

In summary, small, noncalcified retinal astrocytic hamartomas may cause macular exudative retinal detachment. Tumors may be subtle. Optical coherence tomography may aid in the diagnosis in patients without a history of retinal astrocytic hamartomas or tuberous sclerosis. Photocoagulation may be considered for tumors causing persistent subretinal fluid and visual loss. Visual outcome may be limited in some cases.

REFERENCES

1. Nyboer JH, Robertson DM, Gomez MR. Retinal lesions in tuberous sclerosis. *Arch Ophthalmol* 1976;94:1277-1280.
2. Arnold AC, Hepler RS, Yee RW, Maggiano J, Eng LF, Foss RY. Solitary retinal astrocytoma. *Surv Ophthalmol* 1985;30:173-181.
3. Sahli O, Sickenberg M, Piguat B. Exudative parafoveal astrocytic hamartoma associated with Bourneville tuberous sclerosis: spontaneous evolution. *Klin Monatsbl Augenheilkd* 1997;210:332-333.
4. Panzo GJ, Meyers SM, Gutman FA, Kollarits CR, Lederman RJ. Spontaneous regression of parafoveal exudates and serous retinal detachment in a patient with tuberous sclerosis and retinal astrocytomas. *Retina* 1984;4:242-245.
5. Bloom SM, Mahl CF. Photocoagulation for serous detachment of the macula secondary to retinal astrocytoma. *Retina* 1991;11:416-422.

TIMP-3 mRNA Is Not Overexpressed in Sorsby Fundus Dystrophy

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PURPOSE: To assess the expression of MMP (matrix metalloproteinase)-2 and -9 and TIMP (tissue inhibitors of metalloproteinases)-1, -2, and -3 in Sorsby fundus dystrophy.

DESIGN: Clinicopathological report

METHODS: A donor eye with a confirmed S181C mutation in the TIMP-3 gene and an age-matched normal donor eye were studied using in situ hybridization technique with MMP -2 and -9 and TIMP -1, -2, and -3 probes.

RESULTS: There is a reduction of mRNA expression of MMP-2 and TIMP-3 in the Sorsby retinal pigment epithelium cells.

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CONCLUSION: Increased expression of TIMP-3 mRNA does not cause accumulation of TIMP-3 in the Bruch membrane of Sorsby fundus dystrophy nor is it likely to cause age-related macular degeneration. (*Am J Ophthalmol* 2003;136:954-955. © 2003 by Elsevier Inc. All rights reserved.)

MORE THAN 50 YEARS AGO, SORSBY AND ASSOCIATES described four families with late-onset, autosomal dominant inheritance of macular dystrophy.¹ Although a rare condition, it is an important disease to study because the clinical phenotype and pathologic features are similar to those of age-related macular degeneration.

Weber and associates identified a point mutation in the tissue inhibitor of the metalloproteinases-3 (TIMP-3) gene.² TIMP-3 is known to be a component of Bruch membrane and is expressed by retinal pigment epithelial (retinal pigment epithelium) cells. The TIMP-3 protein was shown to accumulate in the Bruch membrane of patients with Sorsby fundus dystrophy³ and age-related macular degeneration. This increase can be due to an increase in expression or a decrease in the breakdown of the TIMP-3 protein. In this study, we report the in situ hybridization results of matrix metalloproteinases and their inhibitors in an eye with Sorsby fundus dystrophy to exclude increased expression of TIMP-3 as the cause of the accumulation.

We used the following riboprobes in this study: A 635-bp cDNA fragment of human 72-kD gelatinase (MMP-2), a 634-bp cDNA fragment of human 92kDa gelatinase (MMP-9), a 626-bp cDNA fragment of human TIMP-1, a 626-bp cDNA fragment of human TIMP-2, and a 700-bp cDNA fragment of human TIMP-3.

RNA polymerase-derived sense and antisense RNA probes were made with T3, T7, and SP6 all labeled with ³⁵S-UTP (Amersham, UK). All cDNA probes have been characterized by us, and in situ hybridization was performed as described previously.⁴

The intensity of the different probes was graded arbitrarily, with grade 0 equal to no trace to grade 3 having the strongest intensity when comparing the Sorsby fundus dystrophy eye with two normal control eyes. The control eyes had findings similar to each other and presented together as the control. The results are summarized in Table 1. Considering a two-step change as significant, there is a reduction of mRNA expression of MMP-2 and TIMP-3 in the Sorsby retinal pigment epithelium cells.

The accumulation of TIMP-3 in the Bruch membrane of Sorsby fundus dystrophy has been described.³ It has been unclear whether this accumulation is due to an increase of production or a reduction of degradation of TIMP-3. Our results suggest that this accumulation is not due to overexpression of TIMP-3 mRNA in Sorsby fundus dystrophy, nor, most likely, in age-related macular degeneration.

TABLE 1. Intensity of Various Probes in Different Regions of the Outer Retina in Sorsby Fundus Dystrophy and Normal Control Donors

	RPE		INL	
	SFD	Normal	SFD	Normal
MMP-2	0	++	+++	++
MMP-9	0	0	0	0
TIMP-1	+	+	+	+
TIMP-2	0	+	+	+
TIMP-3	+	+++	+	0

INL = inner nuclear layer; MMP = matrix metalloproteinases; RPE = retinal pigment epithelium; SFD = Sorsby fundus dystrophy; TIMP = tissue inhibitors of metalloproteinases, 0 = no intensity; +++ = maximum intensity.

We have recently shown that TIMP-3 mRNA level does not increase with age but is inversely related to the thickness of the Bruch membrane in normal eyes.⁵ This is consistent with the findings in this study because when the Bruch membrane is more than 20 μm in the Sorsby fundus dystrophy eye, the TIMP-3 mRNA expression is significantly reduced. Combining the result of these two studies, the expression of TIMP-3 is not the cause of accumulation of TIMP-3 protein and thickening of the Bruch membrane in Sorsby fundus dystrophy, nor is it likely to be the source of age-related macular degeneration.

In Sorsby fundus dystrophy, the mutant TIMP-3 is known to form a dimer that might be less amenable to degradation, resulting in accumulation. In age-related macular degeneration, binding of wild-type TIMP-3 to nondegradable extracellular matrix material or forming dimers in the abnormal environment may contribute to the accumulation of TIMP-3. These hypotheses require further investigations.

REFERENCES

1. Sorsby A, Mason MEJ, Gardener N. A fundus dystrophy with unusual features. *Br J Ophthalmol* 1949;33:67-97.
2. Weber BH, Vogt G, Pruett RC, Stohr H, Felbor U. Mutations in the tissue inhibitor of metalloproteinases-3 (TIMP3) in patients with Sorsby's fundus dystrophy. *Nat Genet* 1994;8:352-356.
3. Chong NH, Alexander RA, Gin T, Bird AC, Luthert PJ. TIMP-3, collagen, and elastin immunohistochemistry and histopathology of Sorsby's fundus dystrophy. *Invest Ophthalmol Vis Sci* 2000;41:898-902.
4. Steen B, Sejersen S, Berglin L, Seregard S, Kvanta A. Matrix metalloproteinases and metalloproteinase inhibitors in choroidal neovascular membranes. *Invest Ophthalmol Vis Sci* 1998;39:2194-2200.
5. Bailey TA, Alexander RA, Dubovy SR, Luthert PJ, Chong NH. Measurement of TIMP-3 expression and Bruch's membrane thickness in human macula. *Exp Eye Res* 2001;73:851-858.

Questionnaire Survey on Periodic Ocular Examination in Japanese Diabetic Patients

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PURPOSE: To identify the reasons why diabetic patients do not undergo periodic examination.

DESIGN: Cohort study.

METHODS: A questionnaire survey of 1,333 Japanese type 2 diabetic patients was conducted at Tokyo Women's Medical University. Performance of ocular examinations was investigated over 5 years and the reasons for not undergoing examination were analyzed.

RESULTS: Periodic ocular examination was performed in 69.5% of patients, but not in 30.5%. The questionnaire survey showed that physicians usually explained the risk of ocular complications and recommended periodic examination. More than 98% of the patients were aware of diabetic eye disease. Multivariate logistic regression analysis showed the main reason for skipping examination as a reason was that patients believed they had no diabetic retinopathy.

CONCLUSIONS: Patients should be informed about the necessity of receiving periodic ocular examination even if they do not yet have retinopathy. (*Am J Ophthalmol* 2003;136:955-957. © 2003 by Elsevier Inc. All rights reserved.)

DIABETIC RETINOPATHY IS THE LEADING CAUSE OF blindness in Japan, and Japanese patients seem to miss the appropriate timing of treatment because they fail to undergo periodic ocular examination.^{1,2} A major possible reason for this is poor recognition of the necessity for monitoring.¹⁻³ No survey on awareness of the necessity for ocular examination has been performed, however, so the actual reasons are unknown. Accordingly, the objective of the present study was to investigate why patients did not undergo periodic examination.

The subjects were 1,333 type 2 diabetic patients (731 men and 602 women) aged 60.9 ± 13.1 years. The duration of diabetes was 13.2 ± 7.8 years. There were 914 patients without retinopathy, 378 with nonproliferative

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