underlying diagnosis, obtained through a review of the medical records. The mean interval between visits (in months) was recorded. For each eye, the onset and type of RPE atrophy were noted. The presence of neovascularization was diagnosed based on clinical, angiographic, and OCT data. The type of neovascularization was recorded based on the anatomic classification (type 1, 2, 3, or mixed).[27]

Definitions

On each SD OCT scan, the presence and progression of macular atrophy was documented, as well as the status of the ELM and ORT. The atrophic border was defined by the presence of hypertransmission (enhanced SD OCT signal penetration below Bruch's membrane)[28] associated with a termination of the ELM. The shape of the ELM descent at the atrophic border was graded as flat, curved, reflected, or scrolled, and ORT was classified as open or