American Academy of Ophthalmology
The Eye M.D. Association

Bilateral Lacrimal Gland Disease

Clinical Features of 97 Cases

Sunny X. Tang, BA,[1] Renelle P. Lim, MD,[1] Saad Al-Dahmash, MD,[2,3] Sean M. Blaydon, MD,[4] Raymond I. Cho, MD,[5] Christina H. Choe, MD,[6] Michael A. Connor, MD,[7] Vikram D. Durairaj, MD,[8] Lauren A. Eckstein, MD,[6] Brent Hayek, MD,[9] Paul D. Langer, MD,[10] Gary J. Lelli, MD,[11] Ronald Mancini, MD,[12] Alexander Rabinovich, MD,[13] Javier Servat, MD,[14] John W. Shore, MD,[4] Jason A. Sokol, MD,[15] Angelo Tsirbas, MD,[16] Edward J. Wladis, MD,[17] Albert Y. Wu, MD,[18] Jerry A. Shields, MD,[2] Carol Shields, MD,[2] Roman Shinder, MD[1,3]

Objective: Bilateral lacrimal gland (LG) disease is a unique presentation that can result from varied causes. We reviewed the diagnoses, clinical features, and outcomes of 97 patients with this entity.

Design: Case series.

Participants: Ninety-seven patients with bilateral LG disease.

Methods: Retrospective review and statistical analysis using analysis of variance and the Fisher exact test.

Main Outcome Measures: Patient demographics, clinical features, diagnostic testing, diagnosis, and treatment.

Results: Patient age ranging from 8 to 84 years (mean, 46 years). The predominant gender was female (77%), and race included black (49%), white (38%), and Hispanic (12%) patients. Diagnoses fell into 4 categories: inflammatory (n = 51; 53%), structural (n = 20; 21%), lymphoproliferative (n = 19; 20%), and uncommon (n = 7; 7%) entities. The most common diagnoses included idiopathic orbital inflammation (IOI; n = 29; 30%), sarcoidosis (n = 19; 20%), prolapsed LG (n = 15; 15%), lymphoma (n = 11; 11%), lymphoid hyperplasia (n = 8; 8%), and dacryops (n = 5; 5%). Inflammatory conditions were more likely in younger patients ($P<0.05$) and in those with pain ($P<0.001$) and mechanical blepharoptosis ($P<0.01$) at presentation, whereas lymphoma was more common in older patients ($P<0.001$) without active signs of inflammation at presentation. Black patients were more likely to have sarcoidosis ($P<0.01$). Laboratory results showed high angiotensin converting enzyme level being significantly more likely in patients with sarcoidosis ($P<0.05$). However, sensitivity was limited to 45%, with 25% of patients diagnosed with IOI also demonstrating positive results. Corticosteroid therapy was the treatment of choice in 38 cases, corresponding to resolution of symptoms in 29% and improvement in an additional 32%. Overall, chronic underlying disease was found in 71% of patients, among whom 26% achieved a disease-free state, whereas 3% succumbed to their underlying disease.

Conclusions: The cause of bilateral lacrimal gland disease most commonly was inflammatory, followed by structural and lymphoproliferative. Patient characteristics and clinical presentations were key features distinguishing between competing possibilities. Despite local control with corticosteroids or radiotherapy, underlying disease continued in 71% of patients and led to death in 3%. *Ophthalmology 2014;■:1–7 © 2014 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Lacrimal gland (LG) disease is usually a unilateral process and reflects a variety of underlying etiologic factors. However, a minority of cases demonstrate bilateral disease at presentation, constituting a distinct clinical entity from unilateral presentations. To date, there are no large-scale descriptions of bilateral LG disease or its cause, presentation, radiography, treatment, or outcomes. In our literature search, the largest published series of bilateral LG disease involved 12 patients with immunoglobulin (Ig) G4-related disease or lymphoma showing characteristic tumor features, frequent recurrences, high serum IgG4 levels, and steroid responsiveness.[1]

Other published reports describe occasional bilateral LG presentations of inflammatory, lymphoproliferative, and structural conditions.[2–15] One inflammatory cause is idiopathic orbital inflammation (IOI), which represents nongranulomatous acute or subacute steroid-responsive inflammatory disease of orbital tissues and encompasses the subtype of IgG4-related disease.[2,3] Other inflammatory and lymphoproliferative causes of bilateral LG disease can reflect systemic diseases including sarcoidosis,[4,5] Sjögren's syndrome,[6] and lymphoma.[7–10] In contrast, structural causes of bilateral LG disease usually are limited to the orbit and include dacryops[11–13] and LG prolapse that may be

ISSN 0161-6420/14/$ - see front matter
http://dx.doi.org/10.1016/j.ophtha.2014.04.018

Table 1. Bilateral Lacrimal Gland Diseases in 97 Patients: Demographics per Diagnosis

Diagnosis	No. (%)	Age (yrs)		Sex, no. (%)		Race, no. (%)		
		Mean	Range	Female	Male	Black	White	Hispanic
Total	**97**	**46**	**8–84**	**75 (77)**	**22 (23)**	**48 (49)**	**37 (38)**	**12 (12)**
Inflammatory	**51 (53%)**	**42***	**15–84**	**39 (76)**	**12 (24)**	**27 (53)**	**18 (35)**	**6 (12)**
IOI	29 (30%)	42	15–84	20 (69)	9 (31)	12 (41)	12 (41)	5 (17)
Sarcoidosis	19 (20%)	42	26–68	16 (84)	3 (16)	15 (79)†	3 (16)*	1 (5)
Sjögren's syndrome	3 (3%)	48	45–51	3 (100)	0 (0)	0 (0)	3 (100)	0 (0)
Structural	**20 (21%)**	**43**	**8–82**	**17 (85)**	**3 (15)**	**10 (50)**	**6 (30)**	**4 (20)**
Lacrimal gland prolapse	15 (15%)	39	8–64	14 (93)	1 (7)	9 (60)	2 (13)*	4 (27)
Dacryops	5 (5%)	55	34–82	6 (60)	2 (40)	1 (20)	4 (80)	0 (0)
Lymphoproliferative	**19 (20%)**	**57‡**	**15–79**	**15 (79)**	**4 (21)**	**7 (37)**	**11 (58)**	**1 (5)**
Lymphoma	11 (11%)	64‡	46–79	8 (72)	3 (27)	4 (36)	7 (64)	0 (0)
Lymphoid hyperplasia	8 (8%)	49	15–63	7 (88)	1 (13)	3 (38)	4 (50)	1 (13)
Uncommon entities	**7 (7%)**	**51**	**10–78**	**4 (57)**	**3 (53)**	**4 (57)**	**2 (29)**	**1 (14)**
Rosai Dorfman disease	3 (3%)	47	10–78	1 (33)	2 (67)	2 (67)	1 (33)	0 (0)
Erdheim Chester disease	2 (2%)	58	56–60	1 (50)	1 (50)	1 (50)	0 (0)	1 (50)
Necrotizing granulomatous disease	1 (1%)	38	—	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)
Extramedullary hematopoiesis	1 (1%)	61	—	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)

IOI = idiopathic orbital inflammation.
*$P<0.05$.
†$P<0.01$.
‡$P<0.001$.
Boldface represents categories of disease.

secondary to involutional periorbital changes, floppy eyelid syndrome, or blepharochalasis.[14,15] Uncommon entities also are reported in the literature.[16,17] We herein review bilateral LG disease as a clinical manifestation through our collaborative experience with bilateral LG disease in 97 consecutive patients.

Methods

We reviewed patients with bilateral LG disease between July 2005 and June 2013 from oculoplastic specialists and ocular oncologists from 18 institutions in the United States and Australia. All patients with clinically, radiographically, or biopsy-proven bilateral lacrimal gland abnormalities, or a combination thereof, were included. All data was collected retrospectively. The treating physicians reported details on patient demographic information (age, gender, and race), clinical presentation (presence of palpable LG mass, periorbital edema, pain, mechanical blepharoptosis, conjunctival injection, and globe dystopia), diagnosis, and treatment (observation, corticosteroids, surgery, chemotherapy, radiation therapy, and combinations thereof). Research procedures were approved by the Institutional Review Board of SUNY Downstate Medical Center. The study was conducted in accordance to the Health Insurance Portability and Accountability Act as well as the Declaration of Helsinki.

Statistical analyses were conducted using Stata SE version 12.0 (Stata Corp. LP, College Station, TX). Trends in categorical variables were evaluated using the Fisher exact test, whereas continuous variables were evaluated using the analysis of variance. The 2-tailed significance threshold was set at $P<0.05$.

Results

Demographics and Diagnoses

There were 97 patients with bilateral lacrimal gland disease. Radiography was obtained and reported in 87 patients (90%), laboratory studies were reported in 46 patients (47%), and biopsy results were reported in 74 patients (76%). Seven patients were lost to follow-up, but were included for demographic characteristics, radiography, serologic analysis, diagnosis, and presenting symptoms. Treatment response and outcome were available for 90 patients (93%). One patient with extramedullary hematopoiesis secondary to chronic myeloid leukemia was described previously in a published case report.[16]

Most diagnoses were determined through biopsy and histologic analysis (n = 74; 76%). Tissue samples from patients with lymphoma or reactive lymphoid hyperplasia were evaluated additionally with flow cytometry, immunohistochemistry, and gene rearrangement studies. Of the patients who did not undergo an LG biopsy, the clinical diagnosis was made on the basis of classic clinical and, for certain patients, radiographic presentations of the respective conditions. Five cases of IOI were diagnosed based on acute inflammatory clinical signs, negative laboratory results, and brisk response to steroids. Four cases of bilateral LG enlargement occurred in the presence of already established systemic sarcoidosis, Sjögren's syndrome, or lymphoma. Three cases of dacryops were diagnosed in individuals with classic clinical findings including transillumination of the cyst. Eleven cases of prolapsed LG were diagnosed in patients with stable disease course, lack of inflammatory signs, unremarkable radiography, and negative laboratory work-up. Laboratory studies and radiography were ordered when deemed clinically necessary by treating physicians and pertinent results were reported.

The patient demographics and diagnoses in 97 cases of bilateral LG disease are shown in Table 1. The most prevalent diagnosis was IOI (30%; n = 29), followed by sarcoidosis (20%; n = 19), LG prolapse (15%; n = 15), lymphoma (11%; n = 11), reactive lymphoid hyperplasia (8%; n = 8), dacryops (5%; n = 5), Sjögren's syndrome (3%; n = 3), Rosai Dorfman disease (3%; n = 3), Erdheim Chester disease (2%; n = 2), primary necrotizing granulomatous disease (1%; n = 1), and extramedullary hematopoiesis secondary to chronic myeloid leukemia (1%; n = 1). Altogether, inflammatory diseases (IOI, sarcoidosis, Sjögren's syndrome) were 53% of the sample (n = 51), structural