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Foveal Hypoplasia in Patients with Stickler Syndrome

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Purpose: To determine the microstructure of the fovea in patients with Stickler syndrome using imaging by spectral-domain optical coherence tomography (SD OCT) and swept-source OCT.

Design: Retrospective case series study.

Participants: A total of 39 eyes of 25 patients with genetically confirmed Stickler syndrome were studied.

Methods: All of the patients had mutations in the *COL2A1* gene and were diagnosed with Stickler syndrome. Cross-sectional OCT images, OCT angiography (OCTA), and en face OCT images were assessed. The ratio of the foveal inner retinal layer (fIRL) thickness to the parafoveal inner retinal layer (pIRL) thickness, the ratio of the foveal outer retinal layer (fORL) thickness to the parafoveal outer retinal layer (pORL) thickness, and the size of the foveal avascular zone (FAZ) were determined.

Main Outcome Measures: The degree of foveal hypoplasia and the best-corrected visual acuity in patients with Stickler syndrome.

Results: A persistence of the inner retinal layers in the fovea with an fIRL/pIRL ratio >0.2 was present in 32 of the 39 eyes (82%). Optical coherence tomography angiography showed that the FAZ was smaller, 0 to 0.19 mm^2, than that of normal eyes, in 25 eyes of 17 patients who underwent OCTA. There was no significant correlation between the visual acuities and the fIRL/pIRL ratios.

Conclusions: A mild foveal hypoplasia with a persistence of the IRL is characteristic of eyes with Stickler syndrome. The visual acuities were not correlated with the fIRL/pIRL ratios. *Ophthalmology 2017;■:1–7 © 2017 by the American Academy of Ophthalmology*

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Stickler syndrome is an inherited connective tissue disease that affects the eyes, ears, joints, and midline facial structures.[1] The ocular features are high myopia, vitreous degeneration, cataracts, perivascular retinal degeneration, and a high incidence of retinal detachments.[2] The retinal detachments occur during childhood and can lead to blindness.[3] Stickler syndrome is caused by mutant procollagen genes in which mutations in the *COL2A1* gene account for more than 80% of the patients.[3]

The majority of patients with Stickler syndrome have no visual loss unless they have a retinal detachment, and high myopia is the only sign in childhood. No typical abnormalities of macular function and morphologic features except for premacular vitreous changes have been reported.[4]

Recent advances of optical coherence tomography (OCT) have allowed clinicians to obtain a detailed layer-by-layer structural view of the retina and the ability to follow the development of the macula.[5,6] Of note, OCT angiography (OCTA), and en face OCT images can provide additional information of the retinal surface and microvasculature.[7] In this study, we have for the first time found a persistence of the inner retinal layers in the fovea, that is, a mild form of foveal hypoplasia, by high-resolution spectral-domain OCT (SD OCT) and swept-source OCT in eyes with Stickler syndrome.

The purpose of this study was to characterize the foveal hypoplasia in eyes with Stickler syndrome and to correlate its degree with the visual acuity.

Methods

This was a multicenter retrospective case series study. The procedures used conformed to the tenets of the Declaration of Helsinki, and they were approved by the Ethics Committee of the University of Occupational and Environmental Health Japan, Jikei University, Shiga University of Medical Science, and Kindai University Sakai Hospital. A signed informed consent was obtained from all of the patients or their parents.

Twenty-five patients with Stickler syndrome, 13 male patients and 12 female patients with a mean age of 19.9±14.2 years (range, 4–50 years), were studied (Table 1). The diagnosis was made by the clinical findings and confirmed by genetic analyses. Mutations in the *COL2A1* gene were found in all patients. Twenty-one patients were reported earlier.[8] The remaining 4 patients (patients 22 to 25) in 3 families are newly studied. These 4 patients had known mutations: c.1693C>T (p.Arg565Ser) for patients 22 and 23, c.1957C>T (p.R653*) for patient 24, and c.3624delT (p.P1208fs) for patient 25. Thirty-nine eyes were studied, but 11 eyes from 11 patients were excluded because of phthisis bulbis due to retinal detachments in 5 eyes, undetermined structure of the foveal center including macular

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Table 1. Results of Measurement of Optical Coherence Tomography and Optical Coherence Tomography Angiography in Patients with Stickler Syndrome

Patient	R/L	Family	Kinship	Age (yrs)	Sex	fIRL/pIRL Ratio	fORL/pORL Ratio	FAZ	Refraction (D)	BCVA	Remarks	Patient No. of Early Report[8]
1	L	1	Proband	13	M	0.48	2.07	0	−14	20/22		3
2	L	1	Mother	38	F	0.43	1.33	0	−4.5	NA		4
3	R	1	Sister	10	F	0.41	1.22	0.02	−8.5	20/66		5
	L					0.44	1.37	0	−8	20/20		
4	R	2	Proband	21	M	0.34	1.64	0	−14	20/22	PPV, ENC	8
	L					0.46	1.41	0	−13	20/20	ENC	
5	R	3	Proband	15	M	0.22	1.17	NA	−8	20/17		9
	L					0.09	1.17	NA	−7	20/22	PPV	
6	L	4	Proband	40	M	0.25	1.46	0	−18	20/17		10
7	L	5	Proband	22	M	0.38	1.34	0	−4.5	20/20		12
8	R	6	Proband	17	M	0.59	1.6	0	−9.5	20/20		13
9	R	7	Proband	13	F	0.34	1.31	NA	−8	20/20		14
	L					0.33	1.38	NA	−8	20/40		
10	R	7	Sister	15	F	0.09	1.55	0.162	−3	20/13		15
	L					0	1.39	0.194	−3	20/50		
11	R	7	Mother	36	F	0.42	1.67	0.087	−5.5	20/20		16
	L					0.32	1.72	0	−3.5	20/40		
12	R	8	Proband	35	M	0.48	1.71	0	−8	20/25		20
13	R	9	Proband	10	M	0	1.54	NA	−14	20/33		21
	L					0	1.72	NA	−13	20/200		
14	R	9	Mother	40	F	0.29	1.8	NA	−11	20/17		22
	L					0.6	1.8	NA	−13	20/200		
15	R	10	Proband	39	F	0.36	1.6	NA	−14	20/20		26
	L					0.32	1.71	NA	−10	20/22		
16	L	11	Proband	10	M	0.45	1.36	0	−12.5	20/33		28
17	R	12	Proband	15	M	0.29	1.33	0	−11	20/20		30
	L					0.66	1.43	0	−10	20/33	PPV	
18	L	13	Proband	4	F	0.14	1.2	NA	−3.75	20/25		34
19	R	13	Sister	4	F	0.25	1.67	NA	−7	20/67		35
20	R	13	Father	50	F	0.23	1.31	NA	−8.5	20/25		36
21	R	14	Proband	6	M	0.35	1.65	0	−11	20/20		39
	L					0.08	1.47	0.111	−11	20/17		
22	R	15	Proband	6	M	0.66	1.85	NA	−10	20/22		Not listed
	L					0.47	1.69	NA	−13	20/33		
23	L	15	Mother	29	F	0.55	1.57	0	−15.5	20/29		Not listed
24	R	16	Proband	4	F	0.26	1.52	NA	−13.5	20/100		Not listed
	L					0.25	1.64	NA	−14.5	20/100		
25	R	17	Proband	5	F	0.4	1.57	0	−4	20/25		Not listed
	L					0.44	1.62	0	−4	20/25		

BCVA = best-corrected visual acuity; D = diopter; ENC = encircling; FAZ = foveal avascular zone; fIRL/pIRL = foveal inner retinal layer/parafoveal inner retinal layer; fORL/pORL = foveal outer retinal layer/parafoveal outer retinal layer; L = left; NA = not available; PPV = pars plana vitrectomy; R = right.

edema after retinal detachment surgery in 4 eyes, and poor fixation in 2 eyes. Three eyes of 3 patients who had vitrectomy were included because their eyes did not have obvious epiretinal membranes or macular edema.

All patients had standard ophthalmologic examinations including measurements of the refractive error and best-corrected visual acuity, and slit-lamp biomicroscopy and fundus examinations. The SD OCT and swept-source OCT images were obtained from all patients. The participating institutions had different OCT instruments as follows: the swept-source OCT (DRI OCT Triton, Topcon, Tokyo, Japan), SD OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA), Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), and RS-3000 Advance (NIDEK, Tokyo, Japan).

Optical coherence tomography was performed using the 6×6-mm raster scan mode or a 6-mm (or 12-mm) radial scan mode. Optical coherence tomography angiography (OCTA) images were obtained in 25 eyes of 17 patients, and en face OCT images on the internal limiting membrane were obtained in 21 eyes of 15 patients. The OCTA images of the superficial capillary plexus were obtained with a 3×3-mm scan.

Because a foveal bulge was detected in all scans across the central fovea in all eyes, the images showing the foveal bulge were used as the representative images of the central fovea. The inner retinal layers (IRLs) and outer retinal layers (ORLs) were defined on the basis of the report by Maldonado et al[9] as follows: The IRL included all retinal tissue from the inner aspect of the inner limiting membrane to the outer border of the inner nuclear layer, and the ORL extended from the outer aspect of the outer plexiform layer to the inner border of the retinal pigment epithelium. The thicknesses of the IRL and ORL at the foveal center were manually measured by the caliper function embedded in all OCT devices (Fig 1). The thickness of the IRL and ORL at the parafovea, designated as the parafoveal inner retinal layer (pIRL) and parafoveal outer retinal layer (pORL), were measured at 1000 μm from the foveal center.[9] Henle's fiber layer usually was hyporeflective and overlapped the outer nuclear layer.[9] However,