Ocular Features in Joint Hypermobility Syndrome/ Ehlers-Danlos Syndrome Hypermobility Type: A Clinical and In Vivo Confocal Microscopy Study

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• PURPOSE: To investigate ocular anomalies in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type (JHS/EDS-HT).

• DESIGN: Prospective, cross-sectional study.

• METHODS: Forty-four eyes of 22 consecutive patients with an established diagnosis of JHS/EDS-HT and 44 eyes of 22 age- and gender-matched control subjects. Administration of a standardized questionnaire (Ocular Surface Disease Index) and a complete ophthalmologic examination, including assessment of best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, indirect ophthalmoscopy, tear-film break-up time, Schirmer I testing, axial length and anterior chamber depth measurement, corneal topography, corneal pachymetry, and confocal microscopy. Main outcome measures included comparing ocular anomalies in JHS/EDS-HT and control eyes.

• RESULTS: JHS/EDS-HT patients reported dry eye symptoms more commonly than controls ($P < .0001$). Scores of tear-film break-up time and Schirmer I test were significantly lower in JHS/EDS-HT eyes ($P < .0001$). Minor lens opacities were significantly more common in the JHS/EDS-HT group (13.6%; $P < .05$). Pathologic myopia with abnormal vitreous was found in 7 JHS/EDS-HT eyes (15.9%) and 0 controls ($P = .01$). Corneas were significantly steeper and the best-fit sphere index was significantly higher in JHS/EDS-HT group ($P < .01$). By confocal microscopy, the JHS/EDS-HT group showed lower density of cells in the superficial epithelium ($P < .001$) and higher density of stromal keratocytes in anterior and posterior stroma ($P < .0001$).

• CONCLUSIONS: The most consistent association of eye anomalies in the JHS/EDS-HT group included xerophthalmia, steeper corneas, pathologic myopia, and vitreous abnormalities, as well as a higher rate of minor lens opacities. These findings indicate the need for ophthalmologic survey in the assessment and management of patients with JHS/EDS-HT. (Am J Ophthalmol 2012; xx:xxx. © 2012 by Elsevier Inc. All rights reserved.)

HERITABLE CONNECTIVE TISSUE DISORDERS REFER to a wide range of genetic conditions caused by perturbed biogenesis of various components of the connective tissue. Ehlers-Danlos syndrome (EDS) comprises a clinically variable and genetically heterogeneous subgroup of heritable connective tissue disorders, mainly characterized by generalized joint hypermobility, skin hyperextensibility, and tissue fragility. Among the various EDSs, the hypermobility type (EDS-HT), now considered one and the same with joint hypermobility syndrome (JHS) by an international panel of experts,[1] is likely the most common, with a presumed prevalence of 0.75% to 2% in the general population.[2] JHS/EDS-HT is now considered the most debilitating form of EDS because of the high occurrence of disabling pain and fatigue.[3] However, JHS/EDS-HT is difficult to recognize because of the absence of specific physical findings and known causative gene(s), except for a very few and still debated cases with mutations in tenascin XB and collagen type III α1 genes.[4–6] Nevertheless, tenascin XB-deficient EDS recently was determined to be a distinct form of EDS by further phenotypic refinement.[7] Accordingly, JHS/EDS-HT is still a diagnosis of exclusion based on internationally accepted clinical diagnostic criteria.[8–10] However, the need for revising existing criteria is urgent.[11]

Eye structures typically are involved in specific heritable connective tissue disorders, such as Stickler syndrome, which is characterized mainly by high myopia, vitreoretinal degeneration, and cataract.[12] Among the various EDSs, diagnostic criteria for the kyphoscoliotic type comprise scleral fragility (major criteria) and microcornea (minor criteria).[8] Ocular anomalies also have been included as a minor sign in the revised set of diagnostic criteria for JHS, but very few articles have been published on this topic.[9] Mishra and associates first noted a high incidence of lid laxity and antimongoloid palpebral slants by evaluating 34 patients. Rarer features included myopia,

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TABLE 1. Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type: Applied Diagnostic Criteria

Brighton Criteria (Joint Hypermobility Syndrome)	Villefranche Criteria (Ehlers-Danlos Syndrome, Hypermobility Type)
Major criteria	Major criteria
Beighton score ≥ 4/9	Beighton score ≥ 5/9
Arthralgia for > 3 mos in > 4 joints	Skin involvement (hyperextensibility, smooth, velvety skin, or both)
Minor criteria	Minor criteria
Beighton score of 1-3	Recurring joint dislocations
Arthralgia in 1-3 joints	Chronic joint/limb pain
History of joint dislocations	Positive family history
Soft tissue lesions >3	
Marfan-like habitus	
Skin striae, hyperextensibility, or scarring	
Eye signs, lid laxity	
History of varicose veins, hernia, visceral prolapse	

For the diagnosis, both major, or 1 major and 2 minor, or 4 minor criteria and the exclusion of other connective tissue disorders.

TABLE 2. Main Characteristics of Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type Group at the Beginning of the Study

Manifestation	No. (Total, 22 Patients)	%
Congenital joint hypermobility	15	68.2
Clumsiness in infancy	11	50.0
Beighton score ≥ 4	20	90.9
Chronic/recurrent (> 3 mos) arthralgias	21	95.4
Back pain	19	86.4
Chronic/recurrent myalgias	18	81.8
Recurrent sprains/strains	14	63.6
Recurrent dislocations	16	72.7
Recurrent (> 3) soft tissue lesions	11	50.0
Chronic fatigue	19	86.4
Soft, velvety skin	17	77.3
Hyperextensible skin	8	36.4
Easy bruising	16	72.7
Varicose veins	4	18.2
Abdominal hernias	1	4.5
Bladder/uterine/rectal prolapse	4	18.2
Limb paresthesias	16	72.7
Recurrent tachycardias	14	63.6
Gastrointestinal symptoms	17	77.3

congenital unilateral ptosis, and tilted optic disc.[13] In a survey of Chilean patients, qualitatively assessed blue sclerae were considered common in JHS/EDS-HT.[14] A single instrumental study by corneal topography was performed on 17 EDS-HT patients and failed to identify any specific change.[15] The extreme variability of ocular involvement in heritable connective tissue disorders reflects the heterogeneity in composition of the fibrillar and nonfibrillar components of the connective tissue in the various structures of the eye.

This work is aimed at investigating ocular anomalies in 22 fully characterized JHS/EDS-HT patients compared with 22 age- and sex-matched controls. The findings may be relevant for interdisciplinary management issues of JHS/EDS-HT patients. They also may contribute toward understanding its complex, still largely unknown pathogenesis. Furthermore, some ocular features may be considered in future revisions of the JHS/EDS-HT diagnostic criteria.

METHODS

• **PATIENTS:** Forty-four eyes of 22 patients (mean age ± standard deviation, 35.5 ± 12.1 years; range, 15 to 60 years; 18 women and 4 men) with an established diagnosis of JHS/EDS-HT and 44 eyes of 22 age- and sex-matched control subjects (mean age ± standard deviation, 35.6 ± 11.9 years; range, 14 to 60 years; 17 women and 5 men; $P > .05$ for age and sex) were included in this prospective, cross-sectional study. Patients were recruited consecutively at the joint hypermobility outpatient clinic of the Division of Physical Medicine and Rehabilitation of the Umberto I University Hospital, Rome, Italy, from October 2010 through March 2011. All patients were assessed originally in a multidisciplinary team including physiatrists (C.C., F.C.), physiotherapists, and a clinical geneticist (M.C.).

Diagnosis of JHS/EDS-HT was assessed applying published diagnostic criteria for JHS and EDS-HT.[8,9] In clinical practice, the Brighton criteria are the most stringent for young adults, adults, and older patients, whereas the Villefranche criteria are the best for individuals in the pediatric age range. Patients were included if they met at least either 1 of these 2 sets of criteria. Both sets comprise generalized joint hypermobility as a major manifestation. Accordingly, generalized joint hypermobility was assessed following the Beighton score and was considered present with a score of at least 4 of 9 for the Brighton criteria and at least 5 of 9 for the Villefranche criteria (Table 1).[16] Further maneuvers also were applied to estimate joint mobility outside the joints evaluated for Beighton score calculation. Skin and superficial connective tissue aspects were assessed qualitatively on the basis of accumulated experience by palpation and gentle stretching of the skin at the volar aspect of the palm (at the IV metacarpal), forearm, or both. Healthy controls were enrolled consecutively among the unaffected companions of patients attending the outpatients department of the Eye Clinic of

TABLE 3. Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type Group versus Controls: Clinical and Biometric Data

	Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type (44 Eyes)	Controls (44 Eyes)	*P* Value
Contact lens use	10/44	6/44	.41[a]
Questionnaire (mean ± SD)	2.32 ± 0.62	0.39 ± 0.53	<.0001[b]
Snellen BCVA (mean ± SD)	0.98 ± 0.07	0.99 ± 0.03	.44[b]
Spherical equivalent (D; mean ± SD)	−2.14 ± 4.54	−0.51 ± 1.50	.42[b]
Break-up time (sec; mean ± SD)	4.57 ± 1.73	11.53 ± 1.57	<.0001[b]
Schirmer I test (mm/5 min; mean ± SD)	6.23 ± 2.50	13.39 ± 2.24	<.0001[b]
Lens changes	6/44	0/44	.03[a]
IOP (mm Hg; mean ± SD)	12.9 ± 1.58	13.5 ± 1.61	.26[b]
ACD (mm; mean ± SD)	3.46 ± 0.33	3.47 ± 0.33	.79[b]
AL (mm; mean ± SD)	24.4 ± 1.94	23.7 ± 1.24	.26[b]
Pathologic myopia	7/44	0/44	.01[a]

ACD = anterior chamber depth; AL = axial length; BCVA = best-corrected visual acuity; D = diopters; IOP = intraocular pressure; SD = standard deviation.

[a]Fisher exact test.

[b]Mann–Whitney rank-sum test.

the Umberto I University Hospital from October 2010 through March 2011.

For both JHS/EDS-HT patients and controls, exclusion criteria were: positive history for lymphoproliferative disease, AIDS, sarcoidosis, diabetes mellitus, and corneal dystrophies or inflammations; ongoing systemic treatments with drugs with known corneal toxicity; use of antiglaucoma agents, anti-inflammatory agents, or both; and previous ophthalmic surgery.

• **STUDY PROCEDURES:** All subjects underwent a complete ophthalmologic examination, including screening for strabismus using the corneal light reflection test and the cover test, assessment of Snellen best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement with Goldmann tonometry, and indirect ophthalmoscopy.

Axial length and anterior chamber depth were measured using the Carl Zeiss IOLMaster, (version 4.07; Carl Zeiss Meditec, Dublin, California, USA). Tear film stability was evaluated by measuring the tear film break-up time (TBUT), after instillation of 1 μL of 0.5% unpreserved sodium fluorescein. Tear secretion was measured by the Schirmer I test under topical anesthesia (1 drop of 0.4% oxybuprocaine hydrochloride). All JHS/EDS-HT patients and control subjects were asked if they had any dry eye symptoms according to a standardized questionnaire (Ocular Surface Disease Index).[17] Central corneal thickness was measured by ultrasonic pachymetry (A-Scan Pachymeter, model 5100e; DGH Technology, Inc, Exton, Pennsylvania, USA). The average of 3 measurements was taken as the central corneal thickness. Computerized corneal topography was performed using the Keratron Corneal Analyzer (software version 3.2; Optikon 2000, Rome, Italy). The 3-mm zone was examined using the simulated keratoscope reading and Maloney index analyses. Simulated keratoscope reading 1 (Sim K1) and simulated keratoscope reading 2 (Sim K2) represent the mean dioptric power along the steepest and the flattest meridian of the cornea, by definition 90 degrees apart. Simulated keratoscope difference represents the difference between Sim K1 and Sim K2. Maloney indices (best-fit sphere, best-fit cylinder, and topographic irregularity) were provided by the Keratron Corneal Analyzer. These indices are based on the spherocylinder, whose axial powers best fit the axial powers of the central 3-mm diameter of the corneal surface. By definition, the best-fit sphere index is the spherical power of the spherocylinder. The best-fit cylinder index is the difference in power between the principal meridians of the spherocylinder and measures regular corneal astigmatism. The topographic irregularity index is the error of the least squares fit of the spherocylinder. The refractive power (in diopters) at each point on the best-fit surface is determined. This is compared with measured power at the corresponding point on the topography map. The difference between these values is squared and added to a weighted running total for all points within the 3 mm of the corneal apex. Then, the square root of this sum is calculated as the topographic irregularity index.

In vivo confocal microscopy was performed by 1 masked expert (I.M.) operator, using the Confoscan 3.0 (Nidek Technologies, Vigonza, Italy). Examination was conducted in an area of approximately 440 × 330 μm at the corneal apex. A drop of anesthetic (oxybuprocaine chloride 0.4%) was instilled in the lower conjunctival fornix before examination. During the test, the objective lens of the

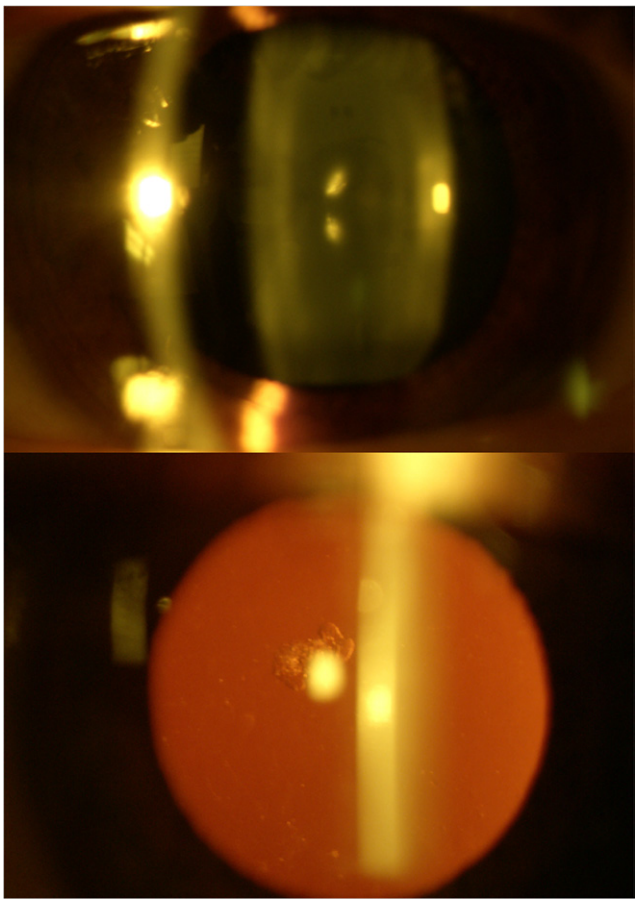

FIGURE 1. Lens changes in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. (Top) Opacities in the fetal nucleus of a 39-year-old woman (spherical equivalent, −0.50 diopters [D]; axial length, 22.95 mm). (Bottom) Subcapsular lens opacity in a 15-year-old boy (spherical equivalent, 0.25 D; axial length, 23.52 mm).

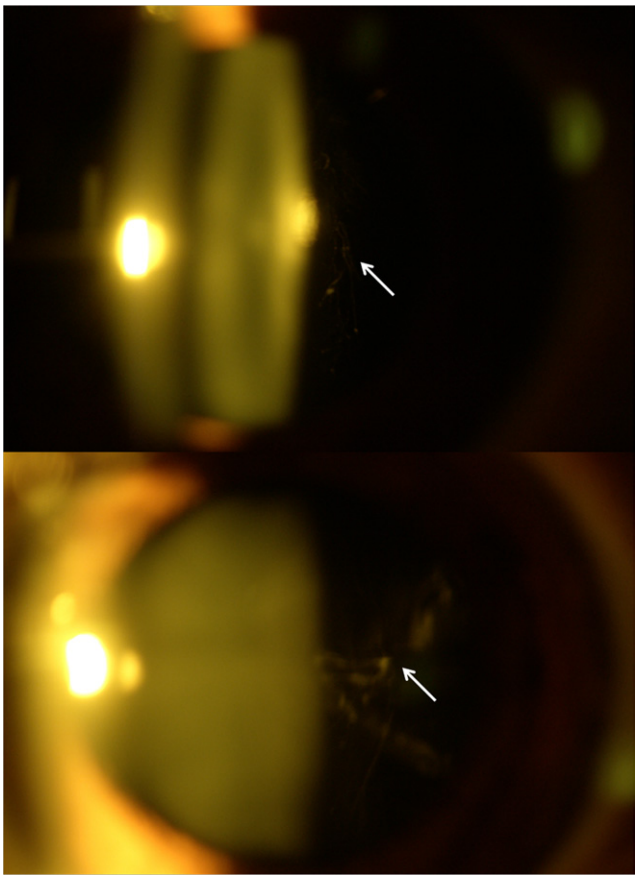

FIGURE 2. Vitreous abnormalities in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. (Top) Right eye of a 47-year-old woman (spherical equivalent, −6.75 diopters [D]; axial length, 26.53 mm). (Bottom) Left eye of a 36-year-old woman (spherical equivalent, −10.25 D; axial length, 26.75 mm). Note the fibrillar and beaded appearance (arrows).

microscope was covered by a gel hydroxypropilmetil cellulose 0.3%, Carbopol 980 (Noveon Europe, Brussels, Belgium), and never came in direct contact with the corneal surface. A drop of antibiotic (ofloxacin 0.3%) was instilled in the lower conjunctival fornix at the end of each examination, and the eye was re-examined at the slit lamp to verify the integrity of the corneal surface. A scan of the full thickness of the cornea was performed automatically for each participant; the examination lasted 1.5 to 2.5 minutes. Each scan recorded 350 images at a distance of 1.5 μm, on a *z*-axis, from one another. Each scan presented 2 to 4 complete passages from the endothelium to the superficial epithelium. Examinations were performed with a standard 40× objective lens. The *z*-scan curve (a graphic showing the depth coordinate on the *z*-axis and the level of reflectivity on the *y*-axis) of each scan was studied, and the images relative to the superficial and basal epithelium, to the anterior and posterior stroma, as well as to the subbasal plexus were selected. All areas of the *z*-scan curve, where the superficial epithelium and endothelium peaks were recognizable clearly, were considered. Cell densities of the superficial and basal epithelium and of the anterior and posterior stroma were evaluated. The first stroma photographic frame after an image of an endothelium and the last stroma photographic frame before an image referring to the basal epithelium were used to determine cell densities in the posterior and anterior stroma, respectively. In all cases, cell density was determined over a standardized area of 0.05 mm^2, through the manual cell counting procedure present in the software. The cells partially contained in the area analyzed were counted only along the right and lower margins.[18] Results were expressed in cells per square millimeter. The image of the subbasal plexus, where the highest number of nerve fibers was recognizable, was selected for each scan. Two parameters were taken into consideration: the number of nerves per frame (defined as the sum of the nerve branches observed in a frame) and tortuosity (evaluated and graded based on the scale proposed by Oliveira-Soto and Efron).[19] Two independent, masked investigators (M.G., M.M.) analyzed

TABLE 4. Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type Group versus Controls: Corneal Topography and Pachymetry Data

	Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type (44 Eyes)	Controls (44 Eyes)	*P* Value[a]
Pachymetry (μm)	541 ± 23.8	545 ± 25.4	.49
Sim K1 (D)	44.3 ± 1.17	43.6 ± 1.09	.006
Sim K2 (D)	43.4 ± 1.22	42.7 ± 0.95	.004
Sim dK (D)	1.01 ± 0.54	0.90 ± 0.52	.33
BFS (D)	43.8 ± 1.11	43.1 ± 0.99	.003
BFC (D)	0.97 ± 0.51	0.92 ± 0.47	.64
TI (D)	0.33 ± 0.17	0.26 ± 0.12	.04

BFC = best-fit cylinder index; BFS = best-fit sphere index; D = diopters; Sim dK = difference between Sim K1 and Sim K2; Sim K1 = simulated K1; Sim K2 = simulated K2; TI = topographic irregularity index.

Data are presented as mean ± standard deviation.

[a]Mann–Whitney rank-sum test.

the images, quantifying cell density in the different layers and number and tortuosity of the subbasal plexus nerve fibers. Patients and control subjects were tested with the same protocol.

• **STATISTICAL ANALYSIS:** Measurement values between groups were compared using Mann–Whitney rank-sum test. Categorical variables between the 2 study groups were compared using the Fisher exact test. Bivariate relationships were examined using the Spearman correlation coefficient. Correlation between ocular findings and Beighton score was not investigated because the latter cannot be considered a severity index for JHS/EDS-HT. Statistical significance was fixed at $P \leq .05$. Interobserver variation was calculated by analyzing the variation coefficients of the different groups of data. Statistical analysis was performed with commercial software (SPSS for Windows, version 15.0; SPSS, Inc, Chicago, Illinois, USA).

RESULTS

• **CLINICAL FINDINGS:** General characteristics of JHS/EDS-HT patients are shown in Table 2. No patient was excluded based on the established criteria. Ocular findings are summarized in Table 3. One JHS/EDS-HT patient (4.5%) showed bilateral prominent horizontal folds of upper lid skin and unilateral pseudoptosis versus 0 (0%) of 22 controls ($P > .05$). TBUT and Schirmer I test scores in the JHS/EDS-HT group were significantly lower than those of controls ($P < .0001$). Compared with control subjects, a significantly higher percentage of individuals in the JHS/EDS-HT group (0.39 ± 0.53 vs 2.32 ± 0.62; $P < .0001$) reported dry eye symptoms. Ocular refractive power, measured as spherical equivalent (diopters [D]) ± standard deviation), was not significantly different between groups (−2.14 ± 4.54 D; range, 2.25 to −21 D vs −0.51 ± 1.50 D; range, 4.5 to −3 D; $P > .05$).

Slit-lamp examination revealed lens opacities that did not affect visual acuity in 6 (13.6%) eyes in the JHS/EDS-HT group (patient mean age ± standard deviation, 29.4 ± 11.06 years; range, 15 to 39 years) versus 0 (0%) of 44 controls. One (4.5%) patient had bilateral discrete opacities in the fetal nucleus, and the remaining (18.2%) had minor unilateral subcapsular lens opacities (Figure 1). One eye had myopia (−21 D; axial length, 32.37 mm), and the remaining were emmetropic (mean spherical equivalent ± SD, −0.10 ± 0.22 D; mean axial length, 23.2 ± 0.5 mm). The proportion of eyes with lens changes was significantly higher in the JHS/EDS-HT group ($P = .03$).

Axial length in JHS/EDS-HT patients (24.4 ± 1.94 mm; range, 22.2 to 32.4 mm) did not differ significantly from that of controls (23.7 ± 1.2 mm; range, 21.2 to 26.0 mm; $P > .05$). Pathologic myopia, defined as a spherical equivalent of more than −6.0 D with consistent retinal abnormalities (such as myopic crescent, thinning and loss of choriocapillary, prominent large choroidal vessels, areas of focal atrophy, and lacquer cracks), axial length of at least 26.5 mm, or both, was found in 7 (15.9%) eyes of 4 JHS/EDS-HT patients versus 0 (0%) of 44 control eyes ($P = .01$). Vitreous showed a diffuse fibrillar and beaded appearance in the highly myopic eyes only (Figure 2). Otherwise, the anterior and posterior segments were normal.

• **ULTRASONIC PACHYMETRY AND TOPOGRAPHY DATA:** Pachymetry and topography data are summarized in Table 4. Central corneal thickness was not significantly different between groups (541 ± 23.8 μm in JHS/EDS-HT group vs 545 ± 25.4 μm in controls; $P > .05$). JHS/EDS-HT corneas were significantly steeper (44.3 ± 1.17 D for Sim K1 and 43.4 ± 1.22 D for Sim K2) than those of controls (43.6 ± 1.09 D for Sim K1 and 42.7 ± 0.95 D for Sim K2; $P = .006$ for SimK1 and $P = .004$ for Sim K2, between groups). Among the Maloney indices, the best-fit sphere index was significantly higher in JHS/EDS-HT eyes (43.8 ± 1.11 D) than in control eyes (43.1 ± 0.99 D; $P = .003$). We did not find any overt case of keratoconus among JHS/EDS-HT eyes. However, the topographic irregularity index result was slightly, although significantly, higher compared with that of controls (0.33 ± 0.17 vs 0.26 ± 0.12; $P = .04$).

• **IN VIVO CONFOCAL MICROSCOPY:** Main results at confocal microscopy are given in Table 5. The density of cells in the superficial epithelium was significantly lower in JHS/EDS-HT eyes (1095 ± 257) compared with control eyes (1521 ± 272; $P < .0001$), whereas the density of cells in the basal epithelium was not significantly different ($P >$

TABLE 5. Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type Group versus Controls: Corneal Confocal Microscopy Data

	Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome, Hypermobility Type (44 Eyes)	Controls (44 Eyes)	*P* Value[a]
Superficial epithelium (no./mm^2)	1095 ± 257	1521 ± 272	<.0001
Basal epithelium (no./mm^2)	5860 ± 676	5992 ± 621	.22
No. of nerve fibers per frame	4.89 ± 2.54	4.32 ± 2.29	.36
Nerve fibers tortuosity (grading 0 to 4)	1.59 ± 0.84	1.61 ± 0.72	.78
Anterior stromal keratocytes (no./mm^2)	1215 ± 110	1045 ± 111	<.0001
Posterior stromal keratocytes (no./mm^2)	972 ± 70	760 ± 68	<.0001
Endothelium (no./mm^2)	3006 ± 343	2943 ± 394	.44
Coefficient of variation of cell area (%)	29.8 ± 4.3	29.9 ± 4.4	.52
Percentage of hexagonal cells (%)	59.9 ± 10.1	60.2 ± 9.2	.89

Data are presented as mean ± standard deviation.
[a]Mann–Whitney rank-sum test.

.05). JHS/EDS-HT eyes had a higher density of stromal keratocytes in both the anterior and posterior stroma (1215 ± 110 vs 1045 ± 111 in the anterior stroma, $P <$ .0001; and 972 ± 70 vs 760 ± 68 in the posterior stroma, $P <$ .0001). JHS/EDS-HT endothelial cells appeared regular in both shape and size, and their density (3006 ± 343) was not significantly different than that of controls (2943 ± 394; $P >$ .05). Interobserver variations were 10%, 7%, 5%, 8%, and 6% for the number of subbasal nerves, superficial epithelium, basal epithelium, anterior stroma, and posterior stroma, respectively. Close correlation between the values obtained by the 2 investigators ($P <$ .0001, Pearson correlation) was found in every corneal layer.

• **CORRELATIONS OF CLINICAL AND CONFOCAL DATA:** In the JHS/EDS-HT group, no significant correlation was found between age and any clinical and confocal microscopy variables ($P >$ .05, Spearman correlation), except for corneal endothelial cell density ($P =$ .001, Spearman correlation). A close relationship was noted between TBUT and Schirmer I results ($P =$ .005, Spearman correlation) and between Schirmer I and questionnaire results ($P <$ .0001, Spearman correlation). By comparing clinical and confocal microscopy data, statistically significant correlations were disclosed between questionnaire/TBUT/Schirmer I testing and superficial epithelial cellular density ($P <$ .0001 for questionnaire and Schirmer I; $P =$ .003 for TBUT).

DISCUSSION

ALTHOUGH EYE FEATURES (E.G., MYOPIA AND DOWNSLANTING palpebral fissures) have been included in the revised criteria for JHS,[9] little is known regarding the exact prevalence and extent of ocular signs in JHS/EDS-HT. This study assessed ocular anomalies in a cohort of 22 JHS/EDS-HT patients. The JHS/EDS-HT ocular phenotype consisted mainly of xerophthalmia, steeper corneas, pathologic myopia, vitreous abnormalities, and minor lens opacities.

Dry eye was a commonly reported symptom in our sample, and this finding is consistent with previous observations.[14] More specifically, we found tear film stability alterations and tear film deficiency. A direct correlation also was demonstrated between severity of symptoms and Schirmer test results, thus confirming a direct link between patient symptoms and clinical data. Why xerophthalmia is common in JHS/EDS-HT is unknown. Because tear production is strongly influenced by the autonomic nervous system, a possible autonomic dysfunction underlying tear production deficiency may be put forward. This hypothesis is in line with the repeated observation of cardiovascular dysautonomia signs and symptoms, including palpitations, arrhythmias, postural orthostatic tachycardia, and syncope.[20] In JHS/EDS-HT, the effects of a perturbed autonomic nervous system may be wider than expected and may explain a range of nonmusculoskeletal features, such as hypohidrosis.[20] Accordingly, xerophthalmia may be the ocular counterpart of the reduced sweat production, previously reported in JHS/EDS-HT. Alternatively, tear secretion impairment may result from developmental alterations of the lacrimal gland extracellular matrix, because it may play a role in regulating lacrimal gland secretion.[21] Indeed, abnormal extracellular matrix production may be linked to an inherited defect of a nonfibrillar component of the connective tissue.

In our study, corneas of JHS/EDS-HT patients showed significantly steeper curvature and higher best-fit sphere index compared with those of controls. However, no definite case of keratoconus and no significant differences

in corneal thickness between patients and controls were found. These findings are consistent with the results of McDermott and associates, who studied a cohort of 36 EDS patients, including 17 JHS/EDS-HT subjects, by using ultrasound pachymetry and topography.[15] Similar results also were obtained by Segev and associates in classic EDS.[22] These minor anomalies are likely the secondary changes of an abnormally structured extracellular matrix in JHS/EDS-HT corneas, although it does not apparently reflect an increased corneal fragility in our sample. This is in contrast with other heritable connective tissue disorders with marked ocular involvement, including EDS kyphoscoliotic type and brittle cornea syndrome, in which eye fragility is a prominent feature.[8,23]

An apparently increased rate of myopia was reported in patients with JHS/EDS-HT,[13] and this observation led to the inclusion of eye signs in the revised set of JHS criteria.[9] In our sample, we failed to confirm this evidence; however, we found an increased rate of JHS/EDS-HT eyes with pathologic myopia. In addition, in these highly myopic eyes, the vitreous showed a fibrillar and beaded appearance. An association among heritable connective tissue disorders, high myopia, and vitreous degeneration previously was described in conditions such as Stickler syndrome.[12] Increasing evidence suggests that changes in the structure and composition of the sclera, the vitreous extracellular matrix, or both are major factors regulating axial elongation of the eye. Alterations in any sclera, vitreous extracellular matrix components, or both are likely to change scleral shape, vitreous structure, or both, which in turn could affect the axial length of the eye.[24] Consequently, it could be hypothesized that abnormalities of sclera, vitreous extracellular matrix, or both may contribute to myopia in JHS/EDS-HT. Alterations of the fibrillar components of the connective tissue (i.e., collagen types I, III, and V) are involved in EDS variants that are clinically distinct from JHS/EDS-HT.[25] Accordingly, the molecular defect underlying JHS/EDS-HT may reside in genes encoding nonfibrillar components of the extracellular matrix or enzymes involved in their posttranslational maturation. In particular, mutations in various small-leucin–rich proteoglycans, such as decorin, lumican, and fibromodulin, were associated with both EDS-like phenotypes and myopia in mice.[25–27] Therefore, they all may be possible candidates for JHS/EDS-HT in humans.

Slit-lamp examination failed to identify additional anterior chamber anomalies. However, confocal microscopy showed peculiar subclinical changes, namely decreased cell density in the superficial epithelium and increased stromal keratocyte density. These findings likely are secondary to the ocular surface dryness, as previously demonstrated in other forms of dry eye.[28–30] However, it is difficult to distinguish whether such microstructural changes are closely related to xerophthalmia or rather result from a primary developmental defect. Partially in line with the latter hypothesis, Vij and associates demonstrated that lumican-null mice display increased proliferation and decreased apoptosis of stromal keratocytes during postnatal corneal maturation.[31] Therefore, it may be speculated that, in JHS/EDS-HT, corneal microstructural changes may be the result of an inherited alteration of proteoglycan production. Similarly, minor lens opacities (subcapsular or involving the fetal nucleus) observed in 5 nonmyopic and 1 highly myopic JHS/EDS-HT eyes likely are developmental features of inherited alterations of the connective tissue in the lens, as observed in other heritable connective tissue disorders, such as Stickler syndrome.[12]

In JHS/EDS-HT, the usefulness of a comprehensive ophthalmologic survey has not been emphasized sufficiently in the literature. Our study indicates that in clinical practice, a complete ophthalmologic study, including TBUT and Schirmer I test, allows us to treat some features appropriately, such as xerophthalmia and pathologic myopia, both common in JHS/EDS-HT. Furthermore, ophthalmologic assessment may be of some help in recognizing patients with milder phenotypes on the basis of minor ocular changes (e.g., increased corneal refractive power and lens opacities). Therefore, ophthalmologic consultation should be scheduled not only in JHS/EDS-HT patients after diagnosis establishment, but in all individuals with suspected heritable connective tissue disorder to define the diagnosis better.

The main limitations of this study are the cross-sectional design and the qualitative and subjective nature of the evaluation of corneal changes by means of confocal microscopy. Possible limitations of the confocal microscopy technique include: limited extension of the analyzed area, low resolution compared with electronic microscope, measurements limited to the center of the cornea, and the impossibility of exactly recognizing the depth of the optical section in the stroma.

In conclusion, this study characterized the JHS/EDS-HT ocular phenotype, which mainly consisted of xerophthalmia, increased corneal curvature without ocular fragility, asymptomatic lens opacities, and high incidence of pathologic myopia. These observations may have a role in further revision of the existing diagnostic criteria for JHS/EDS-HT and may stimulate further studies aimed at identifying the molecular basis of such an elusive condition.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF interest and none were reported. Involved in Design of study (M.G., A.M., M.C., C.C., P.G., F.C.); Conduct of study (M.G., A.M., C.C., F.C.); Collection of data (M.M., I.M., F.P.); Management, analysis, and interpretation of data (M.G., A.M., M.C., C.C., F.C., F.P.); Preparation of manuscript (M.G., M.C.); and Review and approval of manuscript (M.G., A.M., M.C., C.C., P.G., F.C.). This study was performed at the Eye Clinic of the Umberto I Hospital of the Sapienza University of Rome, Rome, Italy. The Institutional Review Board of the Sapienza University of Rome prospectively approved a prospective protocol with patients' informed consent to participate in research. All participants signed an informed consent form in accordance with the Italian laws regarding privacy. The study adhered to the tenets of the Declaration of Helsinki.

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Biosketch

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