Pathophysiology of Clinical Symptoms in Acute Viral Respiratory Tract Infections

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Abstract

In this article we discuss the pathophysiology of common symptoms of acute viral respiratory infections (e.g., sneezing, nasal discharge, sore throat, cough, muscle pains, malaise, and mood changes). Since clinical symptoms are not sufficient to determine the etiology of viral respiratory tract infections, we believe that the host defense mechanisms are critical for the symptomatology. Consequently, this review of literature is focused on the pathophysiology of respiratory symptoms regardless of their etiology. We assume that despite a high prevalence of symptoms of respiratory infection, their pathogenesis is not widely known. A better understanding of the symptoms' pathogenesis could improve the quality of care for patients with respiratory tract infections.

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1 Introduction

1.1 Respiratory Tract Infections

The literature reports that each year up to 25 million people in the US visit their doctor because of respiratory tract infections. The upper respiratory tract infections, better known as common colds, are the most common clinical presentation of said infections (Gonzales et al. 2001). Viral lower respiratory tract infections, bronchitis, bronchiolitis, and pneumonia; e.g., with respiratory syncytial virus (RSV) or influenza are generally more common in infants, young children, and in patients with chronic medical conditions, whereas older children and healthy adults usually suffer from

milder upper respiratory tract infections (Eccles 2005). Common cold was the third most common diagnosis made during ambulatory care visits by patients of all ages in the US (Hsiao et al. 2010). It has been estimated that an average adult suffers from 2 to 4 colds per year and a schoolchild suffers from 6 to 10 colds per year (Spector 1995; Johnston and Holgate 1996; Winther et al. 1998; Eccles 2005). Therefore, respiratory tract infections represent a significant clinical and therapeutic problem, and an economic burden (Wat 2004). Upper respiratory tract infections are generally mild, self-limiting, and viral in their origin (Johnston and Holgate 1996; Snow et al. 2001; Turner 2011; Kennedy et al. 2012). In experimental studies, the infections have been defined as a short mild illness, with the early symptoms being headaches, chills, sneezing, and a sore throat, and delayed symptoms being nasal obstruction or discharge, cough, and malaise (Jackson et al. 1958). The duration of symptoms varies from 7 to 10 days, with a peak occurring on the 2–3rd day. However, some symptoms may be observed up to 3 weeks after the onset of the infection (Heikkinen and Järvinen 2003; Eccles 2005). Common colds are triggered by rhinovirus (RV) coronavirus, influenza and parainfluenza viruses, and RSV (Wat 2004; Eccles 2005; Kennedy et al. 2012). The diagnosis of upper respiratory tract infections is based on symptoms and, with the exception of antivirals which may be used in influenza, treatment remains symptomatic. Studies on different viruses responsible for the upper respiratory tract infections have shown that it is not possible to identify the virus based on the symptoms (Johnston and Holgate 1996; Eccles 2002). Not only is the clinical presentation of these infections similar regardless of their etiology, but the order in which the symptoms develop is also similar. If the etiology of infections cannot be determined on the basis of clinical symptoms, the host reaction must play a major role in their pathogenesis. The similarities in the clinical presentation of viral upper respiratory tract infections stems from the same immune response pattern to different etiologic agents (Eccles 2005). Furthermore, in acute respiratory tract infections a routine diagnosis to determine the etiology is not usually carried out in primary care settings.

Advances in molecular biology help explain the mechanisms that generate the symptoms of viral respiratory tract infections. Nevertheless, the practical use of the pathophysiology of common symptoms seems relatively poor compared with the amount of scientific knowledge available.

1.2 Symptomatology of Respiratory Tract Infections

Clinical manifestations of respiratory tract infections are familiar and well-known (Eccles 2005; Turner 2011). Although the symptomatology depends, to some extent, on the type and location (e.g., pharyngitis, rhinitis, sinusitis, and bronchitis), the etiology of respiratory infection (viral or bacterial), patient's age, general health, co-morbidities, immunity, and on whether the infection is primary or secondary, e.g., in RSV or influenza there is a great amount of variation and overlap in both etiology and symptoms of individual infections. Consequently, even defining the exact syndrome, like common cold or influenza-like morbidity, is difficult and problematic (Eccles 2005).

The most significant signs of viral respiratory tract infections include sneezing, rhinorrhea (runny nose and nasal discharge), nasal congestion, cough, tachypnea, and fever. Subjective symptoms include a sore throat, malaise, shivering (chills), shortness of breath, muscle aches and weakness, fatigue, and a loss of appetite and headaches (Snow et al. 2001; Wat 2004; Eccles 2005; Kennedy et al. 2012). Febrile seizures are a rare but important symptom in young children up to 6 years of age (Schuchmann et al. 2011). Symptoms of upper respiratory tract infections have been traditionally classified as early or late (Jackson et al. 1958; Eccles 2005). The early symptoms are those that develop quickly and resolve rapidly after 1–2 days, like headaches, sneezing, chills, sore throat, and malaise. In children a high fever may be observed, complicated by seizures in some cases (Monto et al. 2000; Schuchmann et al. 2011). Late symptoms include nasal discharge, nasal obstruction, and cough. The later symptoms develop over several days and are present one week after

experimental infection (Jackson et al. 1958; Eccles 2005). The development of sneezing before coughing in patients with a common cold may be partly explained by the involvement of the upper airways first and the infection subsequent spread to the lower respiratory tract (Eccles 2005).

The aim of this review is to discuss the pathophysiology of symptoms of respiratory tract infections. We focused on the most significant symptoms of acute viral respiratory infections: sneezing, nasal discharge and obstruction, sore throat, coughing, muscle pains, malaise and mood changes, fever, and febrile seizures in children. We believe that despite a high prevalence of the symptoms, their pathogenesis is not widely known and a better understanding should have a beneficial effect on the therapeutic approach and should improve the quality of patient care.

2 Methods of Literature Selection

We searched the literature to identify relevant data. Medline, Scopus, Web of Science, Cochrane databases and respiratory-specific journals such as Respiratory Physiology & Neurobiology, American Journal of Respiratory and Critical Care Medicine, Thorax, Chest, Journal of Allergy, Asthma and Clinical Immunology, European Respiratory Journal, American Journal of Respiratory Cell and Molecular Biology, American Journal of Physiology – Lung Cellular and Molecular Physiology, BMC Pulmonary Medicine, Respiratory Research, Current Opinion in Pulmonary Medicine, Expert Review of Respiratory Medicine, Respiratory Research, Seminars in Respiratory, Critical Care Medicine, and Lancet Infectious Diseases were searched with the following key words: (Pathophys* or Pathogen*) and (Resp* symptom or Resp* infection or Common cold) from January 1990 through May 2014. If possible the results of the search were sorted according to 'relevance'. Due to a large number of articles, exceeding 20,000 (e.g., PubMed), only the first 250 were analyzed. References from relevant articles were also identified. Studies were included if they met the following two criteria: published in English and containing valid, consistent, and relevant data. The first two authors of the present review independently assessed all titles and abstracts to determine whether the inclusion criteria were satisfied. If either of the assessors considered the abstract potentially suitable, full-text articles were retrieved and then assessed by both assessors for their suitability for inclusion. Eventually, 129 publications were selected and studied by each of the authors before the manuscript was prepared.

3 Results

3.1 Significant Etiologic Viral Agents of Upper Respiratory Tract Infections

3.1.1 Rhinoviruses

Rhinoviruses are the most common etiologic agents of common cold. They are responsible for one-third to half of all upper respiratory tract infections reported in adults annually (Proud et al. 1990; Hendley 1998; Heikkinen and Järvinen 2003; Ruuskanen et al. 2013). Improved knowledge about the structure and function of rhinoviruses has been acquired in recent years using virus culture techniques and new molecular genetics methods available. Currently, more than 100 serotypes have been identified with HRV-A and HRV-B being the most important of them all (Heymann et al. 2005; Peltola et al. 2008; Bochkov et al. 2011; Kennedy et al. 2012). It has been demonstrated that the pathomechanism of symptoms in rhinoviral respiratory tract infections does not result from the cell damage, unlike influenza virus or RSV action (Winther et al. 1990). Rather, rhinovirus disrupts the tight junctions of the epithelial barrier, which facilitates the translocation of pathogens and stimulates the host's innate and adaptive immune responses (Rezaee et al. 2011; Kennedy et al. 2012). Over 90 % of rhinovirus serotypes enter the nasal epithelial cells through the host receptor with the intercellular adhesion molecule-1 (ICAM-1) being a glycoprotein immunoglobulin expressed on non-ciliated epithelial cells and on the basal surface of the

ciliated epithelium of nasopharyngeal mucosa, while only around ten rhinovirus serotypes use a minor group of receptors, low-density lipoprotein (LDL) (Bardin et al. 1994; Winther et al. 1997; Whiteman et al. 2003; Bella and Rossmann 2000; Vlasak et al. 2005; Kennedy et al. 2012). Newly discovered and sequenced human rhinovirus-C (HRV-C) is somehow unique as the virus isolates do not grow in typically used cell cultures, e.g., embryonic lung fibroblasts. *In vitro* growth of HRV-C was successfully performed using the sinus mucosal tissue as a substrate (Bochkov et al. 2011; Kennedy et al. 2012). Furthermore, studies on the structure and function of HRV-C have shown that the virus enters the cells using neither the ICAM-1 nor LDL receptor and the pathomechanism of the HRV-C infection remains unclear (Arden and Mackay 2010; Simmonds et al. 2010; Bochkov and Gern 2012; Lee et al. 2012; Ruuskanen et al. 2013).

In otherwise healthy individuals, rhinovirus infections are generally limited to the upper respiratory tract with rhinorrhea and nasal obstruction being the most prominent symptoms (Kennedy et al. 2012). Entry of the rhinovirus triggers the release of interleukin-8 (IL-8) a major cytokine in the recruitment of polymorphonuclear cells (Hendley 1998). IL-8, which is produced locally, increases the production of nasal secretions and causes an influx of neutrophils (Douglass et al. 1994). Oxidative stress caused by viral infection is probably responsible for the cellular mechanisms that lead to the production and release of IL-8 (Zhu et al. 1997). Studies of volunteers infected with a rhinovirus show a local infection in a small proportion (1–2 %) of nasopharyngeal epithelial cells (Turner et al. 1982; Bardin et al. 1994; Arruda et al. 1995). The higher the nasopharyngeal viral load the more severe is the disease (Esposito et al. 2014). Vasoactive kinin peptides are other important mediators produced on-site in nasal mucosa and submucosa in rhinovirus-infected humans. Kinins released in the nose following plasma exudation increase the symptoms of rhinoviral infection and cause an increase in vascular permeability, vasodilatation, and glandular secretion. Bradykinin applied to the nasal mucosa causes symptoms that mimic the common cold, including rhinitis, nasal obstruction, and sore throat (Proud et al. 1988, 1990). Symptom scores correlate with an increase in the kinin concentration. While nasal secretion in adults with symptomatic experimentally-induced rhinovirus infection contain significantly higher concentrations of bradykinin and lysyl-bradykinin, asymptomatic infections do not result in increased kinin concentrations (Naclerio et al. 1988). Interestingly, the presence of rhinovirus has been detected by RT-PCR in 20 % of asymptomatic people who had an infected family member (Jartti et al. 2008).

3.1.2 Coronaviruses

The coronavirus (CoV) is the second etiologic agent of upper respiratory tract infections (Eccles 2005; Mesel-Lemoine et al. 2012). The most common human-infecting coronaviruses include 229E, OC43, SARS-CoV, and the recently discovered NL63 and HKU1 (Arden et al. 2005; Esper et al. 2005; Vabret et al. 2005; Pyrc et al. 2007). The virus is transmitted by aerosol inhalation and reinfections often occur due to a short-lived immunity (Callow et al. 1990; Wat 2004). As a result, coronavirus accounts for 15–30 % of upper respiratory tract infections in humans. These infections are limited predominantly to the upper respiratory tract and rarely spread to lower airways and lungs (Mesel-Lemoine et al. 2012). The coronavirus infection can occasionally involve other organs (Arbour et al. 2000; Collins 2002; Desforges et al. 2006). It has been reported that the two new members of the coronavirus family, NL63 and HKU1, especially the NL63, could also trigger severe lower respiratory tract infections and abdominal disorders such as pain and diarrhea (Arden et al. 2005; Esper et al. 2005; Vabret et al. 2005; Pyrc et al. 2007). Epidemics caused by CoV-NL63 and CoV-HKU1 have been observed every 2–3 years (Kahn 2006; Jartti et al. 2012). Studies have confirmed that the infection with CoV-NL63 is associated with croup and acute respiratory disease mostly in children, the elderly, and patients with chronic diseases, with some fatal cases being reported (van der Hoek et al. 2005; Han et al. 2007; Wu

et al. 2008; Oosterhof et al. 2010; Sung et al. 2010; Milewska et al. 2013). The growth of coronaviruses using standard tissue cultures is poor and advanced molecular methods are needed to isolate the virus, so that most infections may remain undiagnosed (Walsh et al. 2013). Human aminopeptidase N (hAPN), a zinc-binding protein with endopeptidase activity, is used by CoV-229E for entry into the epithelial cells, whereas CoV-OC43 uses hemagglutinin-esterase (HE) and spike (S) – its own surface glycoproteins – to enter the cell (Tyrrell et al. 1993; Künkel and Herrler 1996; Wat 2004). Recent studies have shown the ability of CoV-229E to destroy the dendritic cells, which are essential components of the respiratory tract's immune system, which may explain multiple reinfections with the same type of CoV (Mesel-Lemoine et al. 2012). Although the pathogenesis of infection caused by the two main groups of CoV – 229E and OC43 – is different, the clinical symptomatology is similar (Tyrrell et al. 1993; Wat 2004).

3.1.3 Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is responsible for many flu-like illnesses (Zambon et al. 2001). RSV replication starts in the nasopharynx and then the virus infects the bronchiolar epithelium presumably by cell-to-cell spread or aspiration of secretions. The virus spares the basal cells and subsequently extends to the alveolar pneumocytes. The pathologic findings of RSV are characterized by necrosis of epithelial cells, infiltration with T cells and monocytes around arterioles and with neutrophils between the vascular structures and small airways (Johnson et al. 2007). This leads to airway obstruction, air trapping, increased airway resistance, and is also associated with neutrophilia in bronchoalveolar lavage (Everard et al. 1994). RSV has never been isolated from blood (Peebles and Graham 2005). The immune response to RSV, especially cytokines and chemokines, seems to be responsible for the symptoms and severity of bronchiolitis (Garofalo et al. 2001; Legg et al. 2003). The cytokines IL-8, IL-6, TNF-alpha, and IL-1 beta were detected in respiratory secretions from infected children and high IL-6 concentrations are associated with severe manifestations of the disease (Matsuda et al. 1995; Noah et al. 1995; Smyth et al. 1997). Respiratory secretions from infected children contain chemokines expressed and secreted by T-cells (chemokine ligand 3 – CCL3, i.e. macrophage inflammatory protein-1 – MIP-1 alpha; chemokine ligand 2 – CCL2, i.e. monocyte chemoattractant protein-1 – MCP-1; chemokine ligand 11 – CCL11 – eotaxin, and chemokine ligand 5 – CCL5, i.e. RANTES; regulated on activation). MIP-1 alpha, and to a lesser extent other beta-chemokines, primarily secreted by activated immune cells, are associated with severe manifestations of the disease (Noah et al. 1995; Welliver et al. 2002; Garofalo et al. 2005). Experimental infection of explanted polarized respiratory epithelium in tissue culture generates IL-8 and CCL5 (Mellow et al. 2004). Nonetheless, it is unknown whether the cytokines and chemokines are the cause of disease or are by-products of enhanced inflammatory responses (Barr and Graham 2014).

3.1.4 Influenza Viruses

Whether respiratory tract infections caused by influenza viruses present as common colds with typical symptoms or as severe lower respiratory tract diseases depends on the type of virus, pre-existing immunity, the patient's underlying disorders, and multiple other factors (Wat 2004). The phenomena such as antigenic shift or drift have led to the formation of more recent and increasingly virulent variations of the influenza virus and, consequently, to more serious clinical manifestations (Gething et al. 1980; Treanor 2004). As an example, pandemic influenza A (H1N1)pdm09 affected all age groups, but it was more prevalent in younger patients and children in whom there was the highest rate of hospitalization and pneumonia (Kuchar et al. 2013). It has previously been shown that coughing and fever are the best predictive factors of influenza infections having a positive predictive value (PPV) of 79 % (Monto et al. 2000). However, neither symptom is sufficiently predictive in

children aged 1–4 (Ohmit and Monto 2006). Overall, influenza viruses are generally responsible for 5–15 % of acute upper respiratory tract infections in humans (Wat 2004). The influenza virus causes damage to the epithelial cells and its replication occurs in the airways with predilection to the lower respiratory tract (Hers and Mulder 1961; Hers 1966; Wat 2004). The two main glycoproteins of the influenza virus surface – hemagglutinin (HA) and neuraminidase (NA) – play an essential role in the infection spread. HA targets cells for infection binding to the epithelial sialylated glycans (specific for upper or lower airways) (Shinya et al. 2006; de Wit et al. 2010; Fukuyama and Kawaoka 2011), while NA is responsible for effective viral replication (Pappas et al. 2008). Another viral protein, nonstructural protein 1 (NS1) is also important due to its counteracting IFN-α production in infected cells (Fukuyama and Kawaoka 2011). Viral replication is possible in host cells due to activation of nuclear factor kappa B (NF-κB) and the Raf/MEK/ERK cascade, and then proinflammatory cytokines are produced with interleukin 6 (IL-6) being the most important of them (Kaiser et al. 2001; Pinto et al. 2011; Wine and Alper 2012). IL-6, tumor necrosis factor–α (TNF-α), interferon-α (IFN-α), IL-8, and IL-1β increase significantly in response to the viral invasion resulting in the development of fever, nasopharyngeal mucous production, and respiratory and systemic symptoms. Viral replication and the intensity of the main influenza symptoms are correlated with the level of cytokines, particularly with IL-6 and TNF-α (Hayden et al. 1998; Kaiser et al. 2001).

4　Pathophysiology of Common Respiratory Signs and Symptoms

Evidence presented in our review of the pathophysiology of signs and symptoms in the four most common viral upper respiratory tract infections suggest that the immune system's response to infection rather than the virus-specific damage to the respiratory tract is responsible for the symptomatology (Turner 1997; Hendley 1998; Eccles 2005). Studies on different viruses responsible for upper respiratory tract infections have shown that it is not possible to identify the virus based on the symptoms (Eccles 2005). The pathology of rhinovirus infections consists of the influx of polymorphonuclear leukocytes at the beginning of the infection (Winther et al. 1984). Macrophages play a key role in triggering an acute phase response with the production of cytokines (Beutler 2003), while the release of proinflammatory cytokines and other mediators cause upper respiratory tract infection symptoms (Eccles 2000a, b). Cytokines are responsible for the systemic symptoms (e.g., fever) and bradykinin plays a major role in local symptoms of respiratory tract infections (e.g., sore throat and nasal congestion) (Proud et al. 1988; Shibayama et al. 1996; Conti et al. 2004).

4.1　Sore Throat

A sore throat, irritation, and pain in the pharynx usually appear at the beginning of a respiratory tract infection. A sore throat is most likely caused by the action of prostaglandins and bradykinin on sensory nerve endings in the upper respiratory tract. Intranasal administration of bradykinin causes symptoms of rhinitis and a sore throat, so it is likely to be responsible for these symptoms (Rees and Eccles 1994; Proud 1998). The sensation of pain is mediated by the cranial nerves supplying the nasopharynx. Similar symptoms have been observed in bacterial upper respiratory tract infections, pharyngitis, and tonsillitis (Georgitis 1993).

4.2　Nasal Congestion

Nasal congestion is a subsequent symptom of respiratory infection that develops over the first week of symptoms (Tyrrell et al. 1993). The mechanism of nasal congestion relies on the dilation of the venous sinuses in the nasal epithelium in response to the vasodilator mediators such as

bradykinin (Proud et al. 1990; Widdicombe 1997). Symptom scores increase as kinin concentrations rise (Proud et al. 1990). Dilatation of the sinuses in the narrow nasal valve region causes obstruction of the nasal airway (Eccles 2000b). The so-called nasal cycle (alternating congestion and decongestion of the nasal passages controlled by the sympathetic vasoconstrictor nerves) is accentuated and the asymmetry of nasal airflow is more pronounced during respiratory infection (Eccles et al. 1996).

4.3 Rhinorrhea

A watery nasal secretion often accompanied by sneezing is an early symptom of a respiratory tract infection. Nasal discharge in respiratory infections is a complex mixture of plasma and glandular exudates with cellular elements (e.g., goblet cells, plasma cells, and neutrophils) of variable composition that changes over the course of the infection and severity of the inflammatory response (Eccles 1983). The first phase of nasal discharge consists of a glandular secretion reflex caused by stimulation of the upper airway's trigeminal nerves. Studies have demonstrated that intranasal administration of ipratropium inhibits nasal secretions in the first 4 days of a common cold (e.g., when it is caused by coronavirus) (Akerlund et al. 1993; Hayden et al. 1996). The color of the nasal discharge may change from watery clear to yellow and green during the course of the respiratory tract infection and this reflects the severity of the inflammatory response rather than the etiology of the infection (Stockley et al. 2001). The green or yellow color of nasal discharge is often regarded as a clinical marker of bacterial superinfection and clinical indication to antibiotic treatment, but there is no evidence that supports this concept (Murray et al. 2000). The color change is related to the recruitment of leukocytes into the airway lumen (Stockley et al. 2001). Neutrophils and activated monocytes contain chromatic, green granules (azurophil granules) containing myeloperoxidase with heme pigment. The more leukocytes present in nasal discharge the more

colorful the nasal discharge appears (Stockley et al. 2001). Although the literature is related to sputum color changes, the same mechanisms apply to nasal discharge.

4.4 Sneezing

A watery nasal secretion in the infection's early stage is often accompanied by sneezing. Sneezing together with a sore throat are the early symptoms of respiratory tract infections. Sneezing is a reflex mediated by the trigeminal nerves which supply the nasal epithelium (Leung and Robson 1994; Eccles 2005). The sneeze center in the brainstem coordinates the sneeze reflex. Sneezing is related to inflammatory responses in the nose and nasopharynx that stimulate the trigeminal nerves (Eccles 2005). As intranasal administration of histamine causes sneezing, sneezing is probably mediated by histamine receptors on the trigeminal nerves (Mygind et al. 1983; Eccles 2005).

4.5 Cough

Coughing is the most common clinical symptom and the most frequent reason for visits to see a doctor (McGarvey and Morice 2006). Coughing is a protective reflex that prevents the aspiration of food and fluids into the airway and cleans the respiratory tract of mucus and other foreign bodies. The reflex is mediated exclusively by the vagus nerve (Eccles 2005). Coughing is initiated in the airway through stimulation of the sensory nerves in the larynx or below (Widdicombe 1995). The airway inflammation associated with rhinitis must reach the larynx to cause coughing. The external ear and esophagus are also supplied by the vagus nerve and coughing can also be triggered by gastroesophageal reflux (Morice 2002). Respiratory tract infections are often accompanied by redundant, dry, and unproductive coughing in the first days. The unproductive coughing may be caused by the inflammatory process spreading to the larynx since nasal inflammation causes sneezing rather than

coughing. Coughing in respiratory tract infections is believed to be mediated by hyper-reactivity of the cough reflex due to the effects of inflammatory mediators on the airway's sensory nerve endings (Lee et al. 2002; Eccles and Lee 2004). When the larynx is inflamed and hyper-reactive, coughing may occur spontaneously or in response to stimuli that would not normally cause coughing, e.g., cold air. It may persist for three weeks or longer. Some coughs may be voluntary and related to airway irritation (Lee et al. 2002). Productive coughing usually occurs later in the course of respiratory tract infection and is related to the mucus production associated with inflammation of the lower airways (Eccles 2005). Rhinovirus and coronavirus do not usually cause significant damage to the airway cells and the common cold is typically associated with little, if any, coughing while the influenza virus may cause substantial cellular damage to the respiratory epithelium and an influenza infection is usually associated with coughing (Monto et al. 2000).

4.6 Malaise and Mood Changes

Respiratory tract infections are associated with impaired psychomotor function (Smith et al. 1998). Mood changes and malaise may be explained by the unpleasant objective symptoms of respiratory tract infections such as nasal congestion, rhinorrhea, and coughing (Eccles 2005). These symptoms may cause discomfort and lower the patient's quality of life. However, there is increasing evidence that mood changes may also be caused by the effects of cytokines on the central nervous system (Mahoney and Ball 2002). Interferon alpha treatment for chronic hepatitis B and C is associated with flu-like adverse effects similar to those observed in respiratory tract infections: malaise, fever, myalgia, and mood changes (Schaefer et al. 2002). Psychiatric adverse effects such as depression, irritability, impaired concentration, and psychoses have been reported with interferon alpha therapy. It has been reported that cytokines, e.g., tumor necrosis factor-α (TNF-α)

and interleukins 1, 2, and 6 cause mood changes with anhedonia, cognitive dysfunction, anxiety, irritability, psychomotor slowing, fatigue, anorexia, sleep alterations, and a lower pain threshold (Capuron and Miller 2004). The production of these cytokines is also associated with respiratory tract infections which may mediate mood changes associated with these infections. The exact mechanisms of cytokine action in the brain are poorly understood, but there is a growing body of evidence suggesting that anorexia associated with respiratory infections is mediated by cytokines that act directly on the feeding center in the hypothalamus (Langhans 2000).

4.7 Headache

Headaches are a common early symptom of respiratory tract infections. The majority (60 %) of patients with respiratory tract infections with a sore throat reported headaches in a clinical trial (Eccles et al. 2003). The mechanism of a head-ache associated with a respiratory tract infection is unknown but headaches may be triggered by cytokines released in response to a viral infection (Smith 1992). It has been shown that the admin-istration of some cytokines such as tumor necro-sis factor and interferons cause headaches (Smith 1992; Gold et al. 2005; van Zonneveld et al. 2005).

4.8 Muscle Pain

Myalgia is a common symptom of respiratory tract infections. Around half of patients with a common cold complain about muscle pain (Eccles et al. 2003; Eccles 2005). Myalgia occurs in the acute immune response to infection phase and is related to the effects of cytokines on skel-etal muscles (Baracos et al. 1983). Proinflammatory cytokines including TNF-α have been implicated in the breakdown of muscle proteins (Kotler 2000). Fever and myalgia associated with respiratory tract infection may be caused by the production of prostaglandin E2 in response to cytokines (Baracos

et al. 1983). The cytokine-related synthesis of prostaglandin E2 and the breakdown of skeletal muscle has been inhibited *in vitro* by non-steroidal anti-inflammatory agents and similarly fever and myalgia accompanying acute respiratory infection are relieved with acetylsalicylic acid, a classic anti-inflammatory agent (Eccles et al. 2003). Since prostaglandin E2 is a pain mediator, its increased synthesis may explain the myalgia associated with acute respiratory tract infections.

4.9   Fever and Chills

Fever is a classic response to infection. It is a manifestation of cytokine release in response to a variety of stimuli. It is believed to be beneficial for the host's response to infection (Cabanac 1990; Eccles 2005) and is usually associated with novel or severe viral infections such as influenza (Monto et al. 2000). Consequently, fever is a common symptom in infants, probably because viruses responsible for acute respiratory tract infections are new to the infant and induce a strong immune response. However, in adults who had been exposed to numerous common cold viruses in the past, subsequent infections do not elicit a strong cytokine response and fever is a rare symptom of a common cold in adults (Eccles 2005). On the contrary, some patients experience a transient fall in body temperature during the early stages of acute benign respiratory tract infection and about 1/3 of all patients experience chills (Eccles et al. 2003). Chills associated with a fall in skin temperature related to vasoconstriction of the skin's blood vessels may be explained as an initial stage of fever, but chills may also be unrelated to changes in skin temperature. Chills have developed after administration of exogenous pyrogens, even if the subjects maintained a neutral skin temperature (34.5 °C in water) in experimental human studies (Guieu and Hellon 1980). Chills occur together with shivering and the latter symptom is probably related to the cerebral cortex influence over the shivering control. Both chills and shivering may be caused by cytokines acting on the temperature control center of the hypothalamus. Many cytokines act as endogenous pyrogens and are released from leukocytes in response to infection (Conti et al. 2004). The proinflammatory cytokines (IL-1 and IL-6) are regarded as the most important cytokines for causing fever (Netea et al. 2000; Leon 2002). They are believed to cross the blood-brain barrier and increase the thermal set point in the temperature control center. The hypothalamus then induces shivering, constriction of the skin's blood vessels, and chills (Eccles 2005).

4.10   Febrile Seizures

Febrile seizures are a rare but significant symptom of acute viral respiratory infections in children. They occur in 2–5 % of all children and the majority of febrile seizures are triggered by respiratory tract infection (Schuchmann et al. 2011). Febrile seizures are defined as occurring in children aged 6–60 months with a temperature ≥38.0 °C with no central nervous system infection, metabolic disturbance, or history of afebrile seizure. They are the most common type of seizure in children under 60 months (American Academy of Pediatrics 2011; Graves et al. 2012). Cytokines seem to play a crucial role in febrile seizures, however there is a lot of confusion about the relationship between proinflammatory and anti-inflammatory cytokines and the febrile seizure risk. Is it generally accepted that the genotype IL-1α-889 1/1 and IL-1β-511 T/T homozygote as well as the serum concentration of IL-6 are associated with an increased risk of febrile seizures (Saghazadeh et al. 2014).

5   Therapeutic Points

The treatment of acute viral respiratory tract infections remains primarily supportive. There is evidence that medications like acetaminophen (paracetamol) and non-steroidal anti-inflammatory agents such as ibuprofen or aspirin relieve some symptoms of acute respiratory tract infections (fever, sore throat, pain, and malaise),

but it is debatable whether symptomatic treatment could speed up recovery (Eccles 2005). Many other common advices like drinking plenty of fluids or steam inhalation have not been scientifically proven. Some new agents seem to be promising. For example in a study by Asada et al. (2012) L-carbocysteine reduced the baseline and RS virus infection-induced secretion of pro-inflammatory cytokines, including IL-1β, IL-6, and IL-8 as well as virus titers in the supernatant of human tracheal epithelial cells culture. Although a virus-orientated approach and the development of anti-viral agents should be more beneficial, the diverse etiology makes the development of universal antivirals highly unlikely (Passioti et al. 2014).

6   Conclusions

Since clinical symptoms are not sufficient to determine the etiology of acute viral respiratory tract infections, we believe that the host defense mechanisms are critical to the symptomatology. Immune response seems to be fundamental for understanding the pathomechanisms of these infections. Inflammatory mediators such as prostaglandins and bradykinin are responsible for the local symptoms of nasal congestion and rhinorrhea, while cytokines are responsible for systemic symptoms. A better understanding of the immune response including cytokines interactions will eventually allow for better treatments to be developed and should improve the quality of care for patients with acute respiratory tract infections.

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