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Infections in Children with Asthma

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ABSTRACT

Asthma is a common chronic inflammatory and complex disease in children with many contributing (including genetic and environmental) factors. This study aims to review the impact of infections in children with asthma.

Different websites including Googlescholar, Yahoo, Pubmed, SID.IR, MAGIRAN, IRANDOC, IRANMEDEX, Embase and Hand searching were searched for pertinent articles with keywords asthma, pediatric, infection, virus, bacteria, and fungus. Out of the results, full articles relevant to pediatric asthma were selected.

Acute respiratory infections caused by Chlamydia pneumoniae and Mycoplasma pneumoniae are involved in 5%-30% of wheezing events and asthma attacks. Viral infections were previously found in 24%-34% of asthmatic children, but technological advancements have revealed them to be present in 77%-81% of cases, with rhinovirus found in 47%, Respiratory Syncytial Virus in 21%, and the rest (including influenza, parainfluenza, adenovirus, coronavirus, and enterovirus) accounting for 2%-5% each.

Viral respiratory infections are basically the major trigger for asthma symptoms and attacks in children. No causal relationship has been established between asthma and viruses and bacteria.

Introduction

Asthma is one of the most common chronic and complicated inflammatory disease in children involving numerous genetic and environmental factors such as allergens inside and outside the house, irritating factors like air pollutants, cold, tobacco smoke and respiratory infections. It afflicts upper and lower airways and imposes a tremendous financial burden on families and the

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society. Moreover, it impacts the quality of life in patients and their families and is an important cause of morbidity and even mortality. [1,2]The etiology of asthma is not well understood. More than 300 million people suffer from asthma worldwide, and it is more common in children compared to adults.

Respiratory infections constitute an important environmental factor in asthma. Viral infections are involved in half the cases of asthma development or exacerbation.[3, 4]

Acute respiratory infections caused by Chlamydia pneumoniae (C.Pneumoniae) and Mycoplasma pneumoniae (M.Pneumoniae) are involved in 5%-30% of wheezing and asthma attacks. These factors may be involved in development of the disease or particularly its exacerbation, which remains to be settled. Some studies consider C.Pneumoniae to be more important than M.Pneumoniae in developing and exacerbating asthma symptoms, and vice versa.[5]It is believed that many individuals are asymptomatic or only mildly symptomatic and thus unaware of their disease, when an infection intensifies their symptoms. Most studies concur that viral respiratory infections exacerbate asthma symptoms and that avoiding contact with people with common cold may prevent asthma exacerbation. Asthma is not a contagious disease and cannot be transmitted from one person to another.

The present study aims to review the role of different microbial agents in developing and exacerbating asthma in children.

Method

In order to obtain the articles, different websites including Googlescholar, Yahoo, Pubmed, SID.IR, MAGIRAN, IRANDOC, and IRANMEDEX, Embase and Hand search were searched for keywords of asthma, children, infection, virus, bacteria, fungus. Among the results returned, full articles relevant to the issue of pediatric asthma were selected.

Discussion

Viral Infections

Previously, viral infections were documented in 24%-32% of asthmatic children, which has risen to 77%-81% with development of new techniques.[5]

Many different viruses may exacerbate asthma symptoms, including rhinoviruses, coronavirus, influenza, parainfluenza, adenovirus, enterovirus and Respiratory Syncytial Virus (RSV). Viral agents are basically transmitted in close contact. Viral infections endure longer in crowded environments and are more easily transmitted. Rhinoviruses, RSV and parainfluenza are among the most common infections. Rhinovirus is responsible for 47%, RSV for 21%, and the rest, i.e. influenza, parainfluenza, adenovirus, coronavirus, and enterovirus are each responsible for 2%-5%. RSV-C is more common in winter while rhinovirus is present throughout the year.

Studies dealing with the role of viruses have yielded diverse results. Some report a positive relationship between viruses, such as rhinovirus, adenovirus, or RSV, with asthma exacerbation [6,7] while others have failed to demonstrate any association.[8]

Severe bronchiolitis caused by RSV in early childhood may be associated with recurrent wheezing and asthma later on.[9-11]The relationship between RSV infection in early childhood and development of atopy is still controversial.[9]Rhinovirus is one of the most common viruses found to be involved in asthma attacks in older children.[12]

A study on children with high risk of atopy indicated a significant relationship between rhinovirus and RSV infection in the first year of life with persistent wheezing and asthma at 5 years of age; particularly in children

hospitalized for rhinovirus respiratory infection, the risk of developing asthma at 6 years of age is higher.[13]

Rhinoviruses are often quickly spread in autumn when children go to school. Some studies have shown a strong relationship between respiratory infection and inflammation caused by atopy and persistent asthma.[14,15]

The relationship between respiratory infections and development of persistent asthma and wheezing is of a complex nature and probably involves an interaction between host factors such as age, development stage if innate and specific immune system, and pathogenic factors such as the frequency and severity of infection. Viral infections in general and RSV infection in particular, are capable of modifying immune system functions after birth. Infants hospitalized for wheezing are at higher risk of developing persistent asthma or wheezing throughout their first decade of life.[9-11]

Diagnosis of viral infections is nowadays accomplished by PCR on sputum samples. It is more efficient than traditional methods of serology or immunofluorescence.

Among viral agents accompanying wheezing in children, RSV is more common in children aged below 3 years while rhinoviruses are more frequent in children aged above 3. 100% of children contract RSV by the age of 3. Sometimes RSV may cause severe bronchiolitis with recurrent wheezing and asthma. However, the association between RSV and development of asthma is controversial. It is not clear whether the virus causes asthma directly, or the disease is the result of allergic sensitizations caused by the infection. For instance, one study reported RSV infection during the first 3 years of life to be associated with increased wheezing at 6 years of age [16], but did not show any increase after the age of 13. On the other hand, another study reported that severe bronchiolitis caused by RSV in the first year of life was associated with increased asthma at 7 and 13 years of age, compared to children with mild infection.[9]RSV increases sensitivity to allergens through stimulation of TH2, increased IL-4 levels and increased IgE production, whereas mild inflammation is associated with increased gamma-interferon production.

Moreover, RSV causes neurogenic inflammation of respiratory tract mediated by substance P secreted from the end of non-myelinized fibers. This pathogenesis has been confirmed in rats, and Palivizumab, anti-viral F protein, is shown to reduce inflammation and improve symptoms.[17]

One study reported 60% of upper respiratory infections in asthma attacks to be related to HRV. [18]Certain strains, including HRV-16, are more prominently involved in developing allergies.[19]The virus increased ICAM-1 via NK-Fβ in respiratory tract. In addition, it stimulates TH2 to produce IL-4, IL-6, IL-8, and IL-16 associated with an increase in fibroblasts, neutrophils, eosinophils and monocytes. The levels of eotaxin and ranteschemokines also rise to improve neutrophil infiltration, whereas gamma-interferon lowers their level.

Animal models suggest that influenza and parainfluenza infections increase pulmonary sensitivity through increased eosinophils, lymphocytes and macrophages. Furthermore, they increase the tone of bronchi via M2 muscarinic receptors and increase the parasympathomimetic bronchospasm reflex through inhibition of acetylcholine release.[20] In any case; these viruses increase inflammation, bronchial responsiveness, epithelial damages and bronchili fibrosis (through increased TGF-β). [21]

In infants, RSV-caused bronchiolitis manifests as acute asthma attack, and 30% of them may develop recurrent wheezing later on. [22]Severe cases of bronchiolitis may be associated with asthma. One study indicated that children aged

7.5 years with positive family history of asthma and bronchiolitis had a higher rate of asthma (38%) compared to those who had asthma without bronchiolitis (0%).[9]

In any case, respiratory infections with wheezing caused by RSV in young age are associated with recurrent, persistent wheezing and asthma in school years.[23,24] Other studies, however, did not show this relationship at 11 years of age.[16,25]A higher load of Human rhinovirus(HRV) is more probable to cause asthma attacks.[26] One study reported 48% of wheezing patients positive for HRV and 21% positive for RSV. The study indicated that the risk of asthma is higher when the RSV or HRV caused wheezing occurs at 3 years of age rather than 1 year.[23]In any rate, sensitivity to airborne allergens without wheezing in the first year of life, and wheezing without sensitivity to airborne allergens were associated with increased risk of asthma at 6 years of age. [23]

The greatest impact is observed when HRV-caused wheezing is simultaneous with airborne allergens: these two factors have synergistic effect for asthma, although they are independent risk factors.

Exacerbation of asthma symptoms and its attacks are the main cause of morbidity in these patients at all ages. Another study indicated that some 50% of asthma attacks are associated with respiratory infections such as HRV.[27] Although PCR has high sensitivity and specificity for diagnosis of infectious agents; it is not a quantitative method.

Influenza virus and RSV are involved in asthma exacerbation with even higher pathogenicity compared to HRV.

HRV has 99 serotypes, classified as A, B, or C.[26] Of course, the clinical significance of these groups requires further studies.

There is not strong evidence to suggest that asthma patients catch common cold more [28]; some studies, however, indicate that the symptoms of common cold are more severe and last longer in asthma patients.

Infection in patients with allergic asthma results in poorer control compared to those with non-allergic asthma. Thus, patients with allergic asthma experience more severe symptoms when contracting viral infections.

HRV reduces α and γ interferon in mononuclear cells. An increased TH1 response (ratio of gamma-interferon to IL-5) is associated with milder symptoms and faster viral cleaning.[29] Asthma patients have diminished β and γ interferon response in their epithelial cells.[30]

Increased level of TH2 cytokines such as IL-4, IL-5 and IL-13 are among risk factors for allergy and HRV infection. It has been said that allergic sensitization, at least in children, is an important risk factor for HRV-caused wheezing and the IgE-mediated response may be associated with common cold wheezing.[31]

In school season, the elevated stress level, accumulation of airborne allergens and viral respiratory infections all contribute to exacerbation of asthma attacks. Respiratory infections and allergens both harm the respiratory epithelium. Respiratory infections weaken the epithelium and increase inflammation through increased absorption of allergens and stimulants.[32]

Moreover, toxic agents like tobacco smoke or nitrogen dioxide increase the risk of wheezing caused by viral infections.

As mucus-secreting goblet cells are more frequent in asthma patients, inflammation is more severe because HRV proliferates preferably in this cells.[33]

There are studies that indicate a mutual relationship between allergic inflammation and antiviral immunity. Allergic inflammation may suppress the interferon response of innate immunity under certain circumstances. [34]Some studies believe young age infection with viral agents as a factor for increase allergy and asthma.[35]

Other studies suggest that rhinovirus plays a role in exacerbation of asthma symptoms and reduction of pulmonary function (reduced FEV1 and PEF) in children. [36]The viral load on BAL is directly proportional to the severity of symptoms and compromise of pulmonary function. [37]The virus prolongs the response of respiratory tract to allergens (38). This harms the epithelium via increase pre-inflammatory mediators. Increased levels of IL-11, IL-8, IL-6, ECP and ICAM-1 are involved in asthma exacerbation with rhinovirus infection.[39-41]

ICAM-1 improves viral adhesion to human epithelial cells, and also plays a role in allergy through leukocyte infiltration. HRV reduces TH1 response and improves TH2 response which leads to incomplete virus cleaning.[29] β and γ interferon production is compromised; these interferons have antiviral properties and their concentration is inversely related to viral load on BAL, severity of symptoms and inflammation of respiratory tract. Metapneumovirus, bocavirus, coronavirus (HKU1, SARS, NL63) and poliomavirus may cause exacerbate asthma attacks and wheezing in children.[42] HRV-C strain is more involved with asthma attacks and wheezing in children.

Some studies have indicated that wheezing caused by virus in infancy is associated with higher risk of recurrent wheezing later one [9,23]and even higher risk of asthma. Another study shows that RSV does not have a causal relationship with asthma.[25] In any case, the type of virus plays an important role in development of respiratory symptoms and asthma.[23,24]

Other studies show that host factors are crucial in development of wheezing and asthma following viral infections, including:

1- Low lung volume on birth, especially in preterm children

2- Atopy status of the infant

3- Intensity of mucus production in response to infection

4- Response of neurotrophic pathways to airway hypersensitivity by infection

5- The capability of an infant with wheezing to provide immune response to viruses, including γ-interferon, interferon 1 and 3 [43]

Some studies show that after 3 years of age, viral respiratory infections and allergies increase wheezing and asthma attacks in a synergistic manner.[24,44-45]

HRV is the main trigger for asthma attack in all ages, and it is also responsible for development of asthma. Li CZ conducted a study in asthmatic children to demonstrate that in 48% of them, antibodies were against non-bacterial respiratory agents, including 25% for MP, 9% for adenovirus, and 9% for influenza B. In some patients, multiple factors were found simultaneously. The most common age of involvement was 1-6 months (67%). The pathogens were more common in patients with asthma compared to those with bronchitis, and more common in the latter compared to patients with bronchiolitis. Infected patients had lower eosinophil levels but higher IgE levels.[46]

Similar to other studies, Benitez demonstrated that respiratory infections exacerbate asthma symptoms. [47]

Holt PG et al reported that increased respiratory infections are associated with exacerbated symptoms, prolongation of the disease, and poor control of asthma in atopic patients compared to non-atopic asthma patients. FCR1 is expressed to a greater extent on dendritic cells and monocytes of patients with atopic asthma, indicating greater allergic inflammation of respiratory tract. Type C HRV causes greater wheezing.[48]

Another study by the same author mentions that early in life, allergic sensitivity is converted to atopic asthma when atopy is accompanied by viral respiratory infections. Thus, the immune response in allergic individuals may have protective or aggravating properties for asthma

depending on other conditions and even infections. Controlling allergy in young age may lower the risk of asthma.[49]

Bacterial infection

Infections such as M. pneumonia and C. pneumonia and (especially in chronic and stable asthma) play a pivotal role in asthma pathophysiology (3,4). They are found in 53% of cases, and thus it is said that chronic asthma accompanies chronic infection.

Although these agents do not act via IgE to create asthma symptoms, previous studies indicate an increase in mast cells in the respiratory tract, suggesting the relationship between infection and sensitization to allergens.[8] Inhalational steroids may help reduce inflammation and the microorganism count. [50]C. pneumonia and M. pneumonia each account for 2%-5% of infectious etiologies in asthmatic children.[51]But the rate of finding the organism is reportedly 4.5%-25% for C. pneumonia, and 5%-22.5% for M. pneumonia in other studies. [51-53]Some studies fail to establish the relationship.[54]

It is said that acute C. pneumonia and M. pneumonia infections are associated with acute asthma attacks, while their chronic infections lead to persistent and stable asthma. Antibiotic therapy is not recommended in acute asthma attack, unless there is evidence of bacterial infection.[55]

It is said that in allergic inflammation increases after C. pneumonia infection, which may result in exacerbation of asthma symptoms. [56,57]Children hospitalized with asthma attacks following C. pneumoniaand M. pneumonia infection have longer and more resilient symptoms.[52]

Antibacterial therapy for M. pneumonia and C. pneumonia has yielded different results in terms of asthma symptoms. Some studies report negligible effect [58], while other show excellent improvement in symptoms.[59]

C. pneumonia

C. pneumonia is a Gram-negative, obligate intracellular bacterium targeting monocytes, macrophages, and epithelial and endothelial cells in the respiratory system, resulting in upper and lower respiratory infection. Repeated and chronic infection with C. pneumonia exacerbates asthma.[60] Genetic and environmental factors, including other diseases, smoking and steroids, render an individual susceptible to persistent C. pneumonia infection. The symptoms are more severe in asthmatic patients with C. pneumonia infection requiring higher steroid doses. [58]Whether the relationship between C. pneumonia and asthma is causal or simultaneous is not clear yet. Some studies have reported that treatment with macrolides improves PEF and FEV1 and reduces respiratory tract response.[58,61] On the other hand, other studies have reported no impact on respiratory symptoms and function. [62]In most individuals, C. pneumonia is asymptomatic or with mild symptoms only. Repeated infection is common leading to chronic intracellular inflammation.[63] Chronic and stable infection may exacerbate asthma.

Some researchers believe that C. pneumonia infection is not different in asthmatic and normal individuals (64, 65). Other studies indicate that C. pneumonia is positive in 33% of patients with wheezing compared to 17% of patients without wheezing, whereas the related figures in asthmatic patients are 80% and 53%, respectively.[66,67] C. pneumonia causes wheezing in asthmatic children and its treatment improves the symptoms. [3]Patients with recurrent asthma attacks experience longer and more frequent C. pneumonia infection compared to the normal population.[68] IL-5 levels are higher in these patients. One study reported C. pneumonia infection in 4.5% of children hospitalized for severe asthma using PCR.[51]

Therefore, previous studies indicate that C. pneumonia infections are associated with asthma and lowered FEV1/FVC ratio.[67-69]Children with C. pneumonia and M. pneumonia infection on their first asthma attack are more liable to recurrent attacks (62% versus 27%).[53] Some studies do not demonstrate this relationship and even suggest a protective effect for asthma.[64,70] Acute C. pneumonia and M. pneumonia infections cause 5%-30% wheezing or asthma attacks in children.[71]

Chronic C. pneumonia infection is associated with more severe asthma. [72]Via an increasing level of IgA and Heat Shock Proteins, C. pneumoniainfection is associated with lower pulmonary function, more severe symptoms and more severe asthma. [72,73] C. pneumonia infection causes respiratory symptoms in atopic children [74]; another study, however, did not find a significant difference between asthmatic and normal children.[64]

M. pneumonia

M. pneumonia is an intra- and extracellular microbe and basically infects ciliated epithelial cells and alveolar macrophages. It may be isolated from sputum weeks or even months after infection. It jeopardizes cilia, epithelium, and the physiology of respiratory tract. It is involved in many diseases including rhinitis, pharyngitis, otitis, atypical pneumonia, bronchitis, lung cancer and even chronic obstructive pulmonary disease (COPD) in different age groups.[75,76]

M. pneumonia exacerbates asthma in children and even adults greater than C. pneumonia. It is sometimes involved in development of asthma in children.[53]Other studies show that it prolongs asthma symptoms or creates resistance to steroids.[77] Others believe that asthmatic patients are more susceptible to this infection.

Previous studies reported 25%-40% wheezing in M. pneumonia infection in children.[78] In children hospitalized with severe asthma, M. pneumonia was positive in 2.2% of cases with PCR [51], while another study reported 20% of children hospitalized with asthma to be positive for M. pneumonia, with 50% positive M. pneumonia in children experiencing their first asthma attack.[53] Many studies have demonstrated the relationship between C. pneumonia and M. pneumonia infection and acute asthma attacks.[66,68,79]

Other studies pose the possibility of C. pneumonia and M. pneumonia involvement in development and exacerbation of asthma symptoms in children.[68]M. pneumonia is asymptomatic in 20% of cases.[80]It is more frequent in children than adults, and exacerbates asthma symptoms more in children than adults.[81] No chronic carrier of the microbe has been observed in immunocompetent individuals, thus its chronic infection has no role in exacerbating asthma. M. pneumonia colonization and infection is more common in asthmatic patients than others.[61]

Following M. pneumonia infection, tissue mast cells increase.[82] M. pneumonia infection is also associated with increased IL-1B, IL-6, IL-8, TNF-α, RANTES, and TGF-β. [83]

Previous studies indicate that treating M. pneumonia infection with macrolides and steroids reduces inflammation in the respiratory tract and improves clinical symptoms and respiratory function.[72] Other studies show that macrolides may improve symptoms in asthmatic patients as anti C. pneumonia and M. pneumonia, as well as anti-inflammatory agents.[84]

Conclusion

There is not enough evidence to support a causal role for C. pneumonia and M. pneumonia in developing pediatric asthma. Most studies indicate a significant relationship between M. pneumonia and C. pneumonia infections and

chronic, persistent asthma; however, it remains to be discovered whether this reflects a causal relationship or simultaneous susceptibility.

Hygiene theory

Contracting infections in childhood reinforces TH1 and reduces TH2, thus lowering the risk of allergic diseases. Microbes direct lymphocytes towards TH1 through stimulation of gamma-interferon, IL-12, and IL-18.[85]Delayed hypersensitivity to TB (Mycobacterium tuberculosis) reduces the risk of atopy (86). Other studies, however, do not corroborate these reports.[87]Overall, this theory still has certain challenges to answer.[88,89]

Other infections

Helicobacter pylori (H.Pylori) enter human body early in life and remains there for almost the entire lifetime. It is transmissible unless eradicated by medication. Some studies indicate a relationship between H.pylori and asthma. One study demonstrated an inverse relationship between H.pylori infection and prevalence of asthma, allergic rhinitis (AR) and atopy.[90]

Other studies, however, have reported controversial results [91] with OR=0.41, 95% CI: 0.24-0.69.

Other studies indicate that treating non-respiratory infections in the first year of life is associated with increased risk of asthma, revealing the protective role of H.pylori in asthma. [92]

In other studies, hepatitis A virus, Herpes Simplex Virus type 1 (HSV-1), and toxoplasma have been incriminated as possible risk factors for asthma.[93]

Holster IL reported that in children aged 7-9 with allergic symptoms, H.pylori prevalence was significantly lower in children with wheezing compared to others, while the prevalence of H.pylori was not significantly different in allergic patients, including asthma.[94]

A study by Capili CR indicated that patients with asthma had a higher risk of pertussis infection compared to the control group (38% versus 26%). They recommended DTap reaction in older children as booster vaccination.[95]

Brar T et al reported that an ensemble of risk factors, including allergens and infections, are involved in the pathogenesis of asthma. Microbes play a role in asthma exacerbation and may even be involved in its development.[96]

Sinusitis and Asthma

Half of patients with moderate to severe asthma suffer from chronic sinusitis. Sinus infection affects asthma symptoms. Sinusitis is associated with more severe asthma and poorer asthma control. Treating either asthma or sinusitis will improve the symptoms of the other.[90]Thus; respiratory infections exacerbate symptoms more in patients with uncontrolled asthma. It must be remembered that bacterial infections have little role in asthma exacerbation and antibiotic therapy is not indicated for asthma management.

Conflict of Interest

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