The anatomical and functional relationship between allergic conjunctivitis and allergic rhinitis

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ABSTRACT

There are numerous anatomic connections between the allergic conjunctivitis and allergic rhinitis. The most obvious reason is the physical connection via the nasolacrimal apparatus. However, a closer look at innervation, circulatory, lymphatic, and neurogenic systems reveals much more than a physical connection. The eye is richly innervated by parasympathetic nerves that enter the eyes after traveling in conjunction with the parasympathetic input to the nasal cavity. Parasympathetic innervation governing the tear film and nasal secretion can intersect at the pterygopalatine ganglion. Neurogenic inflammation affects both the eye and the nose as evidenced by the presence of the same neurogenic factors. Venous flow is in the SOV area connecting the eye and the nose, once thought to be without valves. In the past, this thinking is the basis for concern about the danger triangle of the face. Recent literature has shown otherwise. Although valves are present, there are still pathways where bidirectional flow exists and a venous connection is made. The most likely area for venous communication is the pterygoid plexus and cavernous sinus. The venous flow and connections also offers a pathway for allergic shiners. Understanding the mutual connections between the nasal mucosa and the ocular surface can also affect treatment strategies.

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The prevalence of allergic rhinitis (AR) and allergic conjunctivitis (AC) has been described to be ~70%.1–3 The purpose of this article is to examine the connections between the allergic target organs leading to the two most common allergic conditions from a clinical, anatomic, functional, and treatment perspective.

ONE AIRWAY, ONE DISEASE

In the 1990s, the concept of “one airway, one disease” considered asthma and AR as a continuum of inflammation within a common airway. Clinically, the one airway concept was based on the relationship evident in the 60–78% prevalence of patients suffering from both conditions. Not only is the comorbidity high, many of the therapeutic interventions have common mechanisms of action.4,5 There has been some discussion as to whether AC should be a part of the one airway concept. Both share continuous epithelial surfaces and have a physical connection via the nasolacrimal sac and both have similarities as part of the epithelial barrier defect.6,7 Just like with asthma, AR has a high comorbidity with AC.1,2,8,9 Past studies on prevalence of both conditions are as high. For patients with AR in response to cypress pollen, the prevalence of AC was ~88%.1,8 Another investigation of hay fever sufferers showed 8% ocular symptoms without nasal symptoms, 6.7% nasal symptoms without ocular symptoms, and 85.3% for both nasal and ocular symptoms.1,2 In a survey of 20,010 people, 29.7% reported both ocular and nasal symptoms.3 Finally, >50% of patient with nasal allergy stated that watering and red/itching eyes were “moderately bothersome” to “extremely bothersome” in the recent Allergies in America survey.1 The literature clearly points to the connection and it is reflected in clinical practice. As with any concept, there are some that believe one airway philosophy is an oversimplification. The respiratory system and related structures share a number of common clinical and immunopathophysiological features in the development of allergic inflammation. The penetrance of the clinical features of the targeted organs can vary among patients. The occurrence of some allergic disorders, such as bronchial asthma, AR, AC, allergic sinusitis, and secretory otitis media does not automatically mean their comorbidity or their mutual relationship. The one airway philosophy may be an oversimplification because the connection is much more complex. The relationship entails the anatomy, innervation, neurogenic pathways, circulation, and lymphatic systems between the ocular surface and the nose.

OCULAR SURFACE ANATOMY

For AC, the principal structures involved are the conjunctiva, cornea, and tear film. These three structures make up the ocular surface. The conjunctiva comprises
The tear film offers several functions: refracting surface, lubricant, supports corneal transparency, nutrition, and immunologic factors in a “soup” that bathes the epithelium. The lacrimal gland secretes the bulk of the aqueous layer of the tear film. The goblet cells in the palpebral conjunctiva secrete mucous (MUC5AC) and form the bulk of the mucin layer of the tear film. The meibomian glands located in the eyelids form the lipid layer.10–12

Between the ocular surface and nose, the nasolacrimal apparatus is a direct physical connection. The main function is drainage of the tears from the ocular surface. The tears drain into the puncta and flow into the lacrimal sac and nasolacrimal duct.泪水 empty out into the inferior turbinate of the nose. Seventy-five to 80% of the tears are drained through the nasolacrimal system. Gravity, capillary attraction of the puncta, and blinking provide drainage forces.10,11

**NASAL ANATOMY**

The nasal cavity is the narrowest part of the respiratory tract. The nasolacrimal duct opens into the inferior meatus, the portion of the nasal cavity lateral to the inferior turbinate. The highest number of mucus-secreting goblet cells are in the posterior nasal cavity.13

**OCULAR SURFACE SENSORY INNERVATION**

The sensory nerves of the ocular surface come from the ophthalmic nerve of the trigeminal. Figure 1 shows the innervation of the ocular surface and nose (Fig. 1). The ophthalmic nerve branches are lacrimal, frontal, and nasociliary. The lacrimal nerve innervates the upper lid and superior conjunctiva and the frontal nerve branch innervates upper lid and conjunctiva via the supraorbital and supratrochlear nerves. Branches of the nasociliary nerves innervate the conjunctiva, cornea, and sclera.10,14,15

**NASAL SENSORY INNERVATION**

The sensory nerves to the nose come from the maxillary nerve. The posterior superior and inferior nasal branches and nasopalatine nerves originate from the pterygopalatine ganglion. Internal nasal branches come directly from the maxillary nerve. The external nasal nerve comes from the ophthalmic nerve.13,16,17

**OCULAR SURFACE AUTONOMIC INNERVATION**

The autonomic nerves for the ocular surface control tear secretion and blinking. The sympathetic nerves to the lacrimal gland come from the superior cervical ganglion via the internal carotid and deep petrosal nerve to the pterygopalatine ganglion. From there, the nerve travels to the lacrimal gland.10,11,15,17–19 Most of the innervation revolving around tear secretion is controlled by the parasympathetic system.10 The postgang-
glionic parasympathetic nerves originate in the pterygopalatine ganglion. (Table 1).

**NASAL AUTONOMIC INNERVATION**

The autonomic nerve supply to the nasal mucous and serous glands control secretion. Sympathetic nerves cause vasoconstriction and suppress glandular secretions. Parasympathetic nerves cause vasodilation and increase secretions. The parasympathetic fibers arise in the sphenopalatine ganglion to form vidian nerve control vasodilation and glandular secretion (Table 2).

**PTERYGOPALATINE GANGLION**

Much of the innervation to the nasal and ocular surface structures comes from the pterygopalatine ganglion. The pterygopalatine ganglion is also known as sphenopalatine ganglion or Meckel’s ganglion. The pterygopalatine ganglion supplies the lacrimal gland as well as the nasal branches (nasopalatine). The pterygopalatine ganglion originates from the maxillary nerve. (Fig. 1)

**NEUROGENIC INFLAMMATION**

The neurogenic system forms another pathway for inflammation. The signal transmission inside the neurogenic system can be direct or indirect. In direct manner, there is a progression of an electromagnetic potential (quantum) through the neurogenic fibers. By the indirect manner, there is transport of the biochemical message by neurogenic messengers. The neurotransmitters are neuropeptides. A stimulatory impulse is relayed centrally, but there is also neurotransmitter release peripherally. Axonal reflex is the peripheral release of neuropeptides and results in neurogenic inflammation. The neurogenic response includes vasodilation, increased vascular permeability, recruitment, differentiation, and activation of inflammatory effector cells. A number of neurogenic compounds have been identified in the respiratory tract, nasal mucosa, and the ocular structures and surface. Such compounds are tachykinins (substance P and neurokinin A), neuropeptide Y, vasoactive intestinal peptide, and calcitonin gene-related peptide (Table 3). Other neurotransmitters associated with neurogenic inflammation found nasal and ocular are nerve growth factor and epidermal growth factor (Table 4).

Histamine release plays a role in neurogenic inflammation. When the mast cells degranulate, the released histamine triggers the receptors on the sensory nerves. In the eye, the response in the conjunctiva travels to the cortex and, in turn, triggers neurogenic inflammation.

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**Table 1** Innervation of the ocular surface

| Function       | Nerves                              | Structures                                                   | Effects                                      |
|----------------|-------------------------------------|--------------------------------------------------------------|---------------------------------------------|
| Sensory nerves | Cranial V: trigeminal branches V1 and V2 | Conjunctiva cornea                                          | Touch sensitivity and sensory reflexes      |
| Parasympathetic nerves | Cranial VII: vidian nerve to pterygopalatine ganglion | Meibomian glands, lacrimal gland, goblet cells, other glands secreting tear film, and conjunctival blood vessels | Tear secretion and vasodilation             |
| Sympathetic nerves | Lateral horn to superior cervical ganglia | Conjunctival blood vessels                                  | Vasoconstriction                            |

*Source: Refs. 10, 11, 15, and 17–20.*

**Table 2** Innervation of the nose

| Function       | Nerves                              | Structures                                                   | Effects                                      |
|----------------|-------------------------------------|--------------------------------------------------------------|---------------------------------------------|
| Smell and other sensory nerves | Cranial nerves 0 and I | Olfactory epithelium receptors                              | Sensory function (?)                        |
| Sensory nerves | Cranial V: trigeminal branches V1 and V2 | Blood vessels, mucous glands, and epithelium                | Sensory reflexes                            |
| Parasympathetic nerves | Cranial VII: vidian nerve to pterygopalatine ganglion | Blood vessels and mucous glands                             | Vasodilation, congestion, and rhinitis      |
| Sympathetic nerves | Thoracic via superior cervical ganglia | Blood vessels and anastomoses                                | Vasoconstriction                            |

*Source: Ref. 13.*
of the conjunctiva. Neuropeptides such as substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide are released from the nerve and stimulate receptors on the mast cells. The result is the release of more histamine51 (Fig. 2).

**NASAL OCULAR REFLEX**

The nasal ocular reflex or naso-ocular reflex has been theorized based on several studies.15–20,25,26 As far back as 1927, the reflex was described by Wernoe. A later report hypothesized a nasolacrimal reflex based on the use of nasal sprays. There were positive effects on ocular allergy symptoms that resulted from nasal sprays.54 One study reported ∼20% of AR sufferer’s experienced ocular symptoms after nasal exposure to grass pollen.55 Another earlier study found eyes would water after unilateral irritation of the nasal mucosa.56 Two double-masked crossover clinical trials investigated the nasal ocular reflex with a nasal allergen challenge and AC.52,57,58 The authors theorized histamine release from the nasal mucosa mast cells initiated rhinitis and AC. The afferent limb of the nasal ocular reflex was located in the nasal mucosa and resulted in nasal and ocular symptoms within minutes of the challenge. Only one nostril was given an antigen on a filter paper disk, with disks placed intranasally and Schirmer strips in the eye. Before the challenge, the

| Neurotransmitter                      | Year Discovered | Peptide Family | Nasal Innervation                                      | Ocular Locations                                                                 | Ocular Receptors |
|--------------------------------------|-----------------|----------------|--------------------------------------------------------|----------------------------------------------------------------------------------|------------------|
| Substance P                          | 193126          | Tachykinin     | CV trigeminal V1, V2; sensory nerves                   | Tears, conjunctiva,27–29 iris and ciliary body,30 and trigeminal ganglion31     | NK-130           |
| Calcitonin gene-related peptide      | 196132          | Calcitonin     | CV Trigeminal V1, V2; sensory nerves                   | Tears,33 trigeminal ganglion,31,34 and conjunctiva34,35                        | Calcitonin gene-related peptide35 |
| Neurokinin A                         | 198326,36       | Tachykinin     | Sensory nerves V Trigeminal V1, V2; sensory nerves     | Iris and ciliary body30 anterior segment, and trigeminal ganglion31              |                  |
| Vasoactive intestinal peptide        | 197037,38       | Vasoactive intestinal peptide | CVII vidian to pterygopalatine ganglion; parasympathetic nerves | Conjunctiva, lacrimal gland, ciliary body, posterior uvea, and pterygopalatine ganglion39 |                  |
| Neuropeptide Y                       | 198242          | Pancreatic polypeptide related | Thoracic via superior cervical ganglia; sympathetic nerves | Tears,33 ciliary body, limbus, choroid, and retina                               |                  |

**Source:** Ref. 25.

*Enhances effect on muscarinic receptors.41

| Year Discovered | Type          | Nasal Locations                                      | Ocular Locations                  |
|-----------------|---------------|------------------------------------------------------|-----------------------------------|
| Nerve growth factor | 195445       | Neurotrophin Nasal mucosa, mucous cells, and epithelial lining of submucosal glands46 | Conjunctival stroma and tears33,47 |
| Epidermal growth factor | 197948       | Growth factor Nasal mucosa50                         | Lacrimal gland50                   |

**Source:** Ref. 25.
patients were treated with either an antihistamine (azelastine) or a placebo control.

The ocular symptoms (itching and watering) and rhinorrhea increased in both nostrils with the placebo. With the antihistamine, there was no increase in rhinorrhea and ocular symptoms.

In a follow-up study, the effects of intranasal steroids on the nasocular reflex were studied. The authors hypothesized that repeated nasal allergen challenges would lead to priming and augmentation of nasonasal and nasal ocular reflexes. Intranasal steroids would decrease inflammation and inhibit both nasonasal and nasal ocular reflexes, resulting in reduction of eye symptoms. Either placebo or fluticasone furoate nasal spray was applied for 1 week and then challenged for 3 days. Pretreatment with fluticasone furoate nasal spray reduced sneezing, nasal secretion weights, amount of eosinophils in nasal secretions, and ocular symptoms.52,57,58 One study showed the first ocular symptoms impacted were tearing on day 2 followed by itching and redness on day 4 with intranasal corticosteroids.59

The naso-ocular reflex is not without controversy. The use of the term “reflex” itself may not be appropriate. Reflex usually means a single response to a single stimulus. Some believe if reflex truly exists, then every stimulation and/or irritation of the nasal mucosa, even in the healthy subjects, should lead to and result in a conjunctival (ocular) response. Increased tear production, hyperemia, and conjunctival injection would always occur with nasal stimulation, which is not the case. One school of thought is the term “na so-ocular reflex” may be better substituted by another term, such as “naso-ocular relationship.” The improvement of AC symptoms after an intranasal treatment with steroids or antihistamines may be caused by the drug effects on lymphatic tissues, cellular elements, classic mediators, cytokines, lymphokines, and neuropeptides, rather than the naso-ocular reflex. The lymphatic and/or neurogenic pathway may account for the nasal and ocular connection. Supporters of this concept propose there may be another form of AC, a secondary AC related to the stimulus of the nasal mucosa. Primary AC is caused by direct stimulation of the ocular surface. The responses can vary to an allergen challenge, i.e., early phase, late phase, and delayed.21–23

AC AND DRY EYES

AC and dryness of the ocular surface has been shown to have overlap. For 689 patients, the 57.7% of the ocular itch patients had dry eyes. This leads to the likelihood that itch or AC patients are 2.11 times as likely to also have dry eyes.60

The tear film becomes dysfunctional because it is compromised in dry eye disease. There are generally two types of dry eyes: aqueous deficient and evaporative. Aqueous deficient dryness is largely caused by insufficient secretion from the lacrimal gland. Evaporative dry eye is mostly from poor quality or inadequate lipid layer secreted by the meibomian glands. The tear secretion from the lacrimal gland and the rest of the tear glands are governed by the parasympathetic system.20,61

Blink rate has a large influence over the tear film. The corneal reflex is involuntary and is a response to stimulation of the cornea such as touching, foreign body, or bright lights. The response is primarily to protect the eye. The corneal reflex has trigeminal afferents (nasociliary and supraorbital) and somatic efferent fibers from the facial nerve62 (Table 5). The facial nerve innervates both orbicularis resulting in eyelid closure.
and blinking.\textsuperscript{63,64} The globus pallidus of the lenticular nucleus is thought to control the blinking.

Studies have shown evidence of a sensory reflex that controls blink rate. This is another pathway besides the globus pallidus. There is a connection between bilateral sensory loss and dry eyes. Loss of cornea sensitivity reduces both tear secretion and blink rate. When topical anesthesia (proparacaine) is applied to both eyes, blink rate is reduced by $\sim 30\%$ and tear secretion by $60–75\%$.\textsuperscript{65} Another study showed the effect of tear secretion from the sensory afferents of the ocular surface (ophthalmic nerve). Trigeminal denervation in rabbits reduces the lacrimal gland protein secretion and, therefore, induces dry eyes.\textsuperscript{66,67}

**LYMPHATIC SYSTEM**

The conjunctiva and lacrimal systems are rich in the lymphatic tissue. They have been referred to as “eye-associated lymphatic tissue,” “conjunctiva-associated lymphatic tissue,” “tear-associated lymphatic tissue,” and “lacrimal drainage-associated lymphatic tissue.”

The lymphatic system in the nose is sometimes called “nose-associated lymphatic tissue.” Both eye-associated lymphatic tissue and nose-associated lymphatic tissue belong to the general “mucosa-associated lymphatic tissue.”

Several cells play a role in the mucosa-associated lymphatic tissue and can express mutual communication. Cells include T lymphocytes (subsets “natural killers,” cytotoxic, and helper Th1 and Th2), B lymphocytes (plasma cells) producing immunoglobulins, macrophages, and other cell types.\textsuperscript{23,68–70}

**OCULAR SURFACE AND NASAL ARTERIAL SYSTEM**

Both the nose and the eye share the same arterial blood supply coming from the internal and external carotid arteries.

The arterial blood supply to the nose comes from two branches: internal carotid and external carotid. The internal carotid branches into anterior and posterior ethmoid arteries \textit{via} the ophthalmic artery. The external carotid branches into the sphenopalatine, greater palatine, superior labial, and angular arteries.\textsuperscript{13}

The main ocular arterial supply is by the ophthalmic artery, the first branch of the internal carotid artery. The ophthalmic artery branches to the lacrimal artery and feeds the lateral palpebral arteries; lateral palpebral arteries supply the conjunctiva and eyelids.\textsuperscript{7,14}

**OCULAR SURFACE VENOUS SYSTEM**

The venous system for the eye is complex, variable, and confusing. Unlike the nose, there is no correspondence between the arteries and veins. The two main orbital veins are superior ophthalmic vein (SOV) and inferior ophthalmic vein (IOV). The medial palpebral, lacrimal, and central retinal veins are some of the veins that drain into the SOV. The venous architecture has been shown to be nonsymmetrical between the two eyes. The IOV drainage includes the lower lid and lacrimal sac region.\textsuperscript{7} This can be seen during the physical examination that reveals pale, boggy nasal mucous membranes with congestion leading to an increased bluish hue in the infraorbital region (allergic shiners).
The cavernous sinus receives tributaries from the superior and IOVs. In the past, it was believed blood passes in both directions because there are no valves in place. An example of the connection is the danger triangle of the face or maxillofacial death pyramid. The triangular-shaped region from the angles of the mouth to the nose formed the dangerous triangle. Because of the alleged lack of valves in the facial vein, infection could readily spread to the intracranial venous sinuses. Another example of the connection is nasal and sinus infections may cause cavernous sinus thrombophlebitis. However, Zhang and Stringer harvested 12 SOVs and 8 IOVs from adult cadavers. They found valves present in 75% of the SOVs studied. The same study found no valves in the IOVs. Their findings go against modern clinical and anatomic reference texts. They attribute existence of communications with the cavernous sinus and blood flow direction as factors that spread infection in the face. Another study corroborates their findings and did not find valves in the facial vein.

There seems to be no consensus as to the direction of venous blood flow in the nasal and ocular region. Some feel the flow within the SOV is toward the face; others argue the flow is toward the cavernous sinus, and others still advocate the flow as bidirectional. One study suggests the flow to be temperature dependent. The flow is toward the face in nonthermic conditions and toward the cavernous sinus in hyperthermia and exercise. Based on their dissection work, Zhang and Stringer suggest that blood flow is (a) toward the internal jugular vein in the inferior part of the facial vein, (b) toward the cavernous sinus in the SOV, and (c) either the facial vein or the SOV from the angular vein. The connection between the eye and nose has been characterized as bidirectional (Fig. 3).

**NASAL VENOUS SYSTEM**

The nasal cavity venous system follows the same pattern as the arterial supply. There is direct communication with the cavernous sinus. The anterior and posterior ethmoidal veins drain to the ophthalmic vein. The sphenopalatine and greater palatine veins drain to the pterygoid plexus of veins. Both the ophthalmic vein and pterygoid plexus are directly connected to the cavernous sinus.

The nasal cavity has many venous connections to conjunctiva through the SOV and cavernous sinus. Inflammatory factors can travel along these venous pathways to trigger a response between the nose and eye.

**PTERYGOPALATINE GANGLION, PTERYGOID PLEXUS, AND CAVERNOUS SINUS**

When discussing AR and ocular impact, one commentator appropriately asked, “What is the mechanism?” As mentioned previously, most of the parasympathetic innervation governing secretion between the nose and the eye intersects in the pterygopalatine ganglion. A naso-ocular reflex is most likely located in this area. With respect to the venous system, the pterygoid plexus and cavernous sinus offers direct communication between the nose and the eye. Again, the nose and the ocular surface have another avenue of connection. These areas offer insight on the current research regarding the comorbidity between AR, AC, and dry eyes.

**TREATMENT CONSIDERATIONS**

The connection between the nasal mucosa and ocular surface offers both advantages and disadvantages in treatment. Corticosteroid nasal sprays comprise a large portion of rhinitis treatment. As previously mentioned, nasal sprays have shown an added advantage on ocular allergy by reduction of symptoms. The nasolacrimal apparatus is considered the conduit for many pharmaceutical treatments to potentially reach either the nose or the eye. Nasal sprays have been reported to have a positive impact on ocular symptoms, but that appears to be predominantly through a neurogenic mechanism. Does the effect happen in reverse? For ocular antihistamines, one study showed bepotastine on the eye has an effect in the nose. The topical application of antihistamine reduces rhinitis symptoms. In one study, the topical medication reduced rhinorrhea by 77% 8 hours after dosing. Those studies may offer support for the bidirectionality of the nasal ocular connection. Given the main function of the nasolacrimal apparatus is to drain the tears into the nose, the bidirectional treatment effects run contrary to its intended unidirectional role. Intranasal antihistamines effects on the ocular surface or topical ocular steroidal...
effects on the nasal mucosa have not been studied, to our knowledge.

One possible treatment disadvantage for the eye nose connection may be that the intraocular pressure (IOP) increases with intranasal corticosteroids. Increased IOP is a well-known adverse reaction of topical corticosteroids in the eye.79–84 Does corticosteroid intranasal sprays cause IOP spikes? The studies are mixed on the subject. Some studies show no real effects on IOP, while other studies show significant effects, especially in glaucoma patients.85–91

The effects of antihistamines such as drying can work for and against us in treatment. With nasal sprays, the drying or muscarinic effects on the nasal mucosa are advantageous. Antihistamines are useful in the nose for drying effects. However, for topical ocular antihistamines, this may work against the ocular surface. Ocular dryness can be exacerbated. On the ocular surface, these drying effects are not desirable. Topical ocular antihistamines are ranked in terms of muscarinic effects (less drying to more drying) as follows: alcaftadine, bepotastine, epinastine, ketotifen, olopatadine, and azelastine.92 Olopatadine in the eye has been shown to decrease tear production in animal studies, while other studies show no differences.93,94 The drying effect has also been shown with oral antihistamines.95

One disadvantage of the drying effect may be to induce greater AC itch symptoms. A recent study showed that depressed tear meniscus increases itch severity. Tear meniscus is the reservoir of the tear film. The height indicates the available tear volume. Optical coherence tomography was used to measure tear meniscus heights. Optical coherence tomography yields a moderate negative correlation (Pearson, \( r = -0.432; \ p = 0.05 \)). Itch frequency increases as tear meniscus heights decrease. One theory is the concentration of inflammatory factors in the tear film increases as the tear volume decreases. This may be a trigger for ocular itch.96

CONCLUSION

Mediators, cytokines, chemokines, chemotactic, and other factors released during allergic reaction could reach the nasal mucosa or conjunctiva through the nasolacrimal duct and lacrimal system or indirectly by their transport through the blood stream. The allergic reaction can activate and/or inhibit a number of cell types, such as mast cells, basophils, eosinophils, neutrophils, macrophages, and dendritic cells, and stimulate their migration through the bloodstream. The neurogenic network (sensory, sympathetic, and parasympathetic nerves) can result in release of various neuropeptides triggering neurogenic inflammation.21–23

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