

Interleukin-6, interleukin-8, interleukin-11, and interferon- γ levels in nasopharyngeal aspirates from wheezing children with respiratory syncytial virus or influenza A virus infection

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The differences between respiratory syncytial virus (RSV) and influenza A virus (IFAV) in the pathogenesis of wheezing in young children have not been clearly defined. The aim of this study was to assess the contributions of RSV vs IFAV in the pathogenesis of upper airway inflammation in wheezy young children. We compared interleukin (IL)-6, IL-8, IL-11, and interferon- γ (IFN- γ) levels in nasopharyngeal aspirates (NPA) from non-asthmatic children with respiratory virus infections (RSV in 17 children and IFAV in 13 children), asthmatic children with viral infections (RSV in nine children, IFAV in 10 children), and 22 unaffected healthy children (controls). Levels of IL-11 in NPA from asthmatic children were significantly higher than those from non-asthmatic children with RSV infection, and RSV infection enhanced the IL-11 production in NPA significantly compared to IFAV infection. Nasopharyngeal epithelium from children with RSV infection secreted more IL-6 than that of children with IFAV infection. There was little difference in the IL-8 and IFN- γ levels between asthmatic and non-asthmatic children with RSV or IFAV infection. In conclusion, asthma enhanced IL-11 production in RSV infection rather than IFAV infection in early childhood. There was a trend towards greater IL-6 production in RSV infection compared with IFAV infection.

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Acute bronchiolitis is a viral disease of childhood characterized by inflammatory obstruction of the small airways. A significant number of infants with bronchiolitis have hyper-reactive airways during later childhood (1,2). Epidemiological evidence suggests that there may be synergistic immunological interactions after viral respiratory infections and allergic airway sensitization (3,4). The mechanisms underlying such interactions have not been well defined, although many potential mechanisms have been suggested for the exacerbation of airway hyper-responsiveness as a result of viral infections (5,6). However, each

respiratory virus has been shown to have immunologically different effects on airway inflammation *in vivo*. Cytokines released during the inflammatory response are considered to be important in the pathogenesis of inflammation of the respiratory tract. In this study, our aim was to assess the levels of several cytokines in nasopharyngeal aspirates (NPA) in clinical states of virus-induced asthma and to determine whether the pattern in bronchiolitis was similar to that demonstrated in childhood asthma. Adult studies of respiratory tract inflammation frequently use bronchoalveolar lavage (BAL), an invasive tech-

nique that cannot be easily applied to children. Therefore, aspiration of nasopharyngeal secretions is often used to measure the cytokine responses in children and was chosen for sample collection in this study.

Interleukin (IL)-11 stimulates the production of acute-phase proteins and is a major component of the immune response to many viral, but not bacterial, infections (7,8). IL-11 may be uniquely important in allergic inflammation because its production is correlated to viruses associated with asthma exacerbation, such as respiratory syncytial virus (RSV) (9). IL-6 is considered to be the most important inducer of acute-phase proteins, such as C-reactive protein and haptoglobin, in the initial period of inflammation (10), and is an anti-viral molecule. However, the anti-viral activity of IL-6, which is identical to that of interferon (IFN)- β 2, is controversial (11). In contrast to the pro-inflammatory effects, IL-6 terminates the up-regulatory inflammatory cascade by inhibiting IL-1 and tumor necrosis factor (TNF) synthesis. *In vivo*, enhanced epithelial cell gene expression of IL-6 and IL-8 has been observed to occur in bronchial biopsy specimens of asthmatics (12). The concentration of IL-6 is increased in BAL fluids from symptomatic asthmatic patients, and concentrations of IL-8 are also increased in nasal secretions of allergic subjects after allergen challenge (13). In a previous study, IL-8 production was greatly increased in response to respiratory viruses and bacterial products (14). IFN- γ has pleiotropic biological effects, including intrinsic anti-viral activity as well as stimulation and regulation of immune responses. The effect of IFN- γ is to promote T helper 1 (Th1) cells and macrophage-rich inflammatory reactions (15).

In the present study, we focused on the differential patterns of IL-6, IL-8, IL-11, and IFN- γ concentration in NPA between respiratory virus-induced asthma and respiratory virus-induced bronchiolitis, and evaluated the values of these cytokines in NPA between the presence of RSV and IFAV during early childhood.

Subjects and materials

Subjects

Children with acute viral bronchiolitis. Thirty children were arbitrarily selected from patients younger than 3 years of age who had been diagnosed as having an RSV infection (17 children) or IFAV infection (13 children) between October 1997 and March 1999. Bronchiolitis was defined as acute respiratory illness with

wheezing, tachypnea or dyspnea with intercostal recession, prolonged expiration, and wheezing on auscultation. Their chest X-rays were consistent with a diagnosis of bronchiolitis. The patients had primary viral infections, negative personal and family histories of allergy, and total serum immunoglobulin E (IgE) levels within the age-matched normal range.

Atopic asthmatic children with viral infection. Nineteen asthmatic children (9–35 months of age) with RSV (10 children) or IFAV (nine children) infection were recruited. Asthma was defined as three or more visits to the clinic/hospital for wheezing attacks during the previous 2 years. On admission to the hospital, the asthmatic symptoms were severe in two children (RSV: two), moderate in five children (RSV: three; IFAV: two), and mild in 12 children (RSV: five, IFAV: seven). Atopy was defined as having at least one positive skin prick test (SPT) to common allergens (egg, milk, soybean, hazelnut, peanut, cod, crab, shellfish mix, cat fur, dog hair, grass mix, tree mix, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Cladosporium herbarum*, *Alternaria areata*; ALK, Copenhagen, Denmark), a positive response to histamine, and positive personal or family histories of allergy and age-matched, high IgE level in serum. Candidate subjects who had used topical or systemic corticosteroids within 6 weeks prior to the day of study were excluded.

Controls. Twenty-two non-atopic healthy children, 3–46 months of age, who exhibited no evidence of atopy, asthma, or viral infections, were recruited as controls (Table 1).

The study was performed only after informed consent was obtained and approval of the ethics committee of Hanyang University Hospital had been given.

Collection of NPA and identification of respiratory virus in NPA

Samples of nasopharyngeal secretions were obtained by aspiration from the nasopharynx through catheters after instilling 5 ml of sterile physiologic saline solution into mucus traps at the time of hospitalization. Each specimen was mixed well and centrifuged at 1500 r.p.m. (300 $\times g$) for 10 min. Supernatants were kept at -20°C until required for cytokine measurement. Meanwhile, the precipitate was subjected to the indirect immunofluorescent antibody assay for the qualitative identifications of RSV, adeno-

Table 1. Characteristics of the subjects

Subject group	Subjects (n)	Gender (M:F)	Mean age (months)	Serum IgE level (IU/ml)	Blood eosinophil count (cells/mm ³)
RSV					
Non-asthmatic	17	9:7	13 (2–32)*	56.4 (34.6–74.1)†	47.5 (31.6–132.8)†
Asthmatic	10	6:4	18 (10–46)	213.9 (49.7–619.5)	398.5 (62.5–722.5)
Influenza virus					
Non-asthmatic	13	8:5	19 (4–43)	42.7 (32.4–68.5)	36.1 (25.3–96.9)
Asthmatic	9	7:2	22 (9–51)	288.7 (32.2–734.6)	299.8 (55.1–698.6)
Controls	22	16:6	22 (3–46)	24.1 (12.7–49.6)	62.5 (45.7–137.1)

Values are expressed as: *mean (age-range) and †median (95% confidence interval).

virus, parainfluenza virus types 1, 2, and 3, and influenza virus A and B (Chemicon International, Temecula, CA, USA).

Measurement of total serum IgE level and blood eosinophil count

A 15-ml sample of whole blood was drawn from each 5 ml was used for determination of the eosinophil count the remaining 10 ml was centrifuged and the serum thus obtained used for analysis of IgE concentration. Total serum IgE was measured by radioimmunosorbent assay

(Kabi-Pharmacia, Uppsala, Sweden), with a lower detection limit of 1.5 IU/ml.

Measurement of IL-6, IL-8, IL-11, and IFN- γ levels

IL-6, IL-8, IL-11, and IFN- γ were analyzed by using commercial enzyme-linked immunosorbent assay (ELISA) kits (Quantikine; R & D System, Minneapolis, MN, USA). Each sample was measured in duplicate. The lower detection limits of ELISA kits were: 8 pg/ml for IL-11 and IFN- γ ; 10 pg/ml for IL-8; and 0.70 pg/ml for IL-6.

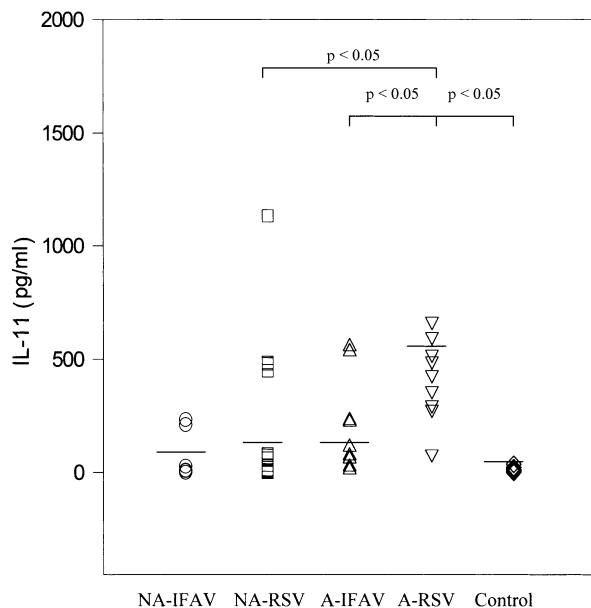


Fig. 1. Comparison of interleukin (IL)-11 levels in nasopharyngeal aspirates from children with or without asthma, with respiratory syncytial virus (RSV) or influenza A virus (IFAV) infection, and controls. The mean level of IL-11 in asthmatic or non-asthmatic children with RSV infection was shown to be higher than that in children with IFAV infection. Asthma enhanced the IL-11 level in nasopharyngeal aspirates (NPA) from children with RSV infection compared with controls ($p < 0.05$). NA-IFAV, non-asthmatic wheezing children with influenza A virus infection; NA-RSV, non-asthmatic wheezing children with RSV infection; A-IFAV, asthmatic children with influenza A virus infection; A-RSV, asthmatic children with RSV infection.

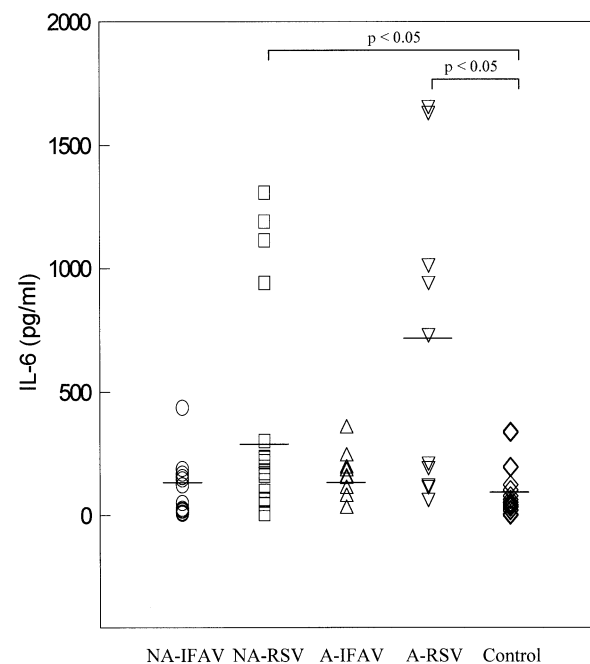
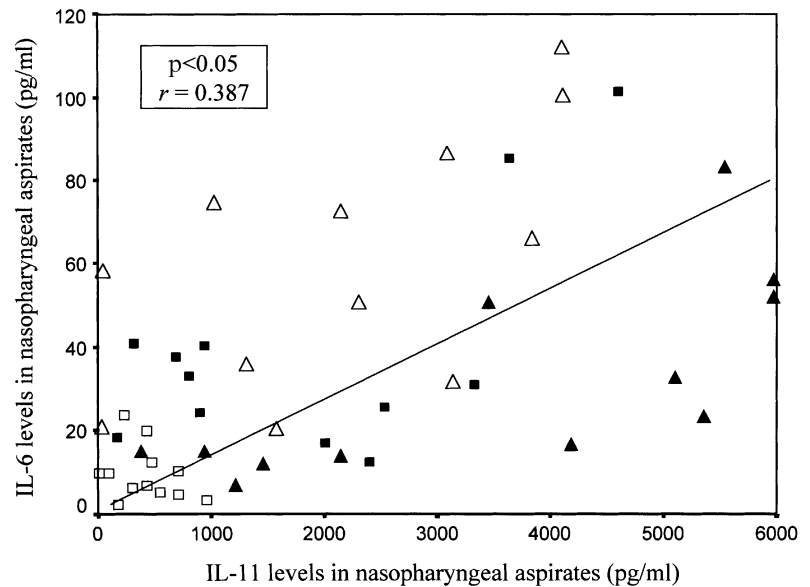


Fig. 2. Comparison of interleukin (IL)-6 levels in nasopharyngeal aspirates (NPA) from children with or without asthma, with respiratory syncytial virus (RSV) or influenza A virus (IFAV) infection, and controls. The mean level of IL-6 in NPA from children with RSV infection ($p < 0.05$) was significantly higher than that from the controls. NA-IFAV, non-asthmatic wheezing children with influenza A virus infection; NA-RSV, non-asthmatic wheezing children with RSV infection; A-IFAV, asthmatic children with influenza A virus infection; A-RSV, asthmatic children with RSV infection.

Fig. 3. Correlation of interleukin (IL)-6 and IL-11 levels in nasopharyngeal aspirates from children with RSV ($\square$) and influenza A virus ($\triangle$) infection, with asthmatic (black color) or without non-asthmatic children (white color).



Statistical analysis

Statistical analyses were performed using SPSS 7.5 for Windows. Statistical comparisons of cytokine levels in NPA were performed using a non-parametric test (the Kruskal–Wallis test). Values of $p < 0.05$ were considered statistically significant. Correlation analysis between cytokines was performed by using the Spearman rank correlation test.

Results

IL-11 levels in NPA

The mean level of IL-11 in NPA from asthmatic children was significantly higher than that from non-asthmatic children in subjects with RSV infection (569.9 ± 260.4 vs. 291.4 ± 135.3 pg/ml, $p < 0.05$). In asthmatic children the levels of IL-11 in NPA were significantly higher in those with RSV infection than those with IFAV infection (569.9 ± 260.4 vs. 202.2 ± 69.5 pg/ml, $p < 0.05$). (Fig. 1).

IL-6 levels in NPA

The mean levels of IL-6 in NPA from asthmatic children with RSV infection (675.6 ± 197.4 pg/ml) and from non-asthmatic children with RSV infection (429.5 ± 169.8 pg/ml) were significantly higher than those from the controls (80.7 ± 21.4 pg/ml, $p < 0.05$) (Fig. 2).

IL-8 levels in NPA

In asthmatic subjects, the mean level of IL-8 in NPA from children with IFAV infection was not

significantly higher than that from children with RSV infection (3014.3 ± 711.4 vs. 1145.1 ± 496.5 pg/ml) or controls (839.6 ± 277.8 pg/ml).

IFN- γ levels in NPA

The mean level of IFN- γ in NPA from non-asthmatic children with IFAV infection was not significantly higher than that from children with RSV infection, in either non-asthmatics or asthmatics.

Correlation among the levels of cytokines in NPA

There was a correlation between IL-6 and IL-11 levels ($p < 0.05$, $r = 0.387$) in NPA from the wheezing children with RSV or IFAV infections (Fig. 3).

Discussion

This study identified significant increases in IL-11 and IL-6 during RSV infection in early childhood and found that asthma augments the production of these cytokines in NPA. On the other hand, IFAV does not affect the release of IL-6, IL-8, IL-11, or IFN- γ from either asthmatic or non-asthmatic children.

The aspiration of nasopharyngeal secretions is a relatively non-invasive procedure that requires no anesthetic or special equipment, and the cells lining the nasal passages are the first to come in contact with an airborne allergen or respiratory virus. However, the relationship of the cellular response in the nasal passages to events in the lower lung is not known. The hypothesis that the

acute cellular response in the nasopharyngeal region may parallel a similar response in the lower respiratory tract, under specific conditions, is supported by previous studies (16,17). In addition, viral titers are more than 100 times higher in nasal turbinate tissue than in the lower respiratory tract during viral infection (18). These attributes make the NPA a very useful tool for identifying airborne allergens and respiratory viruses that can induce inflammation in the respiratory tract of humans.

The mechanism by which RSV can induce asthma, and the factors influencing RSV-induced inflammatory and immune responses in humans and murine models, remain poorly defined, although many studies suggest that pathogenesis could be related to an inflammatory response mediated by cytokines of the T helper 2 (Th2) profile (5,19). On the other hand, influenza virus infection and replication in the respiratory tract directly injures the nasal and tracheobronchial epithelium, causes exfoliation of epithelial cells and increases permeability of the respiratory mucosal barrier to antigen penetration, with the enhanced possibility of IgE antibody sensitization (20). IFAV infection increases IgE production and airway responsiveness in aerosolized ovalbumin-exposed mice (21), and O'Donnel & Openshaw reported that infections with RSV and IFAV augment cellular and humoral immune responses to aeroantigen in a murine model (22). These reports suggest that both IFAV and RSV enhance airway hyper-reactivity. We hypothesized that both viruses promote sensitization to inhaled antigen and may aggravate asthma, and evaluated their relationship to the production of pro-inflammatory cytokines IL-6, IL-8, IFN- γ and IL-11 occurring locally in the upper respiratory epithelium.

IL-11 is an extremely cationic cytokine with the ability to activate B cells via a T-cell-dependent mechanism, in synergy with IL-4. Some studies have demonstrated that IL-11 correlates with clinical bronchospasm and is a potent inducer of airway hyper-responsiveness (23). It is well known that inflammation and smooth muscle abnormalities co-exist in human airway disorders, and inflammation modulates the proliferative and contractile properties of airway smooth muscle cells. Human lung fibroblasts and airway smooth muscle cells produce IL-11 in response to inflammatory cytokines (24), histamine (25), and eosinophil major basic protein (26). In addition, some studies have demonstrated that IL-11 might play a role in the pathogenesis of virus-induced airway hyper-responsiveness (27). We evaluated whether respiratory viral agents that induced

wheezing stimulate the release of IL-11 in NPA *in vivo*. In present study, the levels of IL-11 in NPA from children with RSV infection were significantly higher than those from children with IFAV infection, and asthmatic children in IFAV and RSV infection have increased IL-11 levels compared to non-asthmatic children. These results support the view that RSV is an extremely potent inducer of stromal cell IL-11 elaboration, IL-11 is an inducer of pulmonary inflammation, and that IL-11 may induce airway hyper-responsiveness via its ability to generate local tissue inflammation in asthma (28). Human airway smooth muscle cells are potent producers of IL-11 when stimulated with IL-1 or transforming growth factor- β 1 (TGF- β 1), and IL-1- and TGF- β 1-stimulated human airway smooth muscle cells produce IL-6 (29).

IL-6 has a variety of documented pro-inflammatory effects that are potentially relevant to asthmatic inflammation (30). In contrast, IL-6 has also been demonstrated to diminish tissue inflammation in animal models of hypersensitivity pneumonitis (31). IL-6 possesses a diverse spectrum of biologic activities, both pro-inflammatory and anti-inflammatory. Elevated levels of IL-6 have been reported to occur in the BAL fluid of patients with asthma (32), but the role that IL-6 plays in these asthma states has not been determined. In the present study, RSV enhanced IL-6 production in asthmatic and non-asthmatic children, but IFAV did not stimulate IL-6 release. In addition, our data showed some correlation between the levels of IL-6 and IL-11. IL-11 was initially discovered as the molecule (other than IL-6) in supernatants from stromal cells that stimulated the proliferation of IL-6-dependent plasmacytoma cells (33). It is now classified with IL-6 on the shared use of the gp130 molecule in their multimeric receptor complexes, but the correlation between them remains to be evaluated *in vivo* (8).

Levels of IL-8 in bronchoalveolar lavage fluid have been shown to correlate with symptoms scores in asthmatic children, but not infant wheezers (34). The age range of our patients is very much the same as the infant wheezers in the above study and therefore our observations are consistent. Another group has studied the production of macrophage inflammatory protein-1 α (MIP-1 α) and regulated on activation, normal, T-cell expressed, and secreted (RANTES) in nasopharyngeal secretions from children with acute viral infections. Both these chemokines have an effect on recruitment and degranulation of eosinophils and basophils and were found in the nasopharyngeal secretions

during infections with RSV, adenovirus, influenza and parainfluenza (35). To what extent these mediators might have been affected by IL-11 is of significant interest because they, in turn, may induce eosinophil chemotaxis and degranulation, which could contribute to the development of airway inflammation and wheezing.

In conclusion, asthma enhanced IL-11 production in RSV infection, rather than IFAV infection, in early childhood. There was a trend towards greater IL-6 production in RSV infection compared with IFAV infection, and asthma has a role of decreasing the IFN- γ production in upper airway epithelium. However, the possible role of IL-8 and IFN- γ in the mechanism of RSV and IFAV infection-induced inflammation, especially in asthma, is less clear. Nevertheless, our data could support a model of different contributions of RSV and IFAV to the pathogenesis of upper airway diseases in children.

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