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Global Connections to Study Idiopathic Macular Telangiectasia Type 2

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Idiopathic macular telangiectasia type 2 (Mac Tel type 2), once a poorly characterized and understood retinovascular entity, is the disease studied in a group of papers published in the current issue of *Retina*. Although considered a rare ocular condition, our understanding of Mac Tel type 2 has increased significantly since it was first described by Gass and Oyakawa in 1982.¹ To a large extent, this increased understanding and awareness can be attributed to the establishment of a large, multinational collaborative research project focusing on Mac Tel type 2. This effort grew out of a meeting held in 2004 in response to a family's request to determine if there was work that could be done to better understand, and find a treatment for, MacTel type 2. The affected family member had a delayed diagnosis but, ultimately, was appropriately referred and diagnosed. (Mac Tel type 2 is frequently misdiagnosed, most commonly as macular degeneration due to the pigmentary abnormalities and retinal telangiectasia and/or outer retinal neovascularization.) In searching for a correct diagnosis and information about the disease, the patient and his family learned that little was known about MacTel type 2, and, furthermore, there was no treatment and no active research ongoing. Not content to be given a diagnosis of a disease about which very little was known and no treatments available, the patient and his family decided to fund a program that became known as the MacTel Project. Both clinical and basic science research has been generously supported to study this condition. In the spirit of full disclosure, the authors of this editorial are active participants in this international collaborative research project generously funded by the Lowy Medical Research Institute to investigate the pathogenesis and to find potential treatments for Mac Tel type 2. Currently, there are no proven effective therapies for Mac Tel type 2.

This group of investigators have collaborated since 2005 by conducting the largest observational longitudinal study of Mac Tel type 2 to date.^{2–5} This project has evolved over the decade with strong interactions and collaboration between the clinicians from 31 international clinical sites and investigators from a dozen basic science laboratories located

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in the United States, Europe and Australia. In addition, significant efforts are ongoing to study genetic, high resolution imaging and metabolomics related to Mac Tel type 2. This condition, once thought be vascular in origin, is now considered a neuro/vasculo/glial degenerative disease. This concept is supported by clinical data from *in vivo* adaptive optics imaging⁶ as well as studies of autopsy eyes from patients with Mac Tel type 2.^{7,8} More recently, genetic and metabolomic studies suggest that MacTel may have a genetic/metabolic component with a defect in serine/glycine metabolism.⁹

This clinical research group followed a cohort of affected individuals in a natural history study and completed both phase 1¹⁰ and phase 2 clinical trials in Mac Tel type 2 employing a ciliary neurotrophic factor (CNTF) implant. Five of the current reports in this issue of *Retina* address the correlation of structural with functional changes in Mac Tel type 2. In addition to assessing the natural history of the Mac Tel type 2, one of the goals of the Mac Tel Research group was to develop outcome measurements to conduct clinical trials to test potential treatments for Mac Tel type 2 since traditional visual acuity assessment does not accurately reflect the visual disability experience by most MacTel patients. The first paper evaluated the correlation of best-corrected visual acuity with an important structural change documented on the “en face” view of spectral domain optical coherence tomography (SD-OCT) in Mac Tel type 2, the loss of the ellipsoid zone (EZ), which essentially reflects the loss of photoreceptors and its associated loss of visual function¹¹ In addition, the proximity of this loss of photoreceptors to the center of fovea was calculated, again to assess the potential correlation with functional changes. In this study of 1014 eyes from 507 participants who were followed for a mean of 4.2 ± 1.6 years, visual acuity decreased at the rate of 1.07 ± 0.05 letters (mean $\pm$ SE) per year. The rates of visual acuity loss in eyes with no EZ loss and those with EZ loss that did not affect the center of fovea were similar. However, the rate of vision loss in eyes with EZ loss affecting the center of fovea was significant higher (-1.40 ± 0.14 letters, $p < 0.001$). Visual loss progressed slowly although it was accelerated when the EZ loss affects the center of the fovea. Thus, change in vision would not be a good outcome measure in an interventional study of Mac Tel type 2. However, in this study, it was clear that EZ loss continued through the course of the study. Of those eyes with no EZ loss at baseline, 76% developed a noncentral EZ loss and in eyes with noncentral loss at baseline, 45% progressed to involve the center during follow-up. EZ loss is frequently seen in Mac Tel type 2 and it is an important structural feature that reflects visual function.

The nature of the functional changes associated with the area of EZ loss was studied in another report on a subset of participants from this large natural history study¹² There were 322 participants (632 study eyes) who had microperimetry and SD-OCT imaging in 5 of the 27 clinical centers. A reading center analyzed the data and the number of responses on the microperimetry that was below the threshold of 12, 10, 8 and 0 dB were counted and compared with one another. Absolute scotomas (0 dB) were found in 243 eyes (43%). Majority of the scotomas were found in the temporal quadrant (98%) and were unifocal (99.5%). The features of the scotomas appeared quite consistent throughout the study cohort. The transition from normal unimpaired retina to the area of the absolute scotoma appeared to have rather steep slopes, especially when the scotomas were large.

Another subset (56 eyes/31 participants) of this study was evaluated longitudinally to compare the EZ loss with the functional loss, as retinal sensitivity measured by microperimetry¹³. The analyses were conducted by counting the number of test points on microperimetry, either relative or absolute scotoma. At baseline, the mean area of the EZ loss was 0.59 mm² and this increased by 0.08 mm² per year. The change in EZ loss correlated significantly with change in relative and absolute scotomas ($r=0.62$, $p=0.0001$, $r=0.72$, $p=0.0001$, respectively) but not with visual acuity. The authors concluded the objective measure of the area of EZ loss might be considered a more clinically relevant primary outcome for future studies.

Using the data from the phase 1 safety trial of CNTF implant, the correlation of the retinal sensitivities assessed with microperimetry with the area of the EZ loss were evaluated by two methods.¹⁴ The first method calculated the mean retinal sensitivity values measured within the central 10 degrees of the grid at points not within the area of the EZ loss and that value was considered the background sensitivity. The aggregate loss was the sum of the deviations from the background sensitivity of values measured at the test points within the area of the EZ loss. The second method simply counted the number of points below certain thresholds of retinal sensitivity detected on microperimetry, similar to the method described in an earlier paper. This method was called “thresholding.” These data of the seven well phenotyped participants over a period of four years showed a good correlation of the two methods of measuring functional changes with the area of the EZ loss. For the method of aggregate loss, the r was 0.834, 95% confidence interval: 0.716–0.906. There was also good correlation with the thresholding method for retinal sensitivities below 20 dB ($r=0.843$, 95% CI: 0.755 – 0.906). The authors found the en face OCT mapping of the EZ loss reflected structural changes before the microperimetry can detect a loss of retinal sensitivity.

Our colleagues at Moorfields Eye Hospital also tested the electrophysiologic features of Mac Tel type 2 and their correlation with structural changes found on OCT.¹⁵ The participants ($n= 42$ eyes/21 participants) had full-field and pattern electroretinogram (ERG) with some having additional multifocal electroretinography (mfERG) and electrooculography (EOG). The full field ERGs and EOGs were normal while the mfERG demonstrated reduced response of the central or paracentral stimulus. There was a significant correlation between the size of the EZ break area with the P1 amplitudes and the P1:N1 ratio of the central responses on mfERG. The size of the EZ break area correlates with mfERG reduction. The reduced mfERG P1:N1 ratio suggests inner retinal dysfunction. Although electrophysiologic studies may not be warranted in the diagnosis of patients with Mac Tel type2, such studies may provide insight into the mechanisms of disease.

Another report from the natural history study evaluated the progression of the retinal pigment epithelial plaques that are frequently seen in Mac Tel type 2.¹⁶ Pigment cells from the retinal pigment epithelium initially grow along the blunted and right-angle veins in a “vertical manner,” using the abnormal vessels as a scaffold. As this growth reaches the inner retina, the cells proliferate and spread horizontally. This pigment plaque is associated with decreased retinal function and may be a sign of more advanced severity of disease.

In this series, the authors evaluated 1244 participants (probands from the genetic study) and found signs of a well-known late complication of Mac Tel type 2, subretinal neovascularization (SRNV), in 150 right eyes (12.1%) and 118 left eyes (9.5%). Of these, 114 (75%) had SRNV detected at baseline while 36 eyes (24%) developed SRNV during follow-up in the right eye. In 29 (81%) that developed SRNV during follow-up, pigment was observed prior to the development of SRNV. Similarly, 83% of left eyes had pigment present prior to the development of SRNV. It appears that pigment development heralds a more ominous development of SRNV which causes severe vision loss in affected eyes. This lesion may be an important characteristic for any staging scheme of Mac Tel type 2 as it had a prominent position in the previous classification proposed by Gass and Blodi, namely in the stage 4 of the more severe stage of Mac Tel type2. This analysis of the growth of this important lesion provides more insight into the pathogenesis and natural course of Mac Tel type 2. Because of its association with SRNV, it would seem reasonable to exclude persons with the presence of the pigment from intervention studies.

Drs. Spaide and Yannuzzi, who are active members of this collaborative research group, introduced new clinical concepts in another report. They noted tissue contraction with retinal vascular displacement which was measured on serial fundus photographs using vectors to assess the direction and magnitude of the changes in Mac Tel type 2.¹⁷ This contraction obviously changes the structure and may result in visual impairment. The clinical relevance of these findings may require further studies with larger number of participants affected with Mac Tel type 2.

Another report in this issue of *Retina* found an association of Mac Tel type 2 with sex steroids from participants (n=90) in one clinical center (Moorfields) of the natural history study consortium.¹⁸ Women were more likely to have had medical and surgical therapies that decreased ovarian function and they appeared to have an earlier onset of Mac Tel type 2 than those with no ovarian suppression. Similarly, men were more likely have lower serum levels of testosterone. This interesting association with sex hormone needs to be evaluated in future studies to understand the potential impact of sex steroids on the course of Mac Tel type2. Similarly, another study described the occurrence of central serous chorioretinopathy with Mac Tel type 2 in five patients.¹⁹ Whether these are chance findings of risk factors or co-morbidities, these factors remain to be further assessed. Our later discussion of another report of the structural changes at the apical aspects of the retinal pigment epithelium (RPE) indicates that these potential subclinical changes of the RPE that may indeed predispose persons with Mac Tel type2 to have associated conditions, which may be related to the health of the RPE. The main co-morbidity which was not emphasized or studied in this issue is the strong association of Mac Tel type 2 with type 2 diabetes.⁴ We look forward to future studies that may elucidate the underlying mechanism of this association of these two conditions.

Two very interesting reports evaluated images using the blue light reflectance method. From our natural history study, one of the first indications of the diagnosis of MacTel type 2 is the hyperreflectivity of the parafoveal area that is oval and evident with the blue light reflectance technique of imaging. This is the area dubbed as “MacTel area” by our colleague, Marcus Fruttinger. In the current issue of *Retina*, investigators correlated the blue light reflectance

images with fluorescein angiography, SD-OCT, and the dual-wavelength fundus autofluorescence in a group of participants enrolled in the natural history study.²⁰ The dual-wavelength fundus autofluorescence is ideal for objective evaluation the macular pigment or the luteal pigment, as noted by the investigators. The macular pigment was known to be partially or fully absent in eyes with Mac Tel type 2 from previous reports²¹ and supplementation with lutein resulted in no beneficial effect of increasing the macular pigment.²² The cause for this hyperreflectivity on the blue light reflectance is not known but the lack of macular pigment has been implicated. The investigators found a high correlation of the images from the blue light reflectance with the dual wave-length fundus autofluorescence ($p = 0.917$, 95% CI: 0.855 – 0.954, $p < 0.0001$ for right eyes, $p = 0.952$, 95% CI: 0.916 – 0.973, $p < 0.0001$ for left eyes). The authors concluded that there is localized susceptibility to the disease in the macula and an abnormal metabolic processing of the macula pigment and physical changes result in increased reflectance in the macula, even in the early stages of the disease when minimal changes are detected. The images on the blue light reflectance may indeed be one of the earliest indication of the diagnosis of Mac Tel type 2.

The other report evaluated the blue light reflectance methodology in Mac Tel type 2 in the participants enrolled at Moorfields.²³ A prior report described nine patients with Mac Tel type 2 who displayed the early signs of opacification of the retina (greying of the retina) on color fundus photographs.²⁴ Following a period of exposure to the light of the indirect ophthalmoscope, the greying decreased markedly in intensity. The authors studied this phenomenon by evaluating the effects of dark adaptation and bleaching on the blue light reflectance images in 18 eyes of 16 participants with Mac Tel type 2 and five controls without eye disease. Following dark adaptation of 15 minutes with a patch, blue light reflectance images were taken and subsequent re-dark adapted for another 5 minutes. As noted in the prior report, the hyperreflectivity was enhanced, with a larger difference between the hyperreflectivity of the parafoveal region compared with the background retina in the Mac Tel type 2 affected eyes while the difference was much smaller in the controls eyes. This difference between the hyperreflectivity of the parafoveal region and the retina beyond diminished with increasing exposure to the light of the Heidelberg Spectralis® SLOSLO system (Heidelberg Engineering, Heidelberg, Germany) which was used to obtain the images. It is also well-known that the bleaching has an effect on the routine fundus autofluorescence imaging technique.²⁵ This may play a role. The investigators concluded that bleaching may have increased the reflectivity in the normal area surrounding the parafoveal area of pathology as well as inducing changes in the affected parafoveal area, causing the difference to be less. Dark adaption may be important in obtaining the diagnostic blue light reflectance images for Mac Tel type 2.

Again, in another report, our colleagues from Moorfields confirmed interesting findings on OCT that were previously described by Dr. Spaide on OCT-angiography imaging.^{26,27} In 11 (6.4%) of the 172 eyes from 8 (9.3%) of 86 participants with MacTel from Moorfields, microcystoid spaces were detected mostly in the inner nuclear layer. These microcystoid spaces were found entirely within this assumed MacTel area defined on blue light reflectance imaging, the oval area centered around the fovea. These cysts on average were about 30 μm in diameter. The clinical significance of these microcystoid spaces is not known

but the fact that they are found mostly in the “MacTel” area would point towards an association with the disruption of the Müller cells.

Finally, a very intriguing report described the histopathology of the eyes from four patients who were affected with MacTel type 2.²⁸ The previous reports describe the pathology of MacTel type 2 in a restricted area, a small oval area centered around the fovea in which the glial and photoreceptor cell death occur. Despite the previously described associated diseases such as central serous chorioretinopathy, no pathology associated with MacTel has been described in the retinal periphery. In all eight eyes, using immunohistochemistry and electron microscopy, cellular debris was found in the subretinal space between the photoreceptor outer segments and the apical aspects of the RPE. The debris consisted mainly of the outer segments and RPE components. In normal ocular health, the RPE phagocytoses the tips of outer segments of the photoreceptor cells. In MacTel type 2, the apical surface of the RPE appeared abnormal with no activities involving the outer segments. This report does not reconcile well with the report of the absence ERG abnormalities other than the focal abnormalities in the center of the retina found on multi-focal ERG. Furthermore, rod function does not appear to be compromised in MacTel type 2. To date, there is no *in vivo* correlation of these histological findings with subretinal disease on the SD-OCT imaging. The clinical significance of these findings remains uncertain given the lack of functional correlates and perhaps future histopathological studies may replicate these intriguing findings.

These current reports complement on-going work of the research group. There are interesting novel findings that serve to stimulate further research to understand the role of sex hormones, subretinal debris, and the effects of dark adaptation and bleaching on blue light reflectance. The data from the natural history study showed that en face view of OCT changes with the loss of the EZ progresses throughout the four years of follow-up. The correlation of these changes on OCT with visual acuity is not good. However, the measures of retinal sensitivity on mesopic microperimetry correlate well with the area of the EZ loss. The scotomas resulting from the EZ loss appear to have well demarcated and steep slopes along the margins. Similar to the studies of geographic atrophy, the area of the loss of the EZ appears to be a good surrogate outcome measure of progression of disease. This primary outcome of an increase in the size of the EZ loss has been tested in clinical trials of the CNTF implant. The phase 1 study was a safety study and the phase 2 study has just completed and the results will be reported shortly.

Mac Tel type 2 is an orphan disease that has been extensively studied by a group of dedicated researchers who have had the good fortune of consistent support and an agile administrative system. The regular face-to-face meetings of the clinical and basic science researchers have produced fruitful and stimulating interchanges that help propel research from different perspectives. The global connection is essential because diverse opinions allow for thinking outside the box and better research methodology. This is an interesting and unique example of a collaboration between private philanthropy and public entities and academic centers. We are fortunate to be part of this experiment. With persistence, we hope to find a treatment for this neurodegenerative disease and to contribute to knowledge of retinovascular diseases in general.

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