Salzmann's Nodular Corneal Degeneration Clinical Characteristics and Surgical Outcomes

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Purpose: To characterize the clinical characteristics and surgical outcomes for Salzmann's nodular corneal degeneration (SNCD).

Methods: In this retrospective, noncomparative, observational case series, all patients coded with a diagnosis of SNCD between January 1, 1996, and April 30, 2002 were included. Cases whose clinical description did not match the classic description of this disorder were excluded. Clinical characteristics, surgical procedures, and qualitative outcomes were recorded.

Results: Among 103 patients diagnosed with SNCD, 93 (152 eyes) met inclusion criteria. Eighty-three patients (89.2%) were women ($P < 0.00001$), and 59 patients (63.4%) had bilateral disease. A normal age distribution was noted, with a mean age of 54.3 years (median, 53 years; standard deviation = 16.9). Meibomian gland dysfunction was noted in 51 patients (54.8%), contact lens wear in 31 patients (33.3%), peripheral vascularization in 29 patients (31.2%), pterygium in 15 patients (16.1%), keratoconjunctivitis sicca in 9 patients (9.7%), and exposure keratitis in 4 patients (4.3%). Forty-nine eyes (32.2%) of 37 patients (39.8%) required a total of 62 surgical procedures. Impaired vision led to 53 (85.5%) of these procedures and resulted in improved vision in 42 (79.2%) of these cases. Seven eyes (4.6%) underwent surgical intervention for subjective discomfort or contact lens intolerance, and all had improved symptoms at last follow-up.

Conclusions: SNCD appears to be a disorder that occurs predominantly in middle-aged women and may be associated with chronic ocular surface inflammation and/or irritation. It is important to diagnose properly because of the good prognosis with medical and surgical therapy.

Key Words: Salzmann's nodular corneal degeneration

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In 1925, Maximilian Salzmann described a series of patients with solitary or multiple bluish-white elevated corneal nodules, frequently accompanied by an "eczematous keratoconjunctivitis."[1,2] These cases led to the coining of the term "Salzmann's nodular corneal dystrophy" in 1930 to describe this condition.[2] Subsequently, the common nomenclature has changed to Salzmann's nodular corneal degeneration (SNCD), a disorder that is characterized clinically by yellowish-white to bluish elevated lesions (Fig. 1).[3] They are commonly midperipheral in location, but numerous exceptions occur.[4,5] An iron line may be present along the edge of the lesion. Originally thought to be a clinical diagnosis with variable histopathologic findings,[6] resected nodules are typically composed of dense collagen plaques with hyalinization located between the epithelium and underlying Bowman's layer, which may be replaced completely.[3,5,7] The underlying stroma tends to remain clear.[4] Progression is slow, and, although the nodules may be asymmetric, approximately 80% of patients will have bilateral lesions.[7] Vascularization may occur in proximity to the lesion but should not be a primary portion of the lesion.[3–5]

Salzmann's nodular corneal degeneration has been reported to be idiopathic or associated with common causes of ocular surface inflammation or due to chronic low-grade trauma.[4,5,7] These inflammatory disorders include meibomian gland dysfunction (including ocular rosacea), phlyctenular keratitis, vernal keratoconjunctivitis, trachoma, or interstitial keratitis. Likewise, examples of associated ocular surface trauma include actinic exposure, contact lens wear (especially rigid lenses), recurrent erosions occurring in association with epithelial basement membrane disorders and/or mechanical trauma, exposure keratitis due to exophthalmos, chemical or thermal injuries, and previous corneal surgery. In all likelihood, any type of chronic ocular surface inflammation or trauma may contribute to SNCD.[3–5]

Recognition of this disorder is important because of the good prognosis with medical and surgical management.[5,8] As large clinical reviews of this disorder are absent in the literature, we performed a retrospective chart review of cases of SNCD seen at our institution over a 6-year period.

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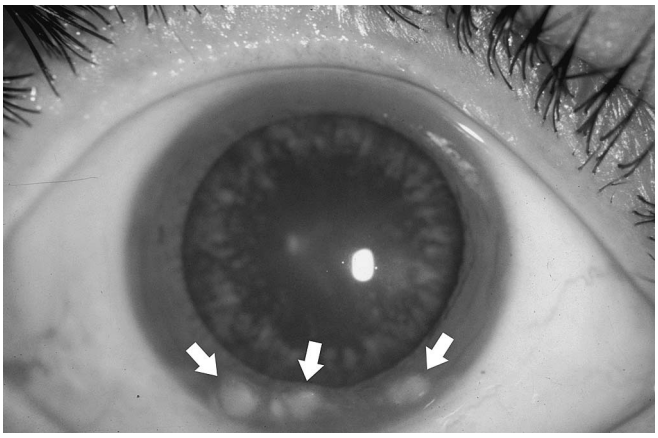

FIGURE 1. Salzmann's nodular corneal degeneration. Note 3 peripheral nodules inferiorly (arrows).

MATERIALS AND METHODS

The study design was a retrospective, noncomparative observational case series. All patients seen in the Cornea and External Diseases Clinic of the Department of Ophthalmology and Visual Sciences at the University of Iowa Hospitals and Clinics between January 1, 1996, and April 30, 2002 coded with a diagnosis of SNCD were included in the chart review. Permission to review the ophthalmic records of this patient population was obtained from the Institutional Review Board before the study commenced. The following data were documented on each patient: sex, age, date of onset of the condition, presence of meibomian gland dysfunction, hard or soft contact lens wear, keratoconjunctivitis sicca, exposure keratopathy, pterygium, peripheral vascularization, and clinical findings consistent with epithelial basement membrane dystrophy/degeneration (EBMD). Cases that were coded for SNCD due to the presence of subepithelial corneal fibrosis but whose clinical description did not match the classic description of this disorder were excluded from the study. Likewise, cases in which a pterygium present were excluded unless the nodules were remote from the pterygium.

In all cases, medical therapy (lubrication, warm compresses, lid hygiene, topical steroids, and/or oral doxycycline as needed) was initiated before consideration of surgical options. Indications for surgical therapy (impaired vision, subjective discomfort, or contact lens intolerance) and surgical treatments (superficial keratectomy, phototherapeutic keratectomy) were recorded. Choice of surgical procedure and timing of retreatment was based on surgeon preference. Three surgeons (A.A.F., J.E.S., M.D.W.) performed the majority of the procedures, and, in general, superficial keratectomy was preferred as the nodules can typically be readily dissected from the corneal surface.

Briefly, superficial keratectomy was performed under standard aseptic conditions with the patient supine under a surgical microscope using a 6400 or 6900 Beaver blade to lift a peripheral edge of the nodule that was then resected or peeled from the corneal surface. Whenever possible, care was taken to avoid violation of Bowman's membrane and when multiple nodules were present, it was often noted that they were thickenings of a continuous membrane. The surface was typically polished under irrigation briefly with a 5-mm mechanical diamond burr. Phototherapeutic keratectomy was performed with a broad beam Summit Apex excimer laser using multiple applications of masking solutions (typically diluted methylcellulose). Postoperatively, a bandage soft contact lens was commonly applied and topical steroids and antibiotics used until corneal re-epithelialization occurred. Statistical analyses were performed with Statistica software (StatSoft, Inc., Tulsa, OK). When necessary, nonparametric testing (ie, Mann-Whitney U test), was performed. A P value <0.01 was considered significant.

RESULTS

One hundred three charts were coded with a diagnosis of SNCD. Ninety-three patients (152 eyes) with clinical findings consistent with the classic description of the disorder were included in this study. Overall, there were 138 eyes (90.8%) of 83 female patients (89.2%), and only 14 eyes (9.2%) of 10 male patients (11.8%) ($P < 0.0001$). Fifty-nine (63.4%) patients (55 women and 4 men) had bilateral disease. Monocular involvement of the right eye occurred in 15 patients (16.1%) and of the left eye in 19 patients (20.4%). The mean follow-up for all patients was 52 months (median, 25.5 months; standard deviation = 63.8; range, 0–271 months). Women in this series were younger than men on average, with 8 men (80%) over the age of 60 and 32 women (38.6%) under the age of 50 (Fig. 2). Of the measured clinical characteristics (Table 1), meibomian gland dysfunction was the most common finding and occurred in 83 eyes (54.6%). This was followed in frequency by a history of contact lens wear in 52 eyes (34.2%), peripheral vascularization in 51 eyes (33.6%), EBMD in 20 eyes (13.2%), pterygium in 15 eyes (9.9%), keratoconjunctivitis sicca in 15 eyes (9.9%), and exposure keratitis in 5 eyes (3.3%).

Although there were no statistically significant gender differences among the measured clinical characteristics, the most striking disparity was that 30 women (37.7%) had a history of hard or soft contact lens wear, as compared with 1 man (10%). Notably, a portion of the nodules were located at or near the 3 and 9 o'clock positions in all patients with a history of contact lens wear. In the absence of contact lens wear, no specific patterns were otherwise identified. Eyes with peripheral vascularization did not have findings consistent with phlyctenular keratitis, and no patient had findings consistent with vernal or atopic keratoconjunctivitis, trachoma, keratoconus, corneal surgery, thermal burns, chemical injury, or actinic exposure resulting in either eyelid or ocular surface tumors. Filamentary keratitis was also absent in these patients. Finally, there was no history of excision of eyelid or ocular surface tumors in any patient in the study.

Overall, 103 eyes (67.8%) of 56 patients (60.2%) responded favorably to medical therapy. A total of 62 procedures were performed on the 49 eyes (32.2%) of 37 patients (39.8%) who failed medical therapy. These included 47 (75.8%) superficial keratectomies, 14 (22.6%) phototherapeutic keratectomies, and 1 (1.6%) lamellar keratoplasty. Of patients who underwent surgical therapy, 6 (16.2%) had 13 secondary

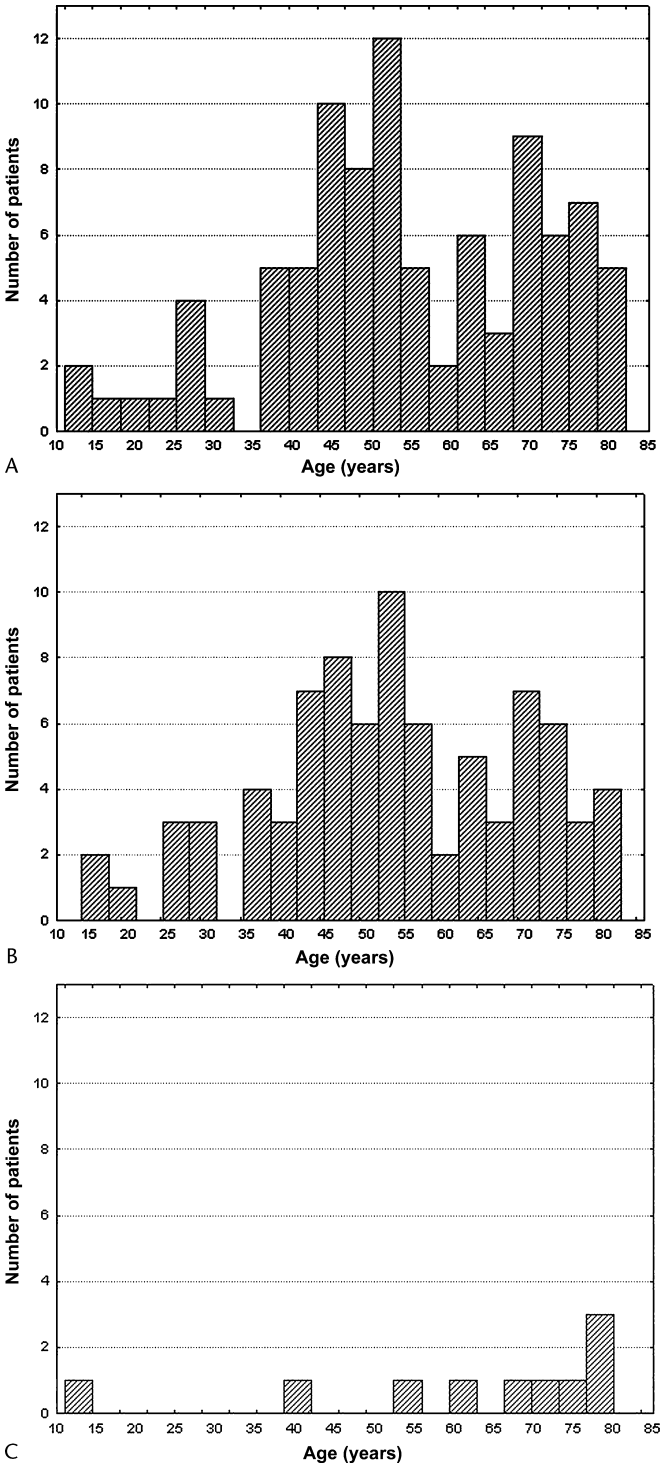

FIGURE 2. Age distribution of all patients (A), female patients (B), and male patients (C).

procedures (8 superficial keratectomies, 4 phototherapeutic keratectomies, and 1 lamellar keratoplasty) for either recurrence of disease or insufficiently improved symptoms. Of these 6 patients, 2 had bilateral retreatments and 4 patients had unilateral retreatments. The sole patient who had lamellar keratoplasty had been successfully treated with superficial keratectomies for 10 years before eventually undergoing transplantation. Repeat procedures were necessary after both primary superficial keratectomy and phototherapeutic keratectomy. The mean follow-up for medically managed patients was 32.6 months (median, 14 months; standard deviation = 44.9; range, 0–174) as compared with 80.7 months (median, 44 months; standard deviation = 76.5; range, 1–271) in surgically managed patients ($P < 0.001$). The 6 patients who required repeat procedures averaged even longer follow-up (mean, 179 months; median, 199; standard deviation = 80.1; range 42–271), a finding that did not reach statistical significance compared with patients managed with a single surgical procedure.

TABLE 1. Patient Demographics and Characteristics

	Female (% patients)	Male (% patients)	Total (% patients)
Age (y)	Range: 14–82	Range: 11–80	Range: 11–82
	Mean: 53.5	Mean: 61.5	Mean: 54.3
	Median: 52	Median: 69.5	Median: 53
	SD: 16.2	SD: 21.6	SD: 16.9
MGD	44 (53.0%)	7 (70.0%)	51 (54.8%)
PV	27 (32.5%)	2 (20.0%)	29 (31.2%)
EBMD	17 (20.5%)	3 (30.0%)	20 (21.5%)
HCL	18 (21.7%)	0	18 (19.4%)
SCL	12 (14.5%)	1 (10.0%)	13 (14.0%)
Pterygium	13 (15.7%)	2 (20.0%)	15 (16.1%)
KCS	8 (9.6%)	1 (10.0%)	9 (9.7%)
Exposure keratitis	4 (4.8%)	0	4 (4.3%)

Total numbers exceed 100% as some patients had overlapping clinical diagnoses.
OU, both eyes; OD, right eye; OS, left eye; SD, standard deviation; MGD, meibomian gland dysfunction; HCL, hard contact lens wear; SCL, soft contact lens wear; KCS, keratoconjunctivitis sicca; PV, peripheral vascularization; EBMD, epithelial-basement-membrane dystrophy/degeneration.

The most common indication for surgical therapy was visual disturbance (Table 2), with 42 eyes (85.7%) undergoing 53 procedures (85.5%). Subjective symptoms of discomfort, most commonly dryness, foreign body sensation, photophobia, and occasionally painful epithelial erosions over very elevated nodules, occurred in 4 eyes (8.2%). Contact lens intolerance was also noted as a consequence to elevated lesions, causing poor peripheral wetting and/or mechanical dislocation of the lens, and resulted in 3 eyes (6.1%) undergoing superficial keratectomy. All patients with contact lens intolerance and subjective discomfort who underwent surgical intervention had successful subjective outcomes at last follow-up. There were no statistically or clinically significant differences in outcome between superficial keratectomy and phototherapeutic keratectomy.

Available histopathologic specimens from 25 superficial keratectomy procedures were reviewed and revealed irregular epithelial thickness, subepithelial lamellar collagenization mimicking corneal stromal collagen, and subepithelial fibrosis. Mild diffuse thickening of the epithelial basement membrane or occasional focal areas of marked basement membrane thickening were present with periodic acid–Schiff (PAS) staining (Fig. 3). These findings were consistent with the diagnosis of SNCD in all cases.

TABLE 2. Qualitative Results of Superficial Keratectomy and Phototherapeutic Keratectomy Procedures

Indication	Total No. of Procedures (eyes)	Superficial Keratectomy		Phototherapeutic Keratectomy	
		Procedures	Outcome (% procedures)	Procedures	Outcome (% procedures)
Visual disturbance	53 (42)	39	Improved: 30 (76.9%) No change: 5 (12.8%) Worse: 4 (10.3%)	13	Improved: 12 (92.3%) No change: 1 (7.7%) Worse: 0
Subjective discomfort	6 (4)	5	Better: 4 (80%) No change: 1 (20%)	1	Better: 1 (100%) Worse: 0
Contact lens intolerance	3 (3)	3	CL+: 3 (100%) CL−: 0	0	

One patient required lamellar keratoplasty to treat persistent visual disturbance after repeated superficial keratectomies.
CL+, resumption of contact lens wear; CL−, could not resume contact lens wear.

DISCUSSION

In his landmark article from 1925,[1] Maximilian Salzmann described the clinical characteristics of 23 patients, accompanied by his original artwork, with a novel corneal "dystrophy."

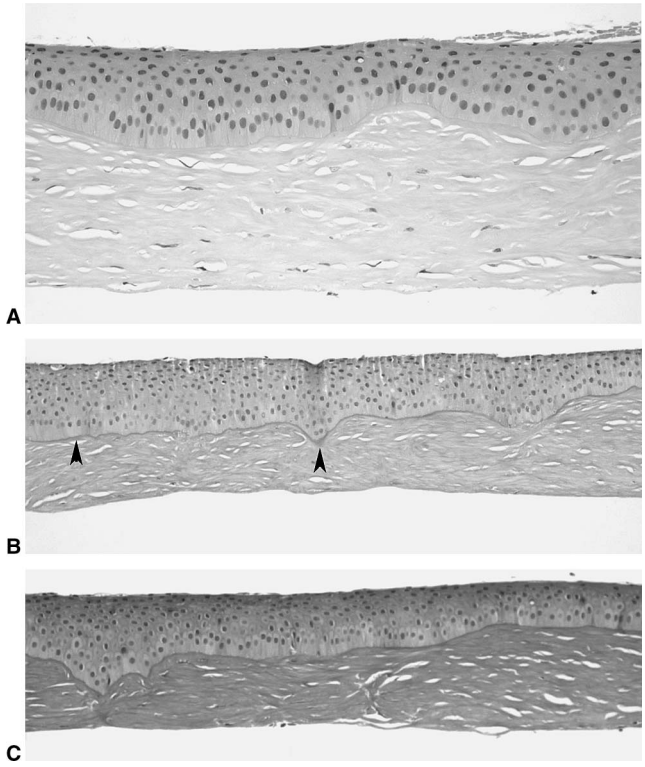

FIGURE 3. A, High-magnification photomicrograph of an excised SNCD nodule. The overlying epithelium is irregular in thickness, does not demonstrate any morphologic abnormalities, and the Bowman layer is absent. The underlying fibrous tissue has a lamellar arrangement mimicking corneal stromal collagen (original magnification ×100; hematoxylin and eosin). B, Periodic acid–Schiff stain demonstrates mild diffuse thickening of the epithelial basement membrane (arrowheads) (original magnification ×50). C, The subepithelial lamellar material stains bright blue with Masson trichrome stain indicating that the material is collagenous rather than hyaline (original magnification ×50).

Although the moniker of this eponymous condition was ascribed by Katz in 1930 after describing a similar case,[2] Salzmann noted that Ernst Fuchs may have made the initial case observation. Indeed, in 1901, Fuchs described a 27-year-old man with bilateral multiple bluish-white corneal lesions that were not sharply defined.[9] Regardless, of the 23 patients Salzmann described, 18 (78.3%) were women and 5 (21.7%) were men. They ranged in age from 12 to 64 years old, and he postulated a bimodal distribution from 15 to 30 years of age and 45 to 55 years old. Of his cases, 18 (78.3%) had unilateral disease, and he estimated from his practice an overall incidence of 1:2400 patients/year having this disorder.

This study, which currently represents the largest reported case series on the subject, has many similarities to the original description. The most striking demographic feature was the overwhelming female preponderance of affected individuals. This predilection is of uncertain etiology and, given the similarity to Salzmann's findings, suggests a predominantly biologic rather than environmental etiology that warrants further investigation. As the majority of female patients were middle aged and most male patients were older, it is tempting to consider the influence of female and male sex hormones in the development of this problem. Specifically, it has been postulated that androgen deficiency can lead to meibomian gland dysfunction, which was highly prevalent in these patients, and subsequent evaporative dry eye[10] and reduced tear production.[11] However, given the retrospective nature of this study, it is difficult to confirm the exact timing of development of the lesions, and the age range may be artificially skewed to older ages.

The age distribution of patients in this series, although similar to Salzmann's, suggests a normal rather than a bimodal distribution. Likewise, in contrast to the original description, we found bilateral involvement in the majority of patients. This may be due to a higher prevalence of bilateral findings noted in our patients such as meibomian gland dysfunction and contact lens wear. The former was the most common clinical association in our series; however, none of the other "classic" associations (phlyctenular keratitis, vernal keratoconjunctivitis, trachoma, or interstitial keratitis) were present. Given this finding, as well as peripheral vascularization and pterygium, SNCD may have developed in these eyes due to chronic low-grade inflammation. It is important, however, to note that as

this series lacks a control group, it is possible that this associated clinical finding may be coincidental rather than causal.

Alternatively, support for the hypothesis that some cases may occur in response to acute or chronic trauma to the ocular surface comes from the presence of contact lens wear and EBMD in many patients in our series. The possible direct correlation between contact lens wear is supported by the characteristic 3 and 9 o'clock positions of the lesions in these cases. The association with EBMD could be postulated to be secondary to the pathologic response to recurrent erosions in these cases. It is interesting to hypothesize that abnormalities in basement membrane synthesis may predispose the subepithelial basement membrane zone to replacement with the characteristic avascular pannus of SNCD. Alternatively, repetitive microabrasions may incite the release of cytokines that facilitate fibroblast proliferation or transformation. However, this is purely speculative and it is possible that the epithelial basement membrane anomalies may be a result, rather than a cause, of the degenerative process.

The majority of patients responded favorably to medical management alone. As this study was performed at a tertiary center, it is possible that the nodules were an incidental finding that triggered a referral. Thus, the medical "successes" may be from treatment of dry eyes, meibomian gland dysfunction, EBMD, or other associated condition rather than the SNCD per se. Reinforcing this notion is that only a minority of patients required surgical intervention for subjective symptoms of discomfort, as most responded well to treatment with topical lubrication and systemic doxycycline (in the presence of meibomian gland dysfunction).

The most common reason for abandoning conservative medical treatment was disturbance of vision. Continuous visual impairment occurred as the nodule or nodules encroached on the central visual axis and induced irregular astigmatism. Intermittent visual disturbance or subjective discomfort, especially during prolonged visual tasks, may be due to tear film abnormalities related to mechanical disruption by the elevated nodules, as well as from underlying meibomian gland dysfunction. Superficial keratectomy, our preferred surgical option, was uniformly successful in reversing contact lens intolerance. Both superficial keratectomy and phototherapeutic keratectomy otherwise appeared equally effective, but this study was neither intended nor designed to compare these procedures. Some eyes from both surgical groups required repeat intervention(s) for the recurrence and/or incomplete eradication of symptoms. The sole patient who required lamellar keratoplasty had the procedure prior to the availability of phototherapeutic keratectomy at our institution and would have likely been treated with the latter modality currently. Alternatively, the authors have more recently performed combined superficial keratectomy and phototherapeutic keratectomy for recurrent disease, and others have reported the use of mitomycin C concomitantly.[12]

Recurrence of SNCD is certainly possible with longer follow-up[13] because the underlying etiology may not be eliminated by the mere removal of the nodules and treatment of ocular surface inflammation. On the one hand, this is borne out by the difference in follow-up times between those requiring medical and surgical intervention. Perhaps with longer follow-up more medical treatment "successes" would require surgical intervention. On the other hand, some patients did not require surgical therapy even after 15 years of follow-up. Likewise, those requiring surgical therapy may be more apt to return for follow-up care (especially those requiring repeat surgical procedures). The retrospective nature of this study limits the ability to address this question.

In summary, Salzmann's nodular corneal degeneration appears to be a disorder of predominantly middle-aged women. In this series, the condition frequently presented concomitantly with meibomian gland dysfunction and contact lens wear, supporting the role of chronic inflammation and/or irritation in the pathophysiology of the disease. Proper diagnosis is important given the good prognosis and functional outcome with medical and surgical management. We anticipate and encourage further studies be performed to better elucidate this condition.

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