REVIEW

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Mechanisms of the symptoms of rhinosinusitis*

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SUMMARY

The review discusses the physiological and pathophysiological mechanisms associated with the symptoms of acute and chronic rhinosinusitis. An understanding of symptom mechanisms is important for the clinical diagnosis of rhinosinusitis and is important in assessing the efficacy of surgical and medical treatments for rhinosinusitis. The review will discuss the four primary symptoms used to diagnose rhinosinusitis: nasal obstruction, nasal discharge, facial pain and loss of sense of smell; and the secondary symptoms, cough, sneezing, sore throat and voice changes, epiphora, fever, and psychological effects and fatigue. The review will highlight that our understanding of a key diagnostic symptoms facial pain is limited, and that the incidence of pain with rhinosinusitis is controversial. Sneezing is a common symptom of acute rhinosinusitis with allergy but is not normally described as symptom in chronic rhinosinusitis and this anomaly is in need of more research. The mechanism of unilateral nasal obstruction with rhinosinusitis is discussed.

Key words: rhinosinusitis, cough, sneezing, headache, facial pain, ostiomeatal complex, nasal cycle

INTRODUCTION

Rhinosinusitis is the most common complaint of mankind as acute viral rhinosinusitis affects all ages every year, and allergic and chronic rhinosinusitis are also very common problems. Rhinosinusitis is primarily diagnosed on symptomatology [(1)], and treatments are mainly symptomatic, yet our understanding of the mechanisms that generate the familiar symptoms is poor compared to the ever increasing knowledge on the molecular mechanisms of the immune response and inflammation associated with rhinosinusitis. An understanding of the mechanisms of symptoms of rhinosinusitis is important, as most treatments are symptomatic, and clinical trials on the efficacy of new treatments usually focus on changes in symptom scores as the main parameter of efficacy rather than changes in immune cells or inflammatory mediators in the airway. Clinical trials on any new medical or surgical treatment for rhinosinusitis will need to demonstrate changes in symptom severity or duration of symptoms, as these parameters are the key benefits for most patients.

The present review will discuss the physiological and pathophysiological mechanisms that generate symptoms associated with rhinosinusitis,

The review content is based on a search of the US National Library of Medicine (PubMed) online database from 1 January 1973 to 01 March 2010. As this review was multi-faceted, a separate literature search was performed for each symptom linked to search terms of 'rhinitis' and 'rhinosinusits'. Key references were also searched for citations by using the ISI Web of Knowledge.

RHINOSINUSITIS

Rhinosinusitis is not a single disease with a single cause, and there is much overlap between the mechanisms of infection, allergy and host response that cause rhinosinusitis. Much discussion has also taken place over the role of nasal and sinus anatomy in the etiology of rhinosinusitis with obstruction of the narrow airways of the ostiomeatal complex proposed as an important mechanism in the generation of symptoms and the etiology of chronic rhinosinusitis [(1-3)]. Although in the past, rhinitis and sinusitis were discussed as separate diseases, there is now a consensus that any inflammatory process in the upper airways involves both the nose and paranasal sinuses and that the correct term for upper airway inflammation is rhinosinusitis [(1)]. Acute viral rhinosinusitis is self-diagnosed as common cold or flu based on a familiar syndrome of symptoms of sore throat, sneezing, runny nose, nasal congestion [(4)]. Flu is usually accompanied by cough and fever and other systemic symptoms such as muscle aches and pains and malaise [(4)]. The acute and often seasonal nature of viral rhinosinusitis associated with cold weather allows easy diagnosis. Rhinosinusitis with allergy can be diagnosed by symptoms of itching, sneezing, runny nose and nasal congestion, and identification of potential allergens that trigger the disease. Chronic rhinosinusitis with or without nasal polyps is defined as a rhinosinusitis lasting for more than 12 weeks with symptoms of facial pain or pressure, loss of sense of smell, nasal obstruction and nasal discharge [(1)].

Symptomatology and inflammatory mediators

Infection and allergy are mechanisms that may generate the symptoms of rhinosinusitis but the contribution of these

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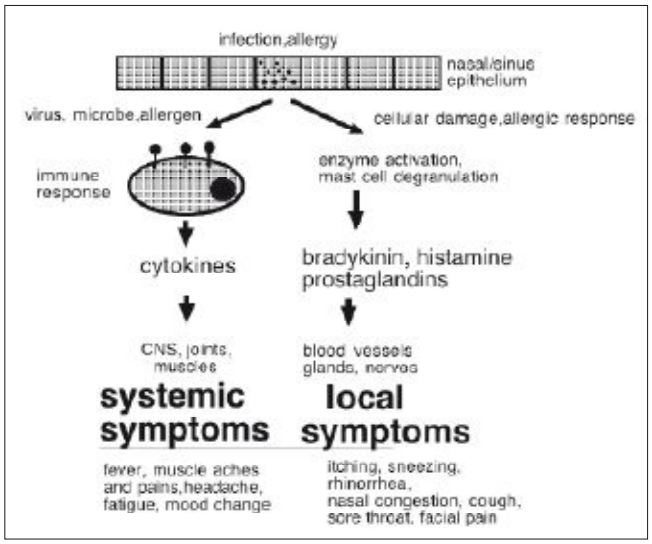

Figure 1. Rhinosinusitis involves symptoms produced by two mechanisms. Local symptoms are caused by the generation of local inflammatory mediators such as bradykinin, prostaglandins and histamine in the respiratory epithelium. Systemic symptoms are caused by the release of cytokines as part of the immune response to infection or allergy.

mechanisms to the development of rhinosinusitis is still poorly understood and there may be an overlap of infective, allergic and host response mechanisms that lead to the development of symptoms. Viral and bacterial infections cause an inflammatory response and production of the inflammatory mediator bradykinin that is responsible for many of the symptoms of infection [4-6], whereas allergic reactions cause the release of histamine from mast cells in the airway epithelium to cause inflammation [7,8]. Bradykinin causes pain related symptoms such as sore throat pain and sinus pain, and by irritation of sensory nerves can trigger sneezing and runny nose, as well as acting as a vasodilator to cause nasal congestion. Histamine causes itching, and by irritation of sensory nerves can trigger sneezing and runny nose, as well as acting as a vasodilator to cause nasal congestion. Specific antihistamine medicines provide no benefit for rhinosinusitis caused by infections such as common cold viruses [9] and this demonstrates that histamine is not involved in the inflammatory response to infection. However, non-specific first generation antihistamines can help to control common cold symptoms by sedating and anticholinergic actions [10]. In contrast, specific antihistamines can help to control the symptoms of itching, runny nose and sneezing associated with allergic rhinosinusitis [11], demonstrating the important role of histamine in allergic inflammation.

The symptoms of rhinosinusitis caused by infection and allergy can be classified as either 'systemic' or 'local' symptoms as illustrated in Figure 1. The systemic symptoms such as fever, muscle aches and pains, headache, fatigue and mood changes are caused by the release of cytokines from immune cells such as neutrophil granulocytes and lymphocytes in response to the presence of the components of viruses and bacteria or the presence of allergens. The local symptoms such as itching, sneezing, nasal congestion etc. are restricted to the upper airways and are caused by the local generation of inflammatory mediators such as histamine, bradykinin and prostaglandins. The mechanisms for the different local and systemic symptoms will now be discussed.

PRIMARY SYMPTOMS OF RHINOSINUSITIS

Nasal obstruction

Nasal obstruction is a diagnostic symptom for both acute and chronic rhinosinusitis [1] and the symptom can be considered as consisting of three components; nasal congestion, nasal fibrosis, and nasal polyps. Nasal congestion is an acute vascular response to inflammation caused by any form of nasal irritation, and by infection and allergy. Nasal fibrosis and nasal polyps are associated with chronic rhinosinusitis.

Nasal congestion is present in both acute and chronic rhinitis and is caused by the dilation of large veins in the nasal epithelium (venous sinuses) in response to the generation of vasodilator mediators of inflammation such as bradykinin and histamine [12]. The large veins are well developed at the anterior end of the inferior turbinate and nasal septum where their congestion in the narrow nasal valve region causes obstruction of the nasal airway. The nasal veins exhibit phases of congestion and decongestion under the influence of the sympathetic vasoconstrictor nerves and this causes reciprocal changes in nasal airflow (often termed the 'nasal cycle'). A model to explain the unilateral nasal obstruction associated with acute viral rhinosinusitis has been previously

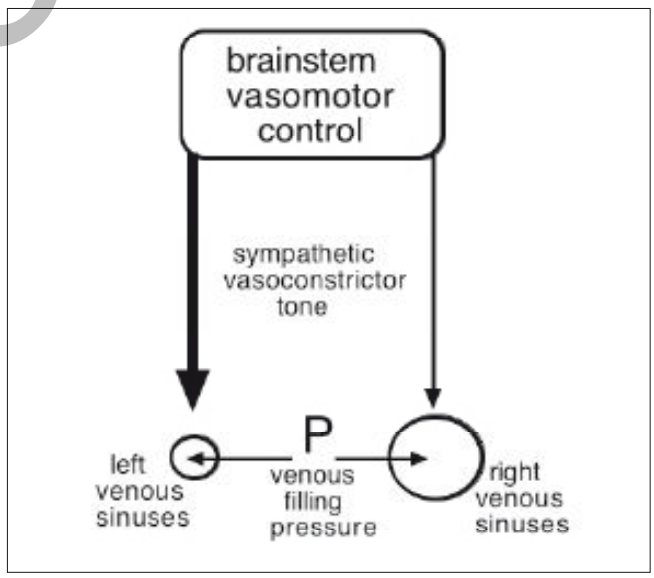

Figure 2. Model of factors influencing the degree of congestion of the nasal venous sinuses. Two factors control the degree of congestion; the asymmetrical sympathetic vasomotor control from the brainstem and the filling pressure of the venous sinuses (P). An increase in the filling pressure associated with inflammation and vasodilation causes an increase in the volume of the venous sinuses on the side of the nose with the lowest vasoconstrictor tone (right side in this model) with little change in volume on the side of the nose with a the higher vasoconstrictor tone (left side in this model). The unilateral obstruction of the nose will alternate, as the sympathetic tone alternates to control the nasal cycle of airflow.

described in the literature [13] and is illustrated in Figure 2. The model demonstrates that there is normally an asymmetry of sympathetic vasoconstrictor tone to the smooth muscle of the nasal venous sinuses and this is responsible for the asymmetry in nasal airflow associated with the nasal cycle [14,15]. The asymmetry of nasal airflow associated with the nasal cycle is increased with acute viral rhinosinusitis and this may result in one nasal passage being patent whilst the other is completely obstructed [13,16]. The unilateral obstruction associated with rhinosinusitis may be explained by vasodilation associated with the inflammation of the airway epithelium causing an increased filling pressure of the venous sinuses. The venous sinuses on the side of the nose with a lower sympathetic vasoconstrictor tone expand to completely occlude the nasal airway.

Acute viral rhinosinusitis always involves the paranasal sinuses and this is illustrated in Figure 3, which is a computed tomographic (CT) scan of a subject with acute viral rhinosinusitis. The CT scan shows the unilateral nasal congestion associated with common cold, and the obstruction of drainage of the ostiomeatal complex and accumulation of fluid in the maxillary sinus.

Nasal obstruction associated with acute viral rhinosinusitis and rhinosinusitis with allergy is readily reversible by treatment with an oral or topical nasal decongestant [17,18]. However, chronic inflammation associated with chronic rhinosinusitis may lead to an increased deposition of fibrous connective tissue and bone in the nasal epithelium and nasal obstruction that is not reversible with a nasal decongestant [19,20].

Nasal polyps are commonly found in patients with chronic rhinosinusitis but their etiology is poorly understood [1]. The polyps originate from within the ostiomeatal complex and consist of loose connective tissue, oedema, inflammatory cells, glands and capillaries, covered with varying types of epithelium but mostly respiratory pseudostratified epithelium.

Nasal discharge

Nasal discharge is found with both acute and chronic rhinosinusitis. The nasal discharge associated with rhinosinusitis is a complex mix of elements derived from glands, goblet cells, plasma cells, and plasma exudate from capillaries, and the relative contributions from these different sources varies with the time course and the severity of the inflammatory response [21]. A watery nasal secretion is an early symptom of acute viral rhinosinusitis and acute exacebations of rhinosinusitis with allergy and is often accompanied by sneezing. This early phase of nasal secretion is a reflex glandular secretion that is caused by stimulation of trigeminal nerves in the airway. Support for the glandular origin of the early nasal secretions comes from studies on anticholinergic medicines such as ipratropium [22], which inhibits secretions in the first few days of acute viral rhinosinusitis. The nasal discharge also consists of a protein rich plasma exudate derived from sub-epithelial capillaries [23] and this may explain why anticholinergics only partly inhibit nasal discharge associated

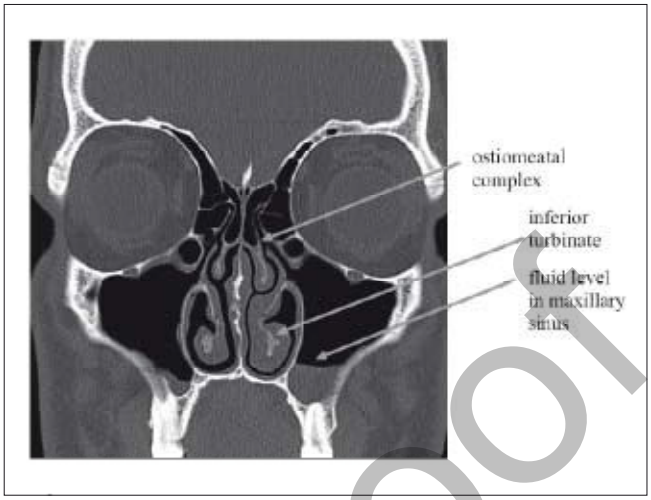

Figure 3. A coronal computed tomographic scan of the nose in patient with acute viral rhinosinusitis. Note the asymmetry of congestion of the nasal turbinates due to the nasal cycle, which also causes congestion in the region of the ostiomeatal complex to block the ostium of the maxillary sinus and restrict clearance of mucus from the sinus. A fluid level is seen in the maxillary sinus. The scan demonstrates the involvement of the sinuses even in an uncomplicated common cold.

with acute rhinitis [21]. In one study on experimentally induced rhinovirus infections, the plasma exudate is reported to predominate in the first few days of infection, whereas the glandular secretions predominate later in the infection [24].

The colour of nasal discharge and sputum is often used as a clinical marker to determine whether or not to prescribe antibiotics, but there is no evidence from the literature that supports this concept for acute or chronic rhinosinusitis [25,26]. Colour changes in nasal discharge reflect the severity of the inflammatory response rather than the nature of the infection as viral or bacterial [4]. Much of the literature relates to colour changes in sputum and the lower airways, but the same concepts apply to the upper airways and nasal discharge [27]. The colour of nasal discharge may change from clear to yellow to green during the course of a viral infection and this colour change is related to the recruitment of leukocytes into the airway lumen and it is a hallmark of airway disease [27]. Neutrophils and pro-inflammatroy monocytes have azurophil granules that owe their green colour to the green protein myeloperoxidase. Nasal discharge with few leukocytes is white or clear, with increasing numbers of leukocytes the nasal discharge appears yellow (pale green) and with large numbers of leukocytes the colour becomes green [27].

Rhinosinusitis may be associated with purulent posterior nasal discharge that is only slowly cleared from the nasopharynx and may be a cause of persistent throat clearing. The term 'post nasal drip syndrome' (PNDS) is generally accepted as a definite clinical condition in the USA and was previously named 'American catarrh' but UK clinicians prefer the term 'rhinosinusitis' and often doubt the validity of PNDS as a specific syndrome [28,29]. The history and etiology of this controversial syndrome has recently been reviewed [29].

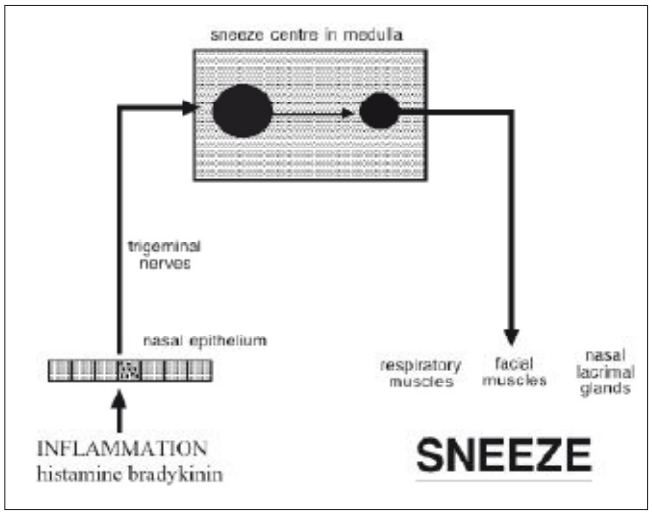

Figure 4. Sneezing is caused by stimulation of trigeminal sensory nerves in the nasal epithelium. The trigeminal nerves provide a sensory input to the "sneeze centre" in the medulla that triggers reflex activation of; nasal and lacrimal glands to cause a rhinorrhea, facial muscles to cause closure of the eyes and grimace, and respiratory muscles to cause inspiration followed by an explosive expiration.

Sinus pain, headache and facial pain

Sinus pain, headache and facial pain are terms that describe painful symptoms associated with rhinosinusitis but there is much overlap and confusion between these terms and they may relate to several different mechanisms of generating pain in the head region. A tension type headache is a common symptom associated with acute viral rhinosinusitis [4] and acute exacerbations of chronic rhinosinusitis due to common cold are usually associated with unilateral sinus pain [30], but headache and facial pain are not a common feature of chronic rhinosinusitis [30].

The concept of sinusitis as a common cause of headache and facial pain is widespread amongst clinicians and the general public but some studies indicate that only a small minority of patients with chronic rhinosinusitis has facial pain or headache. In a hospital practice study of 973 consecutive patients with symptoms of rhinosinusitis or facial pain, only a minority (18%) of patients with demonstrable sinonasal disease had facial pain [32]. Most patients with purulent sinusitis are reported not to have facial pain, and more than 80% of patients with purulent secretions visible at nasal endoscopy are described as having no facial pain [31]. In contrast to these findings a study on 30,000 subjects aged 30 - 44 years reported that compared with the general population, persons with chronic rhinosinusitis have an at least ninefold increased risk of having chronic headache [33].

The mechanisms of facial pain, headache or sinus pain associated with chronic rhinosinusitis are poorly understood and much of the pain may have similarities to tension-type headache [31]. Pain associated with acute viral rhinosinusitis may be due to several mechanisms: pressure changes and inflammation in the paranasal sinuses, inflammation and irritation of sensory nerves serving other structures such as the teeth, central effects of cytokines, and psychogenic causes.

The ostia of the paranasal sinuses are often occluded when the nasal epithelium is inflamed and congested and this may result in gas absorption from the sinus and 'vacuum maxillary sinusitis' [34]. However, sinuses with patent ostia may also be painful and this indicates that the generation of inflammatory mediators within the sinus may be sufficient to trigger the sensation of pain either by direct stimulation of pain nerve fibres or via distension of blood vessels that are also served by sensory nerves [35]. Changes in posture from sitting to supine cause an increase in sinus pain and this may be related to dilation of the blood vessels draining the sinus caused by an increase in venous pressure. However, pain on leaning forward is also found with tension type headache and may be unrelated to any pathophysiology of the sinuses [30]. Pressure changes in the sinus may also cause pain by stimulation of branches of the trigeminal nerve that course in and around the sinuses [34].

Major branches of trigeminal nerves course in and around the nose and paranasal sinuses and inflammation may spread from the airway epithelium to the sensory nerves to cause pain, as for example with odontogenic pain associated with sinusuitis [36].

Headache associated with acute viral rhinosinusitis may be associated with the release of cytokines from immune cells associated with the inflammatory response and these may trigger headache. Administration of cytokines involved in the immune response associated with acute viral rhinosinusits such as tumour necrosis factor (TNF) [37] has been shown to cause headache in humans [38]. The mechanism of headache caused by cytokines is unknown but it is interesting that the headache induced by cytokines is accompanied by symptoms such as fatigue and depression, and these symptoms are commonly associated with acute viral rhinosinusitis and chronic rhinosinusitis [31,39,40].

Loss of sense of smell

A reduction or loss of the sense of smell is a diagnostic symptom of chronic rhinosinusitis [1] and is also commonly found with acute viral rhinosinusitis [41]. The sense of smell may be affected by some physical restriction of airflow and odorants to the olfactory area due to nasal obstruction, or may be due to an inflammation of the olfactory area as part of the generalised inflammatory response of the airway. Opacification of the olfactory cleft (demonstrated by computed tomography, CT) in patients with chronic rhinosinusitis has been shown to have a negative correlation with olfactory function scores [42].

SECONDARY SYMPTOMS OF RHINOSINUSITIS

Sneezing

Sneezing is mediated solely by the trigeminal nerves and these supply the nasal epithelium and the anterior part of the nasopharynx with sensory fibres [43]. Sneezing associated with rhinosinusitis is related to inflammatory responses in the nose and nasopharynx that stimulate the trigeminal nerves. The sneeze response may be mediated via histamine [1] receptors on the trigeminal nerves, as intranasal administration of

histamine causes sneezing [44]. The trigeminal nerves relay information to the sneeze centre in the brain stem and cause reflex activation of motor and parasympathetic branches of the facial nerve, and activate respiratory muscles [45]. A model of the sneeze reflex is illustrated in Figure 4. The sneeze centre coordinates the inspiratory and expiratory actions of sneezing via respiratory muscles, and lacrimation and nasal congestion via parasympathetic branches of the facial nerve. The eyes are always closed during sneezing by activation of facial muscles, and this indicates a close relationship between the protective reflexes of the nose and eyes. A common phenomenon is the 'photic sneeze' caused by a sudden increase in light intensity that again highlights the overlap of protective nasal and eye reflexes [46]. Sneezing activates parasympathetic pathways to nasal glands, and there does appear to be some cholinergic control of sneezing, as anticholinergics such as ipratropium and first generation antihistamines have been shown to inhibit sneezing [10,22].

Sneezing is a common and prominent symptom associated with acute viral rhinosinusitis and acute rhinosinusitis with allergy but it is not a dominant symptom in chronic rhinosinusitis. Sneezing is not mentioned as a symptom of chronic rhinosinusitis in the European Position Paper on Rhinosinusitis [1] and in the BSACI guidelines for the management of rhinosinusitis. Studies on symptom-based presentation of chronic rhinosinusitis [47-49] make no mention of sneezing, even as a minor symptom. The lack of discussion about sneezing as a symptom of chronic rhinosinustis in key position papers on this topic may indicate that sneezing is not a common symptom of chronic rhinosinusitis or that it is of little consequence to the patient. However, the latter explanation does not seem likely, as chronic sneezing can be a disturbing symptom [50]. Atopy has been shown to be associated with sneezing in patients with rhinosinusitis with allergy as one would expect, as sneezing is normally associated with symptoms of allergic rhinitis. However, even in atopic patients with chronic rhinosinusitis, sneezing is not a common symptom. In a study on 193 patients waiting for surgery to treat chronic rhinosinusitis, only 14/193 reported that sneezing was an important symptom and only 7 of these14 were atopic [51].

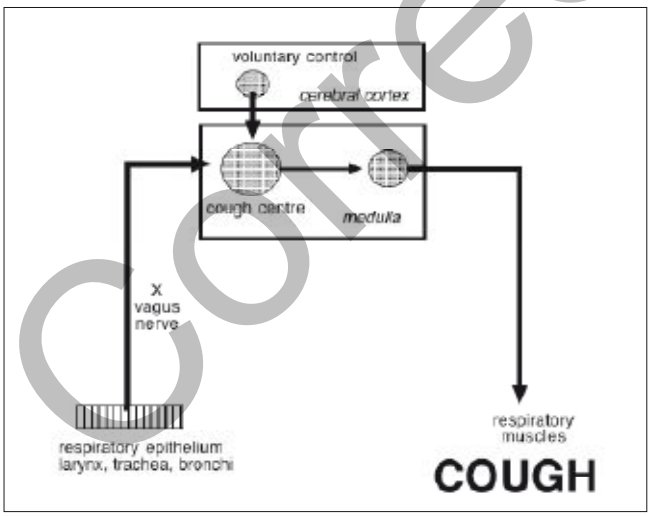

Figure 5. Cough is normally caused by aspiration of food or fluid in the airway and this stimulates sensory receptors supplied by the vagus nerve to trigger cough. Cough associated with URTI is caused by a hyperreactivity of this response, and cough occurs spontaneously. Cough can also be initiated and inhibited by voluntary control and this indicates some control of cough from higher centres such as the cerebral cortex.

The lack of importance of sneezing with chronic rhinosinusitis is unusual, as sneezing is a prominent symptom in acute viral rhinosinusitis and rhinosinusitis with allergy. One would expect that the inflammation of the nasal epithelium associated with chronic rhinosinusitis would trigger sneezing. Sneezing may not be prominent in chronic rhinosinusitis because in some way the sneeze reflex is inhibited or the peripheral nerves become desensitised to the presence of mediators that normally induce sneezing. It would be interesting to study the sneeze reflex in patients with chronic rhinosinusitis to determine if there is any change in the sensitivity of this reflex compared to normal healthy subjects and subjects with acute rhinosinusitis.

Sore throat and voice changes

Sore throat is a common symptom of acute viral and bacterial rhinosinusitis and is most likely caused by the action of prostaglandins and bradykinin. The sensation of throat irritation and pain is mediated by the cranial nerves supplying the nasopharynx and pharynx [4]. With chronic rhinosinusitis other mechanisms may cause throat pain, as frequent throat clearing of posterior nasal discharge and phlegm may irritate and inflame the laryngeal folds. Laryngitis may also occur as part of the general airway inflammatory response of rhinosinusitis as the inflammation involves the whole airway. Voice changes associated with rhinosinusitis are likely due to laryngitis caused by the airway inflammatory response and constant trauma to the vocal cords by throat clearing. Voice pathology associated with rhinosinusitis is poorly researched yet it can have a big emotional impact on the patient and their quality of life even in cases of acute rhinosinusitis with allergy [52].

Watery eyes (epiphora) is a common symptom associated with acute viral rhinosinusitis and rhinosinusitis with allergy [53,54]. The nasolacrimal duct may be obstructed at its opening into the nose by inflammation and congestion of blood vessels in the nasal epithelium around the opening of the duct, and this will cause an accumulation of tears and the symptom of watery eyes. The nasolacrimal duct has been shown to have a vascular plexus of veins (cavernous tissue) similar to the venous sinuses of the nasal epithelium, and congestion of this plexus causes obstruction of the duct [55]. The nasolacrimal cavernous tissue is innervated by parasympathetic and sympathetic nerves that may play a role in controlling the outflow of tears by regulating the congestion and decongestion of the cavernous tissue [56].

Cough

Cough is a common symptom associated with acute viral

rhinosinusitis but its association with chronic rhinosinusitis is controversial. Cough is a protective reflex that prevents aspiration of food and fluid into the airways and that helps to move mucus up from the lower airways. Cough is mediated exclusively by the vagus nerve and this means that cough is initiated in the airway by stimulation of sensory nerves at the level of the larynx or below [57]. Cough associated with rhinosinusitis must involve structures at the larynx or below to stimulate vagal nerves. The cough mechanism is illustrated in Figure 5. Protective cough on aspiration of food and fluid is reflex in nature but most cough associated with rhinosinusitis is under voluntary control [58] and is associated with an urge to cough [59].

Rhinitis has been proposed to sensitise the cough reflex by irritation of nasal trigeminal nerves [60] but this hypothesis is controversial as nasal irritation usually causes sneezing rather than cough. Cough associated with acute viral rhinosinusitis is believed to be caused by hyperreactivity of vagal cough receptors [61]. Chronic rhinosinusitis is often associated with allergy and asthma and it is difficult to separate lower airway inflammation from upper airway inflammation in the generation of cough associated with rhinosinusitis [62]. The role of postnasal drip in the generation of cough associated with rhinosinusitis is controversial [63].

Fever

Fever is a normal response to infection, and acute viral and bacterial rhinosinusitis are often associated with fever in children, but less commonly in adults [4,64,65]. Although some studies report fever as a minor symptom associated with chronic rhinosinusitis in the adult [66], fever has not been found to be present in adult patients awaiting surgery for chronic rhinosinusitis [67].

Cytokines have been implicated as endogenous pyrogens that are released from macrophages and other leukocytes in response to infection, and there is considerable evidence for pyretic and antipyretic effects of cytokines [68]. The proinflammatory cytokines interleukin (IL)-1, IL-6 and the TNF-α, as well as the antiinflammatory cytokines IL-1 receptor antagonist (IL1ra) and IL-10, have been most investigated for their pyrogenic or anti-pyretic action [68]. IL-1 and IL-6 are believed to be the most important cytokines that induce fever [69]. Cytokines are believed to cross the blood brain barrier and/or interact with the vagus nerve endings to signal the temperature control centre of the hypothalamus to increase the thermal set point [69,70]. The hypothalamus then initiates shivering, constriction of skin blood vessels, and a sensation of chilliness.

Psychological effects, fatigue, muscle aches and pains and mood changes are common symptoms associated with acute viral rhinosinusitis and these symptoms may be caused by cytokines released as part of the normal immune response to infection [4]. Fatigue is a common symptom associated with chronic rhinosinusitis, being found in over 80% of patients as a minor symptom [47]. In some cases the fatigue may be correlated with treatment with non-sedating antihistamines [71] but it does appear that fatigue is primarily associated with the inflammatory disease of rhinosinusitis, as surgical treatment of chronic rhinosinusitis is reported to reduce levels of fatigue, especially in patients with fibromyalgia [72]. Fatigue and mood changes may be a direct consequence of the symptoms of rhinosinusitis, especially pain and nasal obstruction that may cause loss of sleep, but they may also be caused by cytokines generated as part of the inflammatory response.

Cytokines, including TNF-α, IL-1, IL-2, IL-6 have been reported to induce the syndrome of 'sickness behaviour' with anhedonia, cognitive dysfunction, anxiety/irritability, psychomotor slowing, anergia/fatigue, anorexia, sleep alterations and increased sensitivity to pain [73] and they may mediate mood changes and fatigue associated with both acute and chronic rhinosinusitis.

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