RETINAL TUBULATION

SUMMARY

The aim of this study is to present a new retinal structure which is detectable on OCT scans - outer retinal tubulations (ORT). The discovery of these structures is related to more and more perfect retinal imaging using the spectral domain optical coherence tomography (SD OCT).
Outer retinal tubulations were first described by Zweifel et al. in the year 2009 in patients with age-related macular degeneration. These branching tubular structures are localized in the outer nuclear layer of the retina. They are of circular or ovoid shape, with hyporeflectivity in the center, their borders are hyperreflective.
Retinal tubulations are mostly seen together with choroid neovasculare membrane or with retinal pigment epithelium atrophy. Typically, they are adjacent to the area of wide damage of the outer retinal structure combined with relatively good preserved photoreceptor layer (respectively junctions between inner and outer photoreceptors segments), often they overlap the area of subretinal fibrosis or RPE (retinal pigment epithelium) damage. In eyes with anti-VEGF (vascular endothelial growth factor) treatment, they do appear in the area, where, before the treatment, the intraretinal fluid was present.
These structures may simulate CME or the presence of subretinal fluid, so their determination plays an important role in the indications of next anti-VEGF drugs' applications. Their non-detection may cause unneeded re-applications of anti-VEGF drugs into the viterous.
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Key words: outer retinal tubulations (ORT), cystoid macular edema (CME), age-related macular degeneration (ARMD), optical coherence tomography (OCT)

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Progress in the area of retinal display methods, primarily the development of SD (spectral domain) OCT (optical coherence tomography) is enabling ever more detailed display of retinal structures). Thanks to the resolution capacities of these instruments, we are capable of performing sections of the retina virtually on a histological level. The possibility of detailed display of the retina connects to a description of new morphological structures of the retina on OCT scans.

One of these newly-described structures is outer retinal tubulation (ORT) (fig. 1). It was first described by Zweifel et al. in 2009 in patients with wet form age-related macular degeneration (ARMD). It concerns tubular structures which are localised in the outer nuclear layers of the retina (i.e. the layer of nuclei of photoreceptors). They have an ovoid shape, inside the hyporeflexive cavity, and are bordered with hyperreflexive edges. The height of the tubules is 40-140 µm, and is limited by their presence inside the outer nuclear layer. The width of retinal tubulations is variable, their distribution within the macula is random (18).

In his study, Zweifel envisages the inception of a process known as "outer retinal tubulation". The precise pathogenesis is not known, but it is evident that this represents the final stage of a range of retinal pathologies. The first step in this process is damage to the photoreceptors, either as a consequence of loss of the connection of the photoreceptors and the retinal pigment epithelium (RPE), or degeneration of the RPE directly. Subsequently damage occurs to the tight junction type connections between the neuronal elements, outward flexion of the layer of photoreceptors, formation of a new tight junction type connection and the formation of a tubular structure (fig. 2). An outer hyperreflexive border is formed by the junction of the outer and inner segment of the photoreceptors (IS/OS junction) and the glial component. Outer retinal tubulations are typically localised in areas with normal retinal thickness close to the preserved layers of the photoreceptors (or undamaged IS/OS junction) (1, 18).

Histopathological studies of eyes of patients with autosomally dominant form of retinitis pigmentosa have demonstrated clusters of the remaining photoreceptors (primarily rods), forming "rosettes", whose lumen contained malformed photoreceptors (15). A similar finding has also been described by Fischer on histopathological samples of eyes of mice with a degenerated retina. According to the authors, the rosettes correspond to tubular structures on OCT (5). The first authors to identify these structures on a histopathological level in eyes with advanced form of ARMD were Curcio et al. (1)

If outer retinal tubulations are formed in eyes with a choroidal neovascular membrane (CNV) following anti-VEGF therapy, damage to the layer of photoreceptors due to the presence of subretinal or intraretinal fluid is expected (18). A detailed analysis of eyes with wet form ARMD with ORT was performed by Wolff with the help of "En face" OCT. This represents display with the help of SD OCT in frontal sections, sometimes indicated as "C-scan OCT". In his study he described three types of ORT – pseudodendritic type, tubular type and type associated with cystoid cavities in connection with reactivation of CNV (17).

The clinical significance of outer retinal tubulations resides in the fact that these structures may imitate cystoid macular edema (CME) or subretinal fluid. As a result it is important to identify them and thereby avoid the unnecessary application of substances against vascular endothelial growth factor (anti-VEGF) to the vitreous area (18). CME is characterised by the presence of cystic cavities in the outer plexiform layer (junction of photoreceptors and bipolar cells). The cystic cavities are not bordered by a hyperreflexive boundary, the typical formation here is a pentaloid structure (fig. 3). Residues of hyperreflexive material may be

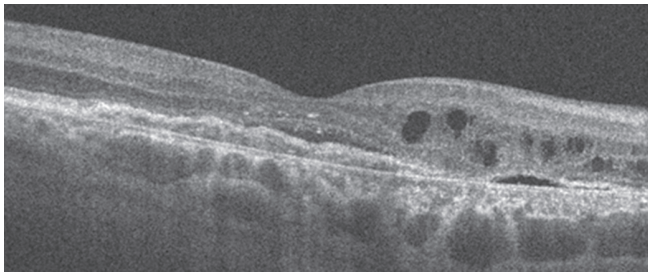

Fig. 1 Outer retinal tubulation (HD OCT Cirrus, Zeiss)

CNV predominated in the group without ORT (4). The higher incidence of ORT in patients with classic CNV is linked to a localisation of CNV or to the fact that classic CNV damages the RPE and penetrates into the subretinal space. This increases the risk of structural damage to the outer parts of the retina (4). Wolff described outer retinal tubulation in as many as 56% of patients with wet form ARMD and in 21% of patients with dry form ARMD (16). It is therefore possible to assume that the problem of outer retinal tubulations is underestimated in regular clinical practice (16). Maftouhi

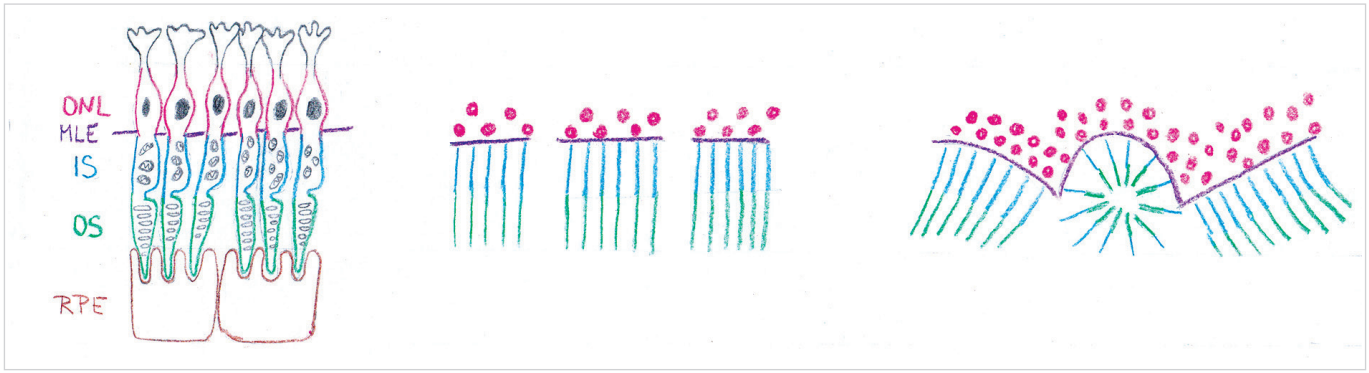

Fig. 2 Formation of outer retinal tubulations (RPE – retinal pigment epithelium, OS – outer segment of photoreceptors, IS – inner segment of photoreceptors, MLE – membrana limitans externa, ONL – outer nuclear layer

present in the lumen on ORT. Outer retinal tubulations have not been described in the case of CME as a consequence of diabetic retinopathy or retinal vein occlusion (18).

Outer retinal tubulations are not a manifestation of CNV activity. Over time outer retinal tubulations remain stable, even in the case of administration of further anti-VEGF therapy. Without anti-VEGF therapy they do not progress and do not impair visual acuity. Here there is only a minimal change in their size and distribution over time (fig. 4). Their identification is important primarily in anti-VEGF therapy guided on the basis of the finding on OCT ("OCT guided") (4). Jung et al. present a case of outer retinal tubulations stable after 7 years in a patient with wet form ARMD treated with ranibizumab (10).

The incidence of outer retinal tubulations in patients with wet form ARMD was focused on in a study by Faria-Correia. He examined 377 eyes with wet form ARMD treated with anti-VEGF therapy. He divided the patients into two groups, one without the presence of outer retinal tubulations and the second with outer retinal tubulations. The author demonstrated statistically significantly worse visual acuity in the group with ORT (35 ETDRS – Early Treatment Diabetic Retinopathy Study – letters in the group with ORT as against 45 ETDRS letters in the group without ORT), and a higher incidence of subretinal fibrosis (80% in the group with ORT as against 18.5% in the group without ORT), as well as more frequent loss of subfoveolar integrity of photoreceptors (100% in the group with ORT as against 64% in the group without ORT). There was also a statistically significant difference in the composition of CNV. In the group with ORT, CNV with a classic component predominated, whereas occult

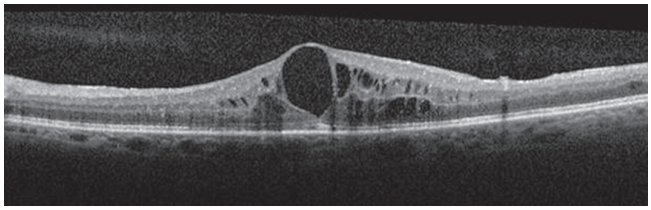

Fig. 3 Cystoid macular edema – CME (HD OCT Cirrus, Zeiss)

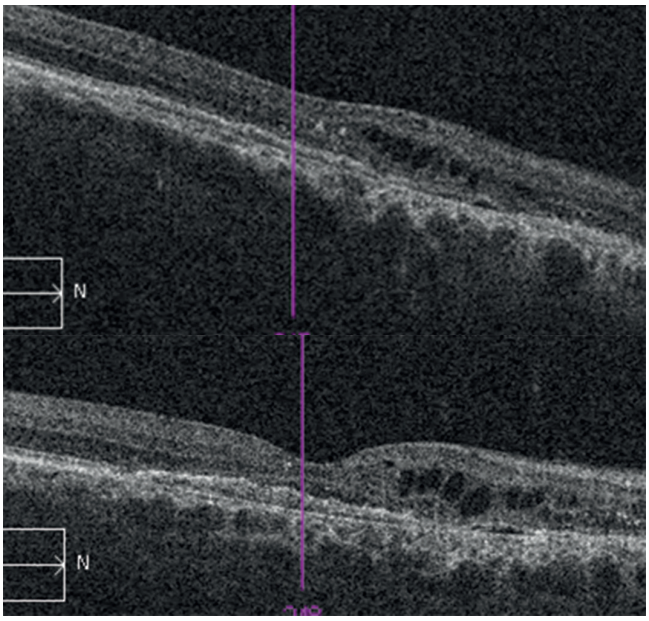

Fig. 4a, b: Outer retinal tubulation – finding in patient at an interval of 6 months with preserved visual acuity (HD OCT

inclines towards the same conclusion in his study (12). In the CATT (Comparison of AMD Treatment Trial) study, the incidence of ORT was recorded in 10% of patients treated with ranibizumab and in 17% of patients treated with bevacizumab after 56 weeks of observation. The absence of diabetes, worse initial visual acuity, greater size of lesion and the presence of subretinal hyperreflexive material at the beginning of therapy have been identified as risk factors for the development of ORT. In patients with ORT after 2 years of treatment, average visual acuity was worse than in patients without ORT (59 as against 69 letters of ETDRS optotypes) (11). Outer retinal tubulations as a prognostic factor in the progression of RPE atrophy in patients with wet form ARMD were the subject of a study conducted by Hariri et al. Enlargement of geographical atrophy was significantly slower in eyes with ORT (8).

The latest study published on this theme is the study by Dirani et al. This study included 546 eyes, and the average observation period was 27 months, minimally 6 months. The authors described ORT in 30% of eyes. During the observation period the authors observed a progressive increase in the incidence of ORT, after 4 years they recorded ORT in 42% of patients. The presence of outer retinal tubulations was linked to worse attained visual acuity. At the same time, worse visual acuity was linked to a higher risk of the development of ORT (2).

Outer retinal tubulations have been localised also in the case of other pathologies in which the outer structures of the retina are damaged. The incidence of outer retinal tubulations in a patient with chronic central serous chorioretinopathy was described by Gallego-Pinazo. This was a 56 year old male patient with a ten-year history of central serous chorioretinopathy (CSCHR) treated by interavitreal applications of bevacizumab. A zone of atrophy of the RPE was evident in the macula of the patient, with connecting outer retinal tubulations (6).

Outer retinal tubulations in a patient with serpiginous choroiditis was recorded by Mateo-Montoya. He describes a case of a 60 year old female patient with serpiginous choroiditis treated with systemic steroids and methotrexate. After one year of therapy there was a development of a post-inflammatory neovascular choroidal membrane. Therapy was commenced by intravitreal injections of ranibizumab. During this therapy there was a development of outer retinal tubulations (13).

In his study, Goldberg focused on the incidence of outer retinal tubulations in the case of macular degenerative disorders without the presence of CNV. He identified ORT in 15 patients, in 14 of whom the finding was bilateral. The most frequent diagnosis was pattern dystrophy, retinitis pigmentosa and Stargardt's dystrophy. In all groups the patients with ORT represented less than 10% of patients (7). A similar study was published with comparable results by Dolz-Marco et al. (3). The same issue was also focused on by Iriyama et al. In contrast with other studies, the author states the most frequent incidence of ORT in the case of retinal pigmentosis (9).

Outer retinal tubulations have also been found in patients with a choroidal nevus complicated by the presence of CNV. This concerned a group of 17 patients who were treated with ranibizumab. ORT was described in 18% of patients (14).

CONCLUSION

Outer retinal tubulations are a new phenomenon described on OCT scans. In differential diagnostics there is a fundamental differentiation of ORT from intraretinal or subretinal fluid. In clinical practice it is important to consider this phenomenon and thereby avoid unnecessary applications of anti-VEGF substances to the vitreous body.

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