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Familial Asymptomatic Macular Telangiectasia Type 2

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Abstract

Objective—To report findings in asymptomatic family members of patients with macular telangiectasia type 2.

Design—Prospective, observational, cross-sectional case series.

Participants—Four patients with symptomatic macular telangiectasia type 2 (index patients) and 5 relatives, including 2 sets of monozygotic twins.

Methods—Screening of family members of participants in a non-interventional natural history study of macular telangiectasia type 2. Ophthalmologic examination included best-corrected visual acuity testing, fundus biomicroscopy, fluorescein angiography (FA), optical coherence tomography (OCT), and fundus autofluorescence (FAF) imaging.

Main Outcome Measures—Evidence for macular telangiectasia type 2 in any of the imaging methods used and visual function of the family members studied.

Results—In the first family, 2 of 3 daughters of a severely affected 68-year-old woman had features of macular telangiectasia type 2. Although one of the daughters was diagnosed by biomicroscopic examination, the second daughter was diagnosed only by subtle changes on OCT and FAF imaging. Both affected daughters were asymptomatic and were unaware that they had the condition. In the second family, clinical examination showed that the 60-year-old brother of the 75-year-old index patient obviously was affected, despite a lack of any subjective visual dysfunction. The 65-year-old monozygotic twin of the third index patient showed a slight retinal thinning within a small area temporal to the foveola in both eyes as well as minor staining on FA and a subtle monocular loss of macular pigment. The 56-year-old asymptomatic monozygotic twin of the last proband had opacification of the retina with leakage on FA in the right eye. The fellow eye was unremarkable except for an abnormal FAF signal that was present in both eyes.

Conclusions—Macular telangiectasia type 2 may be more common than previously assumed, but patients may not seek ophthalmic care if their visual function is normal. The study of these early, asymptomatic cases may yield valuable insights into the pathogenesis of the condition.

Further research is warranted to determine whether there is an underlying, dominantly inherited genetic abnormality in macular telangiectasia type 2 of variable penetrance and expressivity.

Macular telangiectasia type 2 is an uncommon bilateral condition affecting principally the juxtafoveal region with a temporal predilection.^{1–3} Dilated, tortuous capillaries are associated with reduction of macular transparency. Peculiar crystals in inner retinal layers often are found. In more advanced cases, localized intraretinal pigment migration and neurosensory atrophy are associated with pronounced loss of retinal function.⁴ In a subset of patients, neovascular membranes as well as macular full-thickness or lamellar holes^{5,6} may lead to further functional damage. Patients usually seek treatment in their fifth to sixth decades with visual symptoms such as metamorphopsia and decreased reading abilities that may be out of proportion to their central visual acuity, which may be only mildly affected, at least initially.^{7,8}

The few reports of macular telangiectasia type 2 in monozygotic twins^{9–11} as well as in siblings and families^{1,12–16} suggest that the condition may have a genetic component. These earlier reports described familial occurrence only in symptomatic patients. Identification of further affected but as yet asymptomatic family members might have been limited by the lack of a noninvasive diagnostic technology to detect subtle alterations characteristic for early disease stages that might have been missed by biomicroscopy alone.

Optical coherence tomography (OCT),^{17–24} confocal blue reflectance (CBR) imaging,^{25,26} and assessment of macular pigment optical density (MPOD)^{26–28} (for example, by using two-wavelength fundus autofluorescence [FAF]), are now recognized to be sensitive ways of identifying eyes affected with macular telangiectasia type 2. Characteristics on macular OCT imaging include foveal hyporeflective spaces, loss of reflectivity of the presumed junction between inner and outer photoreceptor segments, shortening of the photoreceptor outer segments, and increased reflectivity of the outer nuclear layer.²⁴ A common phenomenon on CBR imaging is an increased reflectivity in the parafoveal area, which was suggested to be the result of a lack of macular pigment.²⁶ The area of increased CBR and reduction of macular pigment was found to be slightly larger than the area of hyperfluorescence on angiography.²⁶

The Macular Telangiectasia Project is an international collaboration of clinical and laboratory research groups that aims to develop treatments for macular telangiectasia type 2 (www.mactelresearch.org; accessed March 23, 2009). The first-degree relatives of each proband currently are being screened for the condition. Reported herein are family members without subjective visual dysfunction who were diagnosed with macular telangiectasia type 2 because of typical findings on various imaging methods.

Methods

Patient Enrollment

This study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committees. Participants in the Macular Telangiectasia Projects' natural history study (index patients) whose diagnosis was confirmed by the Reading Center at Moorfields Eye Hospital, London, were asked to invite their first-degree relatives to contact study personnel to arrange for an eye examination.

Data Collection

All patients underwent a complete ophthalmic examination including best-corrected visual acuity (BCVA) testing, slit-lamp examination with indirect ophthalmoscopy, fundus photography, time-domain OCT, and fundus autofluorescence imaging using a confocal

scanning laser ophthalmoscope (modified HRA classic, HRA2, or Spectralis HRA-OCT; all Heidelberg Engineering, Heidelberg, Germany). Fluorescein angiography (FA) also was performed.

The principles of FAF imaging using a confocal scanning laser ophthalmoscope have been described in detail previously.²⁹ A blue laser is used for excitation at 488 nm, and a barrier filter restricts detection of emitted light to a wavelength range of more than 500 nm. A series of digital images may be averaged by automated alignment using the software of the HRA to improve the signal-to-noise ratio. The FAF signal usually originates from the retinal pigment epithelium and is dependent on the amount of fluorophores (e.g., lipofuscin in the retinal pigment epithelium) as well as the absorption or blockage of the exciting light (e.g., by macular pigment, retinal vessels, blood, unbleached photopigment, media opacities).

In a subset of patients, CBR (using the HRA2) and MPOD (using the modified 2-wavelength HRA classic) were assessed as described previously.^{26,27} Briefly, CBR images are obtained at a wavelength of 488 nm (argon laser). Macular pigment optical density was calculated from 2 averaged FAF images at 488 and 514 nm, respectively, in conjunction with a barrier filter that blocks all wavelengths shorter than 560 nm. The maximum absorbance of macular pigment is at 460 nm. Therefore, depending on macular pigment density, the FAF image at 488 nm shows less autofluorescence compared with the FAF image at 514 nm. Subtraction of the 2 averaged images results in an image representing MPOD distribution.

The OCT images were recorded on a time-domain OCT (Stratus OCT with software version 4.01; Carl Zeiss Meditec, Oberkochen, Germany). The built-in Macular Thickness scan program—consisting of 6 radial scan-lines of 6 mm in length at 30° intervals centered on the fovea—was used. Macular thickness was considered significantly different from normal if values differed more than ± 2 standard deviations from normative values reported by Chan et al³⁰ where not stated otherwise.

In 1 subject, raw scan data were exported from the time-domain OCT device for further analysis. Scan data were opened as a 12-bit grayscale image, resulting in grayscale-values ranging from 0 to 4095 and analyzed as described previously.^{24,31} Light reflection profiles were calculated every 50 μm along each single OCT scan using a commercial software package (IGOR 6.03a; Wavemetrics, Inc., Lake Oswego, OR). Results are expressed as arbitrary units (AU).

In 1 family, spectral-domain OCT images were obtained (using the Spectralis HRA-OCT). This technique not only allows visualizing the retinal cross-sectional structure with more detail, but also enables the measurement of macular volume by analysis of multiple densely recorded horizontal single scans. This allows calculating 3-dimensional topographic maps of the macula.

Results

Family 1

The index patient, a 68-year-old woman, had experienced progressive blurring of vision in both eyes for 20 years and previously had been diagnosed with macular telangiectasia type 2. The BCVA in each eye was 20/100. Fundus examination of both eyes revealed retinal pigment epithelial migration and reduced retinal transparency temporal to the foveola. The OCT images showed central macular atrophy bilaterally and an epiretinal membrane in the left eye. The FA examination revealed predominantly temporal macular telangiectasia in the early phases with diffuse hyperfluorescence in the later phases. On FAF imaging, there was

blockage of the signal within areas of pigment migration and an absence of the usual attenuation of the foveal FAF signal because of lack of macular pigment.

Her 3 daughters all believed that they had normal vision. The eldest daughter (45 years of age) had BCVA of 20/20 in both eyes. Funduscopy revealed some subtle graying of the temporal macula. Fluorescein angiography revealed minor late-phase leakage in the temporal parafovea of the right eye (Fig 1A, B). The FAF imaging showed a slight but well-defined increase in signal temporal to the foveola in both eyes (Fig 1C, D). The OCT imaging revealed central retinal thinning, increased reflectivity within the outer neurosensory retina, and a disruption of the highly reflective band that is thought to represent the border between inner and outer photoreceptor segments (Fig 1E, F). The quantitative analysis of the OCT images showed a reduced foveolar retinal thickness of $142.2 \pm 4.5 \mu\text{m}$ (normal according to Barthelmes et al,²⁴ $194.1 \pm 9.7 \mu\text{m}$ [mean $\pm$ standard deviation]), whereas in the temporal and nasal perifovea, retinal thickness was found to be within normal limits ($230 \pm 9.4 \mu\text{m}$ and $232.2 \pm 10.8 \mu\text{m}$, respectively). An increased reflectivity of the temporal outer nuclear layer of $1369 \pm 164.7 \text{ AU}$ (normal, $1179.2 \pm 81.9 \text{ AU}$) was detected, starting at $220 \mu\text{m}$ temporal of the foveal center, with a length of approximately $680 \mu\text{m}$ at the most temporal extension, whereas the nasal outer nuclear layer had a normal reflectivity of $1099.1 \pm 105.44 \text{ AU}$ (normal, $1181.4 \pm 81.5 \text{ AU}$). The outer segments of foveal photoreceptors were reduced to a mean length of $38.6 \pm 5.6 \mu\text{m}$ compared with $45.1 \pm 10.6 \mu\text{m}$ for normal controls. Except for the normal retinal thickness in the temporal perifovea, the findings are similar to those of previously analyzed patients.²⁴ This woman was diagnosed with early macular telangiectasia.

The 43-year-old daughter in this family had visual acuity of 20/20 in the right eye and 20/25 in the left eye and all other examination results were normal. The youngest daughter (41 years of age), although asymptomatic, had mild reduction in visual acuity to 20/25 in both eyes. A diagnosis of macular telangiectasia type 2 was suggested by clinical examination because there was loss of temporal macular transparency and visible telangiectatic capillaries bilaterally. The diagnosis was confirmed subsequently by FA (Fig 1G, H). On FAF imaging, there was an increased central FAF signal and telangiectatic capillaries predominantly temporal to the foveola (Fig 1I, J). The OCT examination demonstrated characteristic inner foveal hyporeflective spaces (Fig 1K, L).

Family 2

The index patient, a 74-year-old woman, had progressive blurring of vision in both eyes lasting for 10 years. She had been treated for type II diabetes mellitus for 3 years. The BCVA was 20/40 in the right eye and 20/32 in the left eye. The OCT examination showed atrophic changes with hyporeflective spaces at both foveas and FA revealed diffuse leakage in the temporal macula. The FAF imaging revealed an increased signal within the area of angiographic leakage temporal to the fovea bilaterally.

This woman's 61-year-old brother reported normal vision and had been checked by an optometrist every 2 years. Visual acuities were 20/20 bilaterally. Late-phase FA images revealed subtle hyperfluorescence temporal to the foveola of each eye (Fig 2A, B). The FAF imaging showed loss of the attenuation of background autofluorescence in the foveal area that is typical of macular telangiectasia type 2 (Fig 2C, D). The diagnosis of macular telangiectasia type 2 was confirmed by the demonstration of the characteristic hyporeflective spaces in both foveas on OCT imaging (Fig 2E, F).

None of the affected family members of index patients 1 and 2 had a significant medical history. In particular, none was a smoker, nor had any been diagnosed with diabetes.

Family 3

This family included a pair of monozygotic twins. A 56-year-old otherwise healthy woman (index patient) reported bilateral blurred vision for several months. She had a history of phototherapeutic keratectomy on the left eye for corneal scars after virus-induced keratitis. She was otherwise healthy and did not take any medication. Visual acuity was 20/63 bilaterally. Funduscopy showed a loss of macular transparency and superficial crystalline deposits in both eyes. The FA examination revealed parafoveal telangiectatic capillaries predominantly temporal to the foveola with diffuse hyperfluorescence in the late phase (Fig 3A, B). The parafoveal area showed an increase in CBR (Fig 3C), a decrease in MPOD (Fig 3D), and an abnormally high FAF signal in the central retina (Fig 3E). The OCT examination showed typical hyporeflective foveal spaces. Retinal thickness was within normal limits.

The ophthalmologic and medical histories of the monozygotic twin of the index patient were unremarkable. Both twins were otherwise healthy, had never smoked, had always lived in the same area, and led an apparently similar lifestyle. The gestation of the twins was unremarkable. Visual acuity of the index patient's twin was 20/20 and 20/25 in the right and left eyes, respectively. There were no signs of macular telangiectasia type 2 funduscopically (notably no retinal graying), nor did time-domain OCT imaging show significant alterations of macular thickness, hyporeflective spaces, or decreased reflectivity of the border between inner-outer photoreceptor-segments. Early-phase FA was unremarkable (Fig 3F), but the late phase revealed a small area of diffuse hyperfluorescence temporal to the foveola in the left eye (Fig 3G). Within the same region, CBR imaging showed slightly increased reflectance and MPOD was mildly decreased, resulting in a slightly increased FAF signal (Fig 3H–J). The right eye showed unremarkable results on all these imaging methods. However, spectral-domain OCT demonstrated a small area of reduced retinal thickness in both eyes temporally adjacent to the foveola (Fig 4). This alteration was more pronounced in the left eye, where it was related topographically to the findings on confocal scanning laser ophthalmoscope imaging.

Family 4

This family also included a pair of monozygotic twins. A 56-year-old man sought treatment for a decrease in vision in his right eye of 2 months' duration. He was found to have macular telangiectasia type 2 with visual acuity of 20/100 in the right eye and 20/20 in the left eye. His right eye had marked retinal opacification in the parafoveal area (Fig 5A) with topographically related leakage on FA (Fig 5C). The left eye was unremarkable on ophthalmoscopy but showed evidence of minor angiographic leakage temporal to the foveola (Fig 5D). The FAF examination revealed an increased signal in the right fovea and a homogeneous and less well-defined area with a less increased FAF signal in the foveal area in the left eye (Fig 5E, F). The normal masking of the FAF signal by macular pigment at the fovea was not present. The OCT examination of the right eye showed evidence of a hyporeflective space at the fovea (Fig 5G). He was otherwise healthy and was not taking any medication at the first visit, but 4 years later had developed type 2 diabetes.

His monozygotic twin brother had a history of type 2 diabetes of 6 months' duration. He was asymptomatic and he recently underwent an eye examination by a retinal specialist for an assessment for diabetic retinopathy that was said to have shown normal results. His visual acuity was 20/20 bilaterally. In his right eye, there was evidence of predominantly temporal perifoveolar retinal opacification (Fig 5H) that corresponded to an area of leakage temporal to the foveola on FA (Fig 5J). The left eye was unremarkable on ophthalmoscopy and FA (Fig 5I, K). The FAF examination showed an increased foveal signal compared with normal, which was more pronounced in the right than in the left eye (Fig 5L, M). The OCT images

showed retinal thinning at the foveal area of the right eye with no evidence of cystic changes, while the left eye was normal (Fig 5N).

Discussion

This study raises the possibility that macular telangiectasia type 2 is a more common condition than was previously thought. In addition to symptomatic cases, in which the disease is usually visible on biomicroscopic examination, there may be a group of patients in whom the diagnosis is not made because they do not have visual dysfunction. The macular alterations in these subjects may be so subtle that they are missed by standard clinical examination. These cases may be detected using noninvasive imaging techniques that only recently have become available, such as spectral-domain OCT, FAF, or CBR imaging.

Three anatomic alterations detectable with noninvasive imaging technologies seem to be particularly helpful in identifying asymptomatic patients with macular telangiectasia type 2: loss of macular pigment in the temporal foveola (and thus an increased signal in FAF, FA, and CBR imaging), an asymmetric neurosensory thinning within the same area, and hyporeflective spaces within the neurosensory retina on OCT imaging. These findings may represent the earliest stages of the disease and would be consistent with the hypothesis that macular telangiectasia type 2 is primarily a dystrophic macular disease with secondary involvement of the juxtafoveolar capillaries. However, these investigations have not yet been tested systematically in large populations, so their results should be interpreted with care, particularly if abnormalities occur in isolation.

Although macular telangiectasia type 2 previously has not been thought of as a genetic disease, there are a few reports of familial occurrence. Gass and Blodi¹ found the condition in 2 of 89 families. Hutton et al¹² treated 2 affected sisters aged 46 and 56 years. Reporting on 5 patients with diabetes and macular telangiectasia type 2, Chew et al¹³ found the condition also in the nondiabetic brother of 1 patient. Oh and Park¹⁴ described vertical transmission in the 29-year-old daughter of a 58-year-old affected man. Putteman et al¹⁶ reported familial occurrence of macular telangiectasia type 2 in a father and son and also in 2 brothers. Macular telangiectasia type 2 also has been described in 3 separate sets of monozygotic twins.^{9–11} It seems that a lack of visual problems was used by previous surveys to discount the possibility that relatives were affected. All the relatives of the index patients presented in this article would have been overlooked by this approach.

These findings strengthen the hypothesis that there may be a genetic predisposition to macular telangiectasia type 2, on which a second influence acts, either environmental, genetic, or both, to produce clinically evident disease. There may be a vascular contribution to this so-called second hit, which would be consistent with the markedly increased prevalence of hypertension, diabetes, and coronary artery disease in patients with macular telangiectasia type 2 (Clemons TE, personal communication, 2009).

An environmental influence on a genetic defect is suggested particularly by the second twins presented in families 3 and 4, who had very mild, practically asymptomatic disease in 1 eye only, whereas his or her genetically identical sibling had symptomatic disease in both eyes that was easily detected clinically. Previous reports showed very similar disease manifestations in monozygotic twins.⁹ Diabetes¹⁰ or smoking¹¹ were suggested to be possible confounding factors in the twin with the more advanced disease. The monozygotic twins presented as family 3 are otherwise healthy and have never smoked, have lived in the same area always, and have led the same lifestyle. In the second monozygotic twin pair (family 4), diabetes was present in the less affected twin, but developed later in the other. This is in contrast to the report by Siddiqui et al,¹⁰ in which the more affected twin had a

history of diabetes. The very different extent of macular involvement provides further evidence that so far-unidentified confounding factors may have an impact on the disease manifestation and progression. Epigenetic differences are an alternative explanation for phenotypic discordance between monozygotic twins. It has been reported that older monozygotic twins have significant differences in their overall content and genomic distribution of 5-methylcytosine DNA and histone acetylation, which affect their gene-expression profiles.³²

Further research is warranted to confirm the findings of this study. The study of early cases of macular telangiectasia type 2 may lead to a better understanding of the condition. It seems that the FAF changes may precede the angiographic changes, suggesting that the condition may arise elsewhere, perhaps in Müller's cells or in the photoreceptors. The authors previously described a case in which changes typical of cone dystrophy were found to precede the typical vascular changes.³³ It is anticipated that new and emerging imaging technology, such as adaptive optics, spectral-domain OCT, and FAF, will be helpful to untangle the sequence of events in macular telangiectasia type 2. Further research also is warranted to identify whether genetic variants contribute to the condition, and this is being pursued actively.

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Figure 1.

A, B, Fluorescein angiography images of the eldest daughter of the first index patient showing mild late-phase staining in the temporal parafovea of the right eye. **C, D**, Fundus autofluorescence images from this subject demonstrating slightly increased signal temporal to the fovea in both eyes. **E, F**, Horizontal optical coherence tomography scans revealing disruption of the highly reflective band representing the border between inner and outer photoreceptor segments, retinal thinning, and increased reflectivity of the outer nuclear layers in the temporal perifoveas (arrows), more marked in the right than the left eye. **G, H**, Fluorescein angiography images from the youngest daughter of this family demonstrating leakage temporal to the foveola in both eyes. **I, J**, Fundus autofluorescence images showing increased central autofluorescence and telangiectatic capillaries predominantly temporal to the foveola. **K, L**, Optical coherence tomography revealing characteristic inner foveal hyporeflective spaces.

Figure 2.

A, B, Late-phase fluorescein angiographs of the 61-year-old brother of the second proband revealing subtle hyperfluorescence temporal to the foveola of each eye. **C, D,** Fundus autofluorescence (FAF) imaging showing loss of central attenuation of the FAF signal that is typical of macular telangiectasia type 2. **E, F,** Optical coherence tomography images showing characteristic hyporeflective spaces in both foveas also typical of macular telangiectasia type 2.

Figure 3.

Images obtained from monozygotic twins with macular telangiectasia type 2. **A, B**, Fluorescein angiography images obtained from the index patient (twin 1 of family 3) showing typical vascular alterations with ectatic capillaries visible in the early phase and dye leakage in the late phase, predominantly temporal to the foveola. **C**, Increased confocal blue reflectance (CBR) and **(D)** decreased macular pigment optical density (MPOD) are topographically related. **E**, There is also increased fundus autofluorescence (FAF). Angiography image obtained from the asymptomatic patient (twin 2) revealing **(F)** no obvious changes in the early phase and **(G)** only mild late hyperfluorescence in a small area temporal to the foveola (arrow). **H**, Subtly increased CBR, **(I)** decreased MPOD, and **(J)** increased FAF all appeared topographically related (arrow).

Figure 4.

Spectral-domain optical coherence tomography (OCT) images obtained from twin 2 (family 3). **A, B**, Retinal thickness maps showing the location of retinal thinning (blue) in relation to the foveolar location (marked with the small square) in **(A)** the right eye and **(B)** the left eye, respectively. The latter can be defined on the single OCT scans on which the map is based. **C, D**, The location with the largest distance between the 2 outer highly reflective layers was chosen as the foveal center. In both eyes (left more than right), the thinnest area of the fovea is not centered on the foveola, but rather is shifted temporally.

Figure 5.

A, B, Color photographs obtained from a 56-year-old man showing retinal opacification in the **(A)** right perifoveal area while the left appeared normal and **(B)** left perifoveal areas. **C, D,** Fluorescein angiography images demonstrating perifoveal leakage **(C)** in the right eye and **(D)** in the temporal aspect of the left eye. **E, F,** Fundus autofluorescence images showing **(E)** evidence of abnormal hyperfluorescence in the right fovea and **(F)** the absence of the hypofluorescent central area in the left fovea. **G,** Optical coherence tomography scan of the right eye showing evidence of a hyporeflective space at the fovea. **H, I,** Color photographs obtained from the monozygotic twin showing **(H)** evidence of retinal opacification of the right perifoveal area that **(I)** is not evident in the left eye. **J,** Fluorescein angiography image demonstrating perifoveal hyperfluorescence in the area temporal to the right fovea. **K,** Fluorescein angiography image showing a suggestion of early signs of vascular abnormalities with mild leakage in the temporal area of the left eye. **L, M,** Fundus autofluorescence images showing **(L)** central hyperfluorescence in the right eye and **(M)** that the left eye is missing the usual hypofluorescent spot in the fovea. **N,** Optical coherence tomography scan of the right eye showing retinal thinning at the fovea.