



CME Review

Blepharochalasis: A rare cause of eye swelling

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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize the clinical presentation of blepharochalasis
- Discuss the differential diagnosis of eyelid swelling and rash
- Describe treatment and natural history of blepharochalasis

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

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Introduction

Eye and eyelid swelling is a common manifestation of allergic disorders that may occasionally present as a diagnostic dilemma.¹ Allergists need to be familiar with the differential diagnosis of ocular swelling and its uncommon causes.

Clinical Vignette

A 15-year-old South Asian girl presented to our allergy clinic with a chief concern of intermittent right upper and right lower eyelid swelling for past the 13 months (Fig 1). History was provided by the patient and her mother. Positive findings included right eyelid swelling, more notable in the morning and without any visual impact. There was no associated pain, redness, itching, or discharge noted by the patient. The swelling initially presented in May 2015, and at that time, the patient completed a course of oral antibiotics for presumed infection (amoxicillin–clavulanic acid in May and azithromycin in August) without improvement in eyelid swelling. She was also prescribed fluticasone propionate nasal spray and was referred to a pediatric ophthalmologist and allergist for further evaluation.

The results of ophthalmology evaluation were overall unremarkable. Her vision was 20/20 bilaterally, and she had no afferent pupillary defect and no diplopia. Intraocular pressure was normal (14 mm Hg [right] and 15 mm Hg [left]). Right upper and lower eyelid swelling with mild ptosis was noted. The differential diagnosis included gravity-dependent edema, sinus disease, and blepharochalasis. Computed tomography revealed mildly deviated nasal septum and bilateral concha bullosa, which are normal anatomical variants. Paranasal sinuses were also normal, excluding sinusitis as a trigger for palpebral swelling. Blepharochalasis was considered, and palpebral skin biopsy was recommended, but it was deferred by the patient and her parents.

Because of the recurrent nature of the eyelid swelling, the patient subsequently underwent evaluation for contact dermatitis. The patch test results were strongly positive for gold sodium thiosulfate at 72 hours and colophony at 24 hours, with an extreme positive reading at 72 hours. Cosmetic products that contained colophony were eliminated without any improvement in the eyelid swelling. Although in the North American Contact Dermatitis

Group analysis, gold was the most common contact allergen that induced isolated eyelid allergic contact dermatitis (8.2% of patients), our patient did not wear any gold jewelry; therefore, despite a strong patch test result, gold was not a culprit in her symptoms. The otolaryngologic evaluation was also sought and confirmed that sinus disease was not a contributing factor, but no specific diagnosis was made.

Further testing was sought by the family and focused on identifying the specific allergens. At the first allergist's office, extensive evaluations for specific IgE to multiple food and inhalant allergens by skin prick and serologic testing produced negative results. The total IgE level was 9.8 IU/mL (reference range, 0–100 IU/mL); specific IgE was undetectable (<0.35 kU_A/L) for a broad panel of inhalant allergens, including white hickory red maple tree, hamster epithelium, gerbil epithelium, rye, meadow fescue, sweet vernal, red top bentgrass, beech, white oak, bluegrass, Kentucky grass, German cockroach, *Fusarium proliferatum*, *Rhizopus nigricans*, and mountain cedar.

The patient was subsequently referred to our clinic for a second opinion to rule out food allergy. The patient had empirically avoided dairy products for 3 months before presenting to our clinic, but episodic eyelid edema recurred. The results of a review of systems were unremarkable. The patient denied any eye discomfort, discharge, redness, itchiness, visual changes, numbness, asymmetry, hearing problems, weight loss, fever, or neurologic issues. No urticaria or recurrent infections were reported. Family history was negative for atopic disease; her brother had a history of chronic hives. The patient denied any history of smoking or having pets at home. She lived with her parents and a brother. There was no known drug or food allergy. Current medications included doxycycline, clindamycin topical lotion, benzoyl peroxide gel (for acne), and triamcinolone acetonide nasal spray.

On physical examination, the patient was a well-developed and well-appearing girl, with mild right upper and lower eyelid swelling. Right upper and lower eyelids were slightly swollen and painless, without warmth, erythema, or palpable masses. There was no conjunctival erythema, discharge, tearing, or skin changes around the right eye. The visual examination findings were within normal limits, pupils were equal and round reactive to light, ocular motion was intact, and conjunctivae were noninjected; fundi were

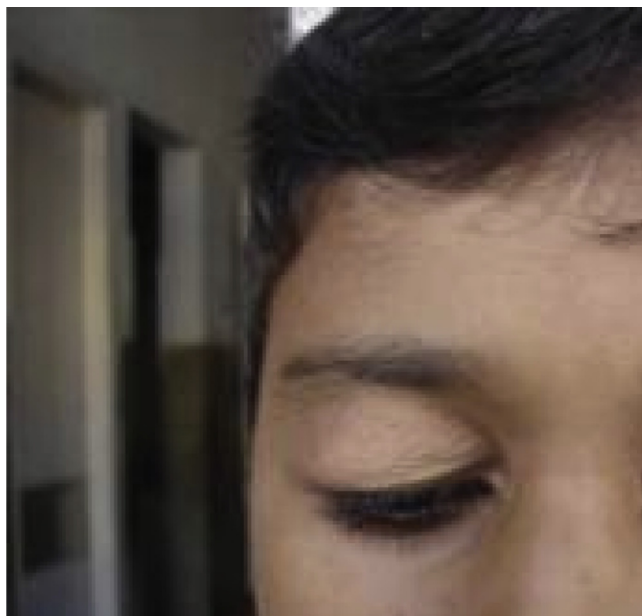


Figure 1. Swelling of the right upper eyelid with wrinkled skin appearance typical of blepharochalasis. Reproduced from: Brar BK, Puri N. Blepharochalasis—A rare entity. *Dermatol Online J.* 14(1). Retrieved from <http://escholarship.org/uc/item/14g254jd>. Copyright 2008 (CC-BY-NC-ND).

not examined. There were no Dennie-Morgan lines and no allergic shiners. Except for the right upper and lower eyelid swelling, there was no facial swelling or asymmetry, and the rest of the physical examination findings were unremarkable.

The results of skin prick testing and serologic testing for specific IgE antibodies were negative to the common inhalant and food allergens: dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), molds, tree pollen mix, dog dander, hen's egg white, cow's milk, soy, wheat, lentil, chickpea, and peanut. The total IgE level was 14 U/mL (reference range, 0–100 U/mL).

We concurred with the ophthalmologist, who considered blepharochalasis in her differential diagnosis; however, to exclude systemic diseases, such as hereditary angioedema, thyroid disease, and lupus, we performed a panel of screening laboratory tests. Laboratory results revealed normal results on the following tests: complete blood cell count, metabolic panel, liver function, thyrotropin, thyroglobulin antibody, thyroid peroxidase antibody, vitamin B₁₂, folate, erythrocyte sedimentation rate, complement C4, and C-reactive protein. Antineutrophil cytoplasmic antibodies were undetectable.

Differential Diagnosis of Eyelid Swelling

Differential diagnosis of eye swelling is extensive (Table 1).^{2–20,33–40}

Our patient presented for evaluation of possible allergic triggers, specifically focusing on foods. On review of the patient's medical history and the physical examination findings, we had a low suspicion for a specific allergic trigger because of the recurrent and chronic nature of her symptoms. In particular, the clinical presentation of our patient was not consistent with an IgE mechanism because the episodes of ocular swelling lasted several days and appeared and subsided without association with a specific food ingestion or any dietary changes. The lack of the temporal association with dietary factors was also not consistent with a non-IgE mechanism of food allergy because there are no known non-IgE-mediated food allergic disorders that manifest exclusively in the palpebral skin without involving other organs. In addition, the age

at onset in adolescence made food allergy less likely, although not impossible. Finally, the empiric trial of elimination of the cow's milk protein from the diet did not lead to the improvement of our patient's symptoms. However, to address the patient's concerns, during the visit, skin prick testing was performed with negative results for the common inhalant and food allergens. We recommended our patient resume an unrestricted diet because her clinical picture and test results were not consistent with food allergy. Because we did not identify specific inhalant allergens, avoidance measures were also not recommended.

Allergic or irritant contact dermatitis was initially considered in the differential diagnosis, given our that patient's patch test result was positive for gold sodium thiosulfate and colophony; however, with avoidance of products that contain colophony, there was no symptom improvement, and our patient did not wear gold jewelry. In addition, clinical findings did not fit the picture of contact dermatitis because there was no reported or observed pruritus, erythema, or surrounding skin changes. An infectious origin was unlikely, given no clinical or laboratory correlations. Thyroid disease was also unlikely given that the laboratory workup results were negative. A malignant tumor was considered highly unlikely in the setting of a normal computed tomography and blood work results and without clinical correlation. We reassured our patient that a systemic process was very unlikely and recommended performing a palpebral biopsy, which the patient and family declined at that time.

We have focused on uncommon causes of eye swelling and identified blepharochalasis as the most plausible cause in our patient. Blepharochalasis is a rare disorder that presents as non-tender, nonerythematous unilateral or bilateral eyelid swelling with intermittent recurrent episodes of exacerbations and remissions with variability in duration.²¹ With age, the frequency of swelling attacks typically subsides; however, unexpected episodes may occur after an extended period of inactivity without any clearly identifiable triggering factors.²²

Blepharochalasis may have an onset from early childhood to late adolescence and consists of 2 stages. During the acute active or early phase with frequent episodes, symptoms may last from hours to days (mean, 2 days).²³ The early phase has a hypertrophied stage (nonpitting edema with boggy appearance), which over time evolves into an atrophic stage (thinning) from frequent exacerbations. Exacerbations lead to breakdown of elastic fibers, atrophy of skin, wrinkling tissue-paper appearance, thinning with discoloration, redundant, superimposed with tortuous vessels, and a common finding of ptosis. The late complications, attributable to continuous underlying structural destruction, include blepharophimosis, prolapsed lacrimal tissue and orbital fat, lower lid retraction, and pseudoepicanthal folds.²³ This transition is defined as the late or quiescent stage.^{21–24} A major review of 67 cases by Koursh et al²¹ concluded that the underlying cause of blepharochalasis is unknown. Given the onset during puberty, it is hypothesized that endocrine and hormonal imbalance maybe a trigger.^{21,23} _ENREF_4Histopathologic findings suggest an autoimmune cause and an underlying complex inflammatory process.

There is generally a loss of elastic fibers with a deposition of IgA antibodies on elastic fibers and collagen fibers and accumulation of neutrophils.^{25–27} In addition, surrounding blood vessels and eccrine sweat glands are also affected, with a large amount of IgA deposition along with the loss of elastic fibers within the papillary dermis.²⁶ Another study found that possible increased expression of matrix metalloproteinase 3 and matrix metalloproteinase 9 may have a role in the development of blepharochalasis. It was postulated that matrix metalloproteinase inhibitors, such as doxycycline, might provide resolution.^{28–30} However, in our patient's case, doxycycline therapy for acne did not improve her symptoms. Oral antihistamines, topical and systemic steroids, sympathomimetic agents, mast cell stabilizers, and cool compresses do not significantly modify the symptoms of acute

Table 1
Differential Diagnosis of Chronic Eye Swelling

Condition	Clinical manifestations	Pathophysiologic mechanisms
Allergic or Irritant		
Allergic rhinoconjunctivitis ²	Eyelid edema, conjunctival injection, chemosis, tearing, rhinorrhea, allergic shiners with history of allergen exposure; findings are usually symmetrical and favorable response to oral antihistamines	Inflammation of mucous membranes caused by allergen-induced IgE activation and release of inflammatory mediators (type I hypersensitivity)
Allergic angioedema ³	Bilateral or unilateral facial swelling, including eyes and lips, urticarial, resolved or improves with oral antihistamines	IgE-mediated type I hypersensitivity in which mast cells and basophils are activated and histamine and leukotrienes are released secondary to allergen exposure
Allergic contact dermatitis ^{4–6}	Acute: pruritic papules and vesicles on an erythematous base; Chronic: lichenified pruritic plaques	T-lymphocyte-mediated delayed type hypersensitivity reaction to contact with an allergen; usually cosmetics or metal
Irritant contact dermatitis ⁷	Eyelid swelling and erythema, pruritus, erythema with history of irritant exposure; favorable response to topical anti-inflammatory agents	Disruption of integrity of epithelial skin barrier by irritant, resulting in permeability and inflammation of skin
Angioedema		
Hereditary or acquired angioedema ⁸	Bilateral or unilateral facial swelling, including eyes and lips, without urticaria, usually lasting 1–2 days and may be associated with severe pharyngeal swelling and risk for obstruction or severe abdominal pain, nonresponsive to antihistamines	Deficiency in the level of C1 esterase inhibitor (C1-INH), resulting in increased bradykinin release Type 1: reduced C1-INH expression; type 2: normal level but dysfunctional C1-INH protein; type 3: mutation in factor XII, estrogen dependent and associated with normal C1-INH and complement C4 level
Lymphedema		
Congenital and/or acquired in adulthood secondary to mass, malignant tumor, surgical procedure, and after radiation therapy ⁹	Swelling of the eyes, face, lips, neck, or area below the chin, decreased vision because of swollen eyelids, difficulty swallowing, speaking, or breathing, drooling or loss of food from the mouth while eating, nasal congestion or long-lasting middle ear pain, if swelling is severe	Local manipulations, removal of the lymph nodes, radiation therapy, trauma, or infections can result in a dysfunctional lymphatic drainage
Rosaceous lymphedema (Morbihan syndrome) ^{10,11}	Chronic erythematous edema (solid facial edema) in the facial region predominantly cheeks, glabella, forehead, usually presents in adulthood	Histopathologic findings may include noncaseating granulomas and abnormal inflammatory and structural changes along with lymphatic abnormalities and need clinical correlation with underlying cause of lymphedema
Infections		
Preseptal or orbital cellulitis ¹²	Eyelid swelling, tenderness, erythema or induration, discharge, fever, pain with eye movement, leukocytosis	Common bacteria: <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , and <i>Streptococcus pyogenes</i> Pediatric cases: <i>Haemophilus influenzae</i> ; Immunocompromised host: mucormycosis (zygomycosis)
Tuberculosis of the eyelid ¹³	Abscess or mass on surface of eyelid, usually localized swelling or palpable mass	Result of hematogenous spread or extension of nearby skin infection with <i>Mycobacterium tuberculosis</i>
Thyroid Disease		
Thyroid ophthalmopathy ¹⁴	Bilateral eye swelling, proptosis, ptosis, and lid lag	Hypothyroidism or hyperthyroidism
Malignant Tumor		
Primary tumor or metastases	Unilateral or bilateral eye swelling, proptosis, ptosis, constitutional symptoms, mass on imaging, lymphadenopathy	Primary: neuroblastoma, rhabdomyosarcoma, lymphangioma, liposarcoma, and lymphoma Metastases: neuroblastoma, breast cancer
Autoimmune or Chronic Inflammatory Diseases		
Idiopathic orbital inflammatory syndrome orbital pseudotumor ¹⁵	Unilateral or bilateral eye swelling, redness, and pain photophobia, proptosis, periorbital edema, chemosis, conjunctival injection, and occasionally diplopia	Mechanism unknown, hypothesized to be autoimmune, mediated by both T cells and B cells; complete remission in response to a high dose of systemic corticosteroids
Juvenile dermatomyositis ¹⁶	Bilateral periorbital edema, Gottron papules, heliotrope rash, proximal muscle weakness	Mechanism not fully understood, thought to be secondary to environmental trigger that causes dysregulation of innate and adaptive immune systems
Sarcoidosis ¹⁷	Unilateral or bilateral orbit swelling, with ptosis, uveitis, and ophthalmoplegia, and systemic involvement (arthralgias, lower respiratory tract, rash)	Unknown cause, associated with noncaseating granulomas, T lymphocytes and phagocytes accumulation in affected tissue
Systemic lupus erythematosus ¹⁸	Multiorgan involvement, including eye swelling, malar rash, and mucocutaneous ulcers, renal failure, fatigue, fever, weight loss, arthralgias	Mechanism hypothesized to be mediated by immune complex, antibody formation and deposition, and complement activation
Wegener granulomatosis ¹	Unilateral or bilateral eye swelling, episcleritis, scleritis, uveitis, proptosis, ptosis, conjunctival injection, with systemic involvement (upper and lower respiratory tract, renal)	Cause still unclear, likely related to antineutrophil cytoplasmic antibody activation of immune system
Rare Disorders of Unknown Cause		
Asher syndrome ^{19,20}	Presentation in adolescence, with a triad of blepharochalasis, recurrent edema of the lip and, in 10% of cases, nontoxic thyroid enlargement	Scant case reports; treatment relies on surgical correction of structural deformities

(continued on next page)

Table 1 (continued)

Condition	Clinical manifestations	Pathophysiologic mechanisms
Blepharochalasis ^{21–32}	Intermittent, nonerythematous cyclical upper eyelid swelling, lasts 1–2 days, may be up to 3–4 attacks per year; the eyelids become wrinkled, redundant, discolored, and thinned	Unknown cause; biopsy reveals atrophy, fragmentation, and markedly decreased amounts of elastic fibers in the dermis; there may be a perivascular infiltration with lymphocytes, histiocytes, mast cells, plasma cells, and eosinophils. Patients may have IgA antibodies directed against elastic fibers.
Cutis laxa ^{33,34}	Loose and pendulous skin; symmetrical folds around eyes, face, head, and neck, and all over body; systemic organ pathologic involvement is common, including pulmonary, cardiovascular, and gastrointestinal abnormalities	Unknown cause, possibly related to elastin degradation
Floppy eyelid syndrome ^{35,36}	Elastic upper eyelid, chronic papillary conjunctivitis with eye tearing and burning, easy inversion of eyes, unilateral or bilateral; associated with obstructive sleep apnea	Associated with decreased tarsal elastin of unknown mechanism
Lax eyelid (dermatochalasis) ^{37,38}	Lax and redundant eyelid skin of the upper and lower lids bilaterally, loss of superior or peripheral vision fields	Normal aging of skin, resulting in loss of elasticity and skin thickness
Melkersson-Rosenthal syndrome ^{39,40}	Swelling of the upper lip, lower lip, one or both cheeks, eyelids, or rarely, one side of the scalp. A fissured tongue is seen in 20%–40% of those affected and may be present since birth. Salivary gland secretion may be reduced, and the sense of taste may be diminished. Facial palsy (unilateral or bilateral) occurs in approximately 30% of those affected and sometimes is the first symptom.	Unknown cause; noncaseating granuloma and lymphocytic infiltrates are seen on tissue biopsy specimen

attacks. Edema relief has been reported in a small case series using oral acetazolamide in conjunction with topical hydrocortisone.^{31,32}

Currently, the primary treatment for blepharochalasis is a corrective surgical intervention that modifies and restructures the redundant skin and prolapsed lacrimal gland and possibly resolves ptosis. Surgery is recommended when the disease is in a late quiescent phase (at least 6 months after the most recent exacerbation), and episodes usually decrease with age; however, recurrence of symptoms may require further procedures.²⁵

Conclusion

Blepharochalasis is a rare disorder that is poorly understood and has unclear mechanisms, with surgical intervention being the primary treatment. It is essential to focus on clinical clues in history and on physical examination and to perform further necessary workup (laboratory tests, imaging, and histopathologic analysis) to provide avoid unnecessary delays and stress for patients and their family members. It is important to exclude other causes and to reassure the patients about an overall favorable prognosis and natural course.

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