

The link between the nose and lung, perennial rhinitis and asthma – is it the same disease?

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Perennial rhinitis and asthma are clinical syndromes representing a range of overlapping pathologies; accurate classification should therefore precede any comparison. Although the sinonasal cavities, trachea and bronchi have a common respiratory mucosa, there are also anatomical differences. For example, the nose has a capacitance vessel network and the lower airways possess smooth muscle, both of which are responsive to neurohumoral influences. The prevalence of rhinitis and asthma has increased over the last three decades. Rhinitis occurs in around 75% of allergic asthmatics while 20% of perennial allergic rhinitics develop asthma. Eosinophils, and their associated proteins and cytokines, may play a central role in both perennial rhinitis and asthma with and without atopy. The characteristic pathology of asthma can be summarized as a chronic, desquamating, eosinophilic bronchitis. Non-allergic rhinitis with eosinophilia is recognized, but without consistent evidence of epithelial damage. Eosinophils are also present in rhinosinusitis with polyposis, particularly in patients with aspirin sensitivity, in whom asthma also often occurs. Increased mast cell activation and mediator release is evident in both perennial rhinitis and asthma following allergen challenge. The importance of mast cells in non-atopic asthma and polyposis is also recognized. Adhesion molecules may also be upregulated, with an increased number and activation of TH₂ lymphocytes. However, allergen-resultant T-cell activation may be less marked in the nose than in the lung. Autonomic imbalance also plays a role in both conditions via changes in neural tone to effector tissues, release of neuropeptides, and interplay with cellular recruitment. Pharmacological manipulation of rhinitis and asthma also illustrates the pathological similarities and differences.

Key words: asthma; eosinophilia; lung; nose; pathology; perennial rhinitis; polyposis

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Rhinitis is a pathological term used to describe a clinical syndrome. This syndrome may represent a range of overlapping pathological processes which, despite the implication, are not always inflammatory; some authors therefore prefer the term "rhinopathy" (1, 2). When inflammation is the dominant disease process, rhinitis should more accurately be considered as "rhinosinusitis", which may also be associated with polyposis (3, 4). Patients with sinonasal symptoms can be classified into four aetiological groups: allergic, infective, structural, and a group of "other" miscellaneous conditions. The latter includes the previously described concepts of intrinsic rhinitis, idiopathic rhinitis, hyperreactive rhinitis, vasomotor rhinitis, and non-allergic rhinitis

with eosinophilia syndrome (NARES) (5, 6). More than one pathological process may be present in the same patient.

Asthma is also a clinical diagnosis based on the symptoms of paroxysmal dyspnoea, wheezing and cough (7). However, no single pathological process should be implicated from the diagnosis. Bronchial hyperresponsiveness is characteristic of asthma but is not always present. Current concepts consider asthma to be primarily an inflammatory disease (8, 9), but this is not always true of rhinitis. Asthma may overlap with chronic obstructive pulmonary disease and other chronic lower respiratory tract disorders, such as bronchiectasis (7), just as rhinitis may be a component of chronic rhinosinusitis.

It is evident that the terms perennial rhinitis and asthma represent clinical syndromes which may result from a range of pathological processes. Therefore, accurate classification, as far as possible, should precede any comparison of the two groups.

Anatomy

The nose, trachea and bronchi are lined by a similar ciliated columnar epithelium, with goblet cells and seromucinous glands, and are served by an autonomic and sensory nerve supply (10). All three areas of the respiratory tract are exposed to inhaled environmental irritants and antigens, and thus it would not be surprising if these sites displayed the same spectrum of pathological processes and mounted similar neurohumoral and immunopathological responses to challenge.

However, anatomical differences exist which may influence these processes and result in different manifestations of what may be the same underlying disease. The nose has vibrissae which contribute to the filtration of particles before they reach the trachea and bronchi to elicit a response, though the potential to mount a lower respiratory tract response may still be present. The nose is predominantly a rigid skeleton, lined by the nasal mucosa, which has a prominent system of subepithelial capillary beds, capacitance vessels, and arteriovenous shunts which help to modulate mucosal thickness and airway resistance (11). Similar systems are present in the trachea, though to a lesser extent, but are not found in the bronchi. On the other hand, the lower airways have smooth muscle, which is not found in the nose. Increased mucosal blood flow is the main contributor to exacerbations of nasal obstruction in perennial rhinitis, while in asthma this is caused by smooth muscle contraction. The lateral nasal wall has narrow bony clefts lined with mucosa; swelling of the mucosa results in apposition of adjacent surfaces, loss of ciliary action, and development of neurogenic, contact inflammation (12). Nasal and bronchial challenges demonstrate these differences in end-organ effector tissues (13, 14).

Epidemiology

The prevalence of both perennial rhinitis and asthma has risen in the developed and third world, in both adults and children, over the last three decades. Asthma affects approximately 20% of children and 0.5–10% of adults (15–17), while perennial rhinitis was found in 13% of patients in a London general practice in 1991 (18). Between 30–60% of subjects are expected to have a positive skin prick test (19).

As well as an increase in prevalence, both diseases often co-exist. Approximately 75% of patients with allergic asthma and 40% of patients with non-allergic asthma will have perennial rhinitis, while 20% of patients with perennial allergic rhinitis have signs of asthma (15, 20). In our series of 130 consecutive patients with chronic rhinosinusitis undergoing endoscopic sinus surgery, 44 (34%) had asthma and 89 (68%) had nasal polyps. Of the latter group, 29/89 (33%) had asthma. Aspirin-sensitive asthma has been reported in 8% of patients with polyposis (21), while a prevalence of 6% was observed in our study.

Upper and lower airway allergy develops simultaneously in 25% of patients, and of the remaining 75%, half develop asthma first and half develop rhinitis first (15). Patients with hay fever have four times the risk of developing asthma compared with asymptomatic individuals (22). Patients with allergic rhinitis may also demonstrate increased bronchial metacholine reactivity despite having no symptoms of asthma (15).

The association of rhinitis, polyposis and asthma, with or without atopy, amongst family members of patients with one or more of these conditions is also recognized, suggesting that common genetic factors are related to these upper and lower airway diseases (16). In our study, a total of 60/130 (46%) patients had a family history of rhinosinusitis, asthma or eczema, and 25 (42%) of the 60 patients had a positive skin prick test to house dust mite.

Perennial allergic rhinitis and allergic asthma

Pathology

Allergy in the nose and lung is characterized by the immunoglobulin E-dependent release of mast cell mediators and cellular infiltration of the mucosa with activated T-lymphocytes and eosinophils (23, 24). The majority of natural state and challenge studies in patients with allergic rhinitis have been undertaken in those with seasonal allergy, and it has been inferred that the mechanisms are the same in patients with perennial disease. Unfortunately, similar studies undertaken in patients with allergic asthma do not always state the degree of chronicity of disease or the responsible allergen.

It is possible that seasonal and perennial allergy may demonstrate quantitative differences in cellular response (25, 26). The late-phase response may also be more important in perennial than in seasonal allergic rhinitis, where nasal blockage due to oedema, rather than histamine-mediated vasodilatation, is the predominant symptom (27). Nasal

insufflation with histamine mimics the nasal symptoms of the early allergic response (13, 28), while the late-phase reaction, which may be due to an influx of inflammatory cells (28) and eicosanoids (29), cannot be reproduced by histamine (28). Furthermore, alleviation of nasal blockage with antihistamines is poor, particularly in perennial allergic rhinitis (30), implying a limited role for histamine in chronic disease (27, 29). Antihistamines also demonstrate minimal benefit in chronic extrinsic asthma.

In our experience, asthma is less common in patients with seasonal allergic rhinitis (hay fever) than in patients with perennial disease. This correlates with observations that positive skin prick tests to house dust mite or animal dander, but not to grass pollen, predict development of asthma (31). Seasonal asthma is usually less severe than perennial asthma and may respond to antihistamines (29). However, without precise population definitions, comparison of the pathology of allergic rhinitis and asthma may not be comparing "like with like".

Mast cell activation and mediator release is central to the development of perennial allergic rhinitis (28) and asthma (32, 33), though these cells may differ in the nose and lung (28, 34), since sodium cromoglycate has been shown to have different effects on mast cell degranulation in lung and nasal tissue *in vitro* (34). Nevertheless, mast cell numbers and activation are increased in both conditions (35, 36). Bronchial and nasal allergen challenge studies also reveal release of histamine, arachidonic acid metabolites, kinins, and tryptase, suggesting a mast cell source (33). However, the clinical late-phase reaction in the nose, unlike the lung, is often weak, and cannot clearly be distinguished from the early-phase reaction (13, 24, 27). Nasal biopsies from patients with perennial allergic rhinitis and bronchial biopsies from perennial allergic asthmatics have also demonstrated mast cell-derived interleukin-4 (IL-4), IL-5 and IL-6 (32, 35, 36), as have studies of the nasal mucosa 24 h after grass pollen challenge (37). The expression of mast cell-derived IL-4, a multifunctional cytokine that promotes allergic inflammation (32), is known to be enhanced in perennial atopic rhinitis (35) and asthma (36).

Mucosal eosinophilia is well recognized in asthma and seasonal allergic rhinitis (33), although it seems to be less marked in perennial disease (26). Eosinophils appear in the bronchial lumen 24–48 h after allergen challenge (9), and in the nasal lavage fluid and nasal biopsies of some patients with allergic rhinitis during the late-phase response (24, 38). Moderate bronchial eosinophilia has also been demonstrated in patients with perennial allergic rhinitis without asthma (33). Cytotoxic protein release may

be responsible for bronchial desquamation, but epithelial disruption has not been described in allergic rhinitis (24). Eosinophils may play a key role in the genesis and maintenance of chronic nasal and bronchial allergy through the release of pro-inflammatory factors such as leukotriene C₄ (LTC₄), platelet-activating factor, and cytokines (39–42). Indeed, airway hyperresponsiveness and disease severity in atopic asthma have been found to correlate with:

- the extent of activated eosinophil infiltration (9, 33, 43, 44);
- serum eosinophil counts and levels of eosinophil cationic protein (ECP) (43); and
- the number of cells expressing IL-5 (44).

ECP levels in nasal washings have also been shown to correlate with symptoms in allergic rhinitis (45), but this finding is contradicted by other investigators (46, 47). Furthermore, nasal reactivity does not appear to correlate with eosinophil or ECP levels (47–49).

Increased numbers of T-lymphocytes, with expression of TH₂-type cytokines (IL-4, IL-5), have been demonstrated in seasonal allergic rhinitis after allergen challenge (24, 37, 50, 51), perennial allergic rhinitis (25), and atopic asthma (44, 51, 52). Raised cellular IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) expression has also been observed in allergic rhinitis and asthma (44, 50), with CD4⁺ T-lymphocyte expression being predominant in the latter case. The increase in CD4⁺ and CD25⁺ cells is relatively small in seasonal (24) and perennial allergic rhinitis (25), whereas activation may be more marked in asthma (33). The level of activation may correlate with disease severity in asthma (9), but such an association has not been demonstrated in rhinitis (33). IL-4, predominantly a product of T-lymphocytes (37), enhances expression of the endothelial adhesion molecule, VCAM-1; increased staining for VCAM-1 has been demonstrated in perennial allergic rhinitis and after bronchial allergen challenge, but not in mild asthma (33). T-lymphocytes may orchestrate allergic inflammation (41), and their level of activation may contribute to the severity of respiratory allergy (33).

Challenge

Bronchial challenge tests are well standardized and bronchial hyperreactivity is recognized in the diagnosis of asthma (7). The nose is thought to be less hyperreactive to challenge than the bronchi in patients with perennial allergic rhinitis (13), and while secretory hyperreactivity to metacholine and histamine has been demonstrated (53, 54), there is

no clear evidence of nasal blockage hyperreactivity in these patients (53–57). Histamine challenge in patients with perennial allergic rhinitis correlates only moderately with nasal symptoms and quality of life scores (58).

Patients with allergic rhinitis and no history of asthma may develop bronchoconstriction and demonstrate inflammatory cells and mediators in bronchoalveolar lavage fluid when challenged with inhaled bronchial allergens (15). This response is less severe, though similar to that observed in asthmatic patients after challenge, who are also more likely to demonstrate a late-phase bronchial response (15). This may again suggest a quantitative rather than a qualitative difference between patients who develop allergic rhinitis, asthma, or both.

Some patients with allergic rhinitis show increased bronchial sensitivity to metacholine which is augmented by β -adrenergic blockade. However, it is not clear why some atopic patients develop asthma and some develop rhinitis. It has been suggested that patients with allergic rhinitis have β -adrenergic hyporesponsiveness, whereas allergic asthma may also be associated with α -adrenergic hyperresponsiveness (59).

Response to treatment

Glucocorticoids are of benefit in both the lung and bronchi owing to their effect of diminishing late-phase inflammatory events (13). Prolonged therapy has also been shown to have beneficial effects on the early-phase response in the bronchi (60) and the nose (61). Decreased numbers of CD25⁺ cells (presumed to be T-lymphocytes), total and activated eosinophils, and cells expressing mRNA for IL-4 have been observed in allergen-challenged seasonal rhinitics after 6 weeks' treatment with fluticasone propionate aqueous nasal spray (61). Studies in perennial allergic rhinitis also demonstrate reduced numbers of Langerhans' cells, mast cells, eosinophils, ECP concentration (62), T-cells, and IL-4 and IL-5 levels (63, 64). Prednisolone has been shown to reduce eosinophil levels and the number of cells expressing IL-4 and IL-5 mRNA in atopic asthma (65). Hyperreactivity in perennial allergic rhinitis and asthmatics is also reduced by glucocorticoids (62, 66). These findings suggest similar pathological mechanisms for both diseases.

Perennial non-allergic rhinosinusitis and asthma

Eosinophilic disease

The characteristic pathology of asthma is a chronic, desquamating, eosinophilic bronchitis (9). Blood

and tissue eosinophilia in asthma is not limited to extrinsic cases and indeed may be greater in the non-allergic patient. In fact, eosinophils in non-atopic asthma have been shown to possess an increased propensity for granule protein release (67). The stimulus for eosinophil recruitment, activation and degranulation is not clear, but as with atopic asthma, increased numbers of T-lymphocytes and mast cells are present. However, these lymphocytes express IL-2, IL-3, IL-5, and GM-CSF. Resident airway bronchial epithelial cells and monocytes may also release cytokines, facilitating eosinophil and T-lymphocyte migration (44). The events initiating this cytokine-driven inflammation are not clear, but non-allergic asthma is known to occur after viral respiratory infection. This type of asthma may persist for years, suggesting autocrine mechanisms of inflammation from recruited cell-derived cytokines.

Chronic polypoid rhinosinusitis is also characterized by eosinophil infiltration regardless of atopic state (68), and elevated levels of IL-5 have recently been described in nasal polyp samples (69). Non-allergic rhinitis with eosinophilia syndrome (NARES) is also recognized; not all cases are associated with nasal polyposis, although the majority will reveal sinus opacities on computed tomography scans (3, 70). Sinus mucosal eosinophilia in patients with negative skin prick tests is particularly marked in cases of chronic sinusitis with concurrent asthma (71). In these patients, extracellular deposition of major basic protein in the sinus mucosa has been observed, with epithelial desquamation and thickening of the basement membrane (71). These are well recognized features in asthma, but they have not been described in rhinitis. Recurrent polyps have been shown to have a higher level of activated eosinophils in asthmatic compared with non-asthmatic patients (72). Unlike intrinsic asthma, CD3⁺ and CD4⁺ T-lymphocytes have not been found in large numbers (73), and activated CD25⁺ lymphocytes are only present in small numbers in nasal polyps (42). Autocrine loops of inflammation driven by tissue structural cell and eosinophil-derived cytokines, particularly GM-CSF, have also been postulated in the pathogenesis of nasal polyposis (42). As for intrinsic asthma, the initiating events in nasal polyp formation remain unclear. Interestingly, three cases of eosinophilic bronchial polyps have been reported in patients with asthma (74).

Abundant eosinophilia is characteristic of nasal polyps (75) and bronchial mucosa (76) in patients with Samter's triad (77) of acetylsalicylic acid-sensitive asthma (ASA) and nasal polyposis. ASA polyposis is often severe and considered to be a diffuse polypoid rhinosinopathy. It has been suggested that

unlike more moderate polyposis, eosinophils are characteristically degranulated in diffuse polypoid rhinosinopathy, in patients with and without ASA (75, 78). As demonstrated for asthma, disease severity in polyposis may therefore be related to eosinophil activation. Eicosanoid metabolites of arachidonic acid (15-HETE, LTC₄) are elevated in ASA polyps (75, 79), and LTD₄, a metabolite of LTC₄, is elevated in the urine, particularly after aspirin challenge in ASA patients (80). This suggests a common pathway for sinonasal and bronchial inflammation in aspirin-sensitive patients.

Corticosteroid treatment has been shown to be effective in non-allergic rhinosinusitis, particularly when associated with eosinophilia (81), polyps (82), or both. Topical intranasal corticosteroids in patients with polyps may reduce the number of CD3⁺ and CD4⁺ T-lymphocytes (83). Fluticasone propionate has also been shown to be of therapeutic benefit in intrinsic asthmatics, reducing airway lymphocyte load and activation (84).

Neurogenic inflammation

Not all patients with asthma (85) or perennial rhinosinusitis (2, 6) demonstrate eosinophilia, and the pathophysiological process giving rise to symptoms in these patients is not always clear. The importance of the autonomic nervous system is well recognized in the development of asthma, with possible cholinergic hyperresponsiveness and overactivity, and diminished β -adrenoceptor responsiveness (86, 87). It is now clear that a non-adrenergic non-cholinergic nervous system of neuropeptides also contributes to lower airway autonomic function, via sensory nerve axon reflex release or parasympathetic neurone co-transmission (10, 88–90). Sensory neuropeptides are capable of producing neurogenic inflammation with many of the features of asthma, such as smooth muscle contraction, vasodilatation, plasma extravasation, and mucus hypersecretion (10, 89–91). Neuropeptide secretion may occur after stimulation of afferent nerve endings following eosinophilic inflammatory epithelial damage. Substance P may also stimulate lymphocytes and other inflammatory cells (92). Axon reflex mechanisms may therefore amplify pathogenetic mechanisms in asthma with bidirectional interaction between neural and humoral systems. It has been postulated that mast cell mediators break down the bronchodilator, vasoactive intestinal polypeptide (VIP), which results in a diminished “braking” effect on cholinergic bronchoconstriction. At present, neuropeptide release and cholinergic hyperresponsiveness are not thought to be primary abnormalities in asthma (86, 88).

It has been suggested that some cases of non-eosinophilic intrinsic rhinitis (vasomotor rhinitis) may primarily be due to autonomic imbalance; these patients are thought to have dominant parasympathetic activity which consequently results in a major complaint of watery rhinorrhoea (2). In support of this mechanism is the response to topical ipratropium bromide (93) and vidian neurectomy (94). Furthermore, patients with dominant rhinorrhoea also have an increased response to metacholine (28), although it has been stated that there are no scientifically sound data to support vascular or neurological nasal dysfunction (95). However, these patients do respond poorly to glucocorticoids, implying a non-inflammatory pathogenesis (95, 96). Blom et al. described a group of patients with non-allergic rhinitis in whom there was no evidence of cellular inflammation and whose symptoms improved with capsaicin (97). Other authors have shown hyperreactivity to capsaicin in patients with non-allergic rhinitis (98) and desensitization and symptomatic improvement with longer-term use (99, 100). This suggests a sensory axon reflex mechanism for rhinitis, mediated either by increased neuropeptide release, which is depleted by capsaicin (101), or hyperreactive efferent cholinergic mechanisms (98). Unlike in asthma, these may be primary phenomena. It has also been argued that capsaicin-sensitive, tachykinin-containing nerves probably subserve a protective function only in the lung, with a minor role in asthma (102, 103). An immunohistochemical study has shown that the amount of nerves containing VIP in the nasal mucosa is increased in patients with non-allergic rhinitis (88, 104). Interestingly, asthma may be associated with non-eosinophilic rhinitis, with the same incidence as in NARES (105).

Hyperreactivity

Hyperresponsiveness to inhaled histamine and metacholine are diagnostic features of non-allergic asthma (7). However, nasal challenge tests with histamine and metacholine, while producing symptoms (13), demonstrated little hyperreactivity in patients with perennial non-allergic rhinitis, though secretory hyperresponsiveness to these two agents and to capsaicin may exist in the subgroup whose predominant symptom is rhinorrhoea and not nasal blockage (2, 98). This suggests different pathogenetic populations of non-allergic rhinitis. Patients with the predominant symptom of rhinorrhoea may represent a group in whom the aetiology of inflammation is neurogenic rather than humoral (28, 98). Primary neurogenic asthma has not yet been described.

Cold, dry air challenge in non-allergic patients with a history of cold air-induced rhinitis produces

nasal symptoms, but this response is absent in non-sensitive individuals. The rhinorrhoea is thought to be parasympathetically mediated and is partially blocked by atropine (95). Cold air bronchial challenge produces bronchoconstriction in asthmatics (106). This mimics exercise-induced bronchoconstriction, and may result from inflammatory cell mediator release, possibly from mast cells (13, 14). In nasal studies, mast cell mediators were also released in responders, demonstrating the close relationship between neural and humoral mechanisms. Similarly, studies of patients undergoing vidian neurectomy have demonstrated a reduction in the number of mast cells and lowering of their degranulation index (107). The importance of mast cells in non-atopic patients with polyposis is well recognized (108–113). A recent study has also shown high levels of substance P in nasal polyp fluid (114), indicating the involvement of both neuropeptides and humoral mechanisms.

Does rhinosinusitis cause asthma?

Nasal stimulation with irritants can produce bronchoconstriction via a rhinosinobronchial reflex (115). Topical nasal histamine in patients with allergic rhinitis may also result in decreased pulmonary function (116) despite having no history of asthma in some cases. From previously mentioned studies, it is also clear that patients with allergic rhinitis, but without asthma, may have bronchial hyperresponsiveness to inhaled allergens and chemical stimulants. It is therefore possible that nasal reflexes may affect already potentially hyper-reactive lower airways. Diminished nasal function may exacerbate the scenario by placing an unaccustomed burden on the lungs (117). It has also been suggested that inflammatory mediators of nasal disease may be inhaled and subsequently initiate tracheal and bronchial inflammation (118). Therefore, treatment of rhinosinusitis may be expected to improve asthma. Indeed, intranasal corticosteroid therapy in patients with rhinitis has been shown to have beneficial effects on concomitant bronchial hyperreactivity or asthma (118–120).

Stammerberger has reported that 70% of patients with intrinsic asthma and chronic rhinosinusitis will gain improvement in asthma symptoms following endoscopic sinus surgery (78). Wigand described an improvement in asthma symptomatology in 57% of patients with asthma and diffuse chronic polypoid sinusitis (121). Furthermore, other authors report a reduction in corticosteroid requirement in 92% of asthmatics following transantral or intranasal sphenoethmoidectomy (122). An improvement in asthma has also been observed in 91% of

patients undergoing radical endoscopic ethmoidectomy for polyposis (123). This improvement included reversal of a previously positive bronchial choline and aspirin sensitivity. However, Settignano described no change in pulmonary corticosteroid requirements following polypectomy (124).

Topical treatment of asthma should, by the same logic, be expected to improve rhinosinusitis. While bronchial challenge with ultrasonic fog in patients with rhinitis has been shown to increase nasal resistance, no studies have demonstrated an improvement in nasal symptoms following asthma therapy.

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