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SINUS AND ADENOID INFLAMMATION IN CHILDREN WITH CHRONIC RHINOSINUSITIS AND ASTHMA

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INTRODUCTION

Chronic rhinosinusitis (CRS) and asthma frequently coexist in both children and adults. It has been reported that 27% of a series of pediatric patients admitted with status asthmaticus had radiologic evidence of sinusitis ^{1, 2}, while in another study 61 of 128 asthmatic children had evidence of rhinosinusitis on endoscopic examination ³. Fewer studies have investigated whether asthma affects the upper airways. Our group has shown previously that children with asthma have worse surgical outcomes after sinus surgery and/or adenoidectomy compared to non-asthmatic children ⁴. Similarly, asthmatic adults undergoing endoscopic sinus surgery (ESS) for CRS have worse surgical outcomes compared to nonasthmatic controls ^{5, 6}.

The epidemiologic link between CRS and asthma has been confirmed by pathophysiologic and therapeutic observations. Histologic studies have shown mast cells and eosinophils both in the nasal mucosa of individuals with allergic rhinitis and in the bronchial mucosa of asthmatics ⁷⁻⁹, and the exposure of patients with rhinitis to specific allergens triggers

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eosinophilic infiltration into both nasal and bronchial mucosa^{2, 10}. Furthermore, several studies have shown that medical management of CRS improves asthma symptoms and lung function^{2, 11-14}, and that surgical management improves asthma symptoms and reduces emergency visits in children with both diseases¹⁵.

Despite this body of work, the precise interaction between asthma and CRS is still poorly understood, especially in children. This is due primarily to the lack of direct measurements of mucosal inflammation comparing the upper airways of non-asthmatic vs. asthmatic children, as most patients are managed medically and do not require surgery. Thus, the primary purpose of the present study was to fill this void by analyzing the expression of a large array of inflammatory cytokines and chemokines in the sinus and adenoid tissues surgically removed from pediatric subjects with CRS refractory to medical management, in comparison with control subjects without upper or lower airway disease.

Furthermore, by defining quantitative and qualitative differences in cytokine expression associated to the coexistence of asthma and CRS in children, we sought to gain a better understanding of the clinical relationship between these highly common pathological conditions and possibly help in the interpretation of clinical trials and in the choice of more targeted therapeutic strategies.

METHODS

A total of 38 children 2 to 12 years of age were included in this prospective, non-randomized study. Twenty-eight children had CRS resistant to maximal medical management and underwent ESS at West Virginia University between March 2010 and September 2011. Surgery involved maxillary sinus lavage, balloon maxillary antrostomy, maxillary antrostomy, or maxillary antrostomy with anterior ethmoidectomy. When indicated, ESS was combined with adenoidectomy. An adenoidectomy was performed on children with CRS based on evidence that adenoids act as a bacterial reservoir in these children and removing the adenoids improved outcomes.⁴ All CRS patients underwent CT scan of the sinuses to confirm the diagnosis of sinusitis and received maximal medical therapy including a 3-week course of antibiotics, topical nasal saline sprays and topical nasal steroid sprays. Exclusion criteria included a diagnosis of cystic fibrosis, congenital syndromes, ciliary dyskinesia, invasive fungal sinusitis, immunodeficiency, and trauma to the affected sinuses. Parental consent and child assent were required to enter this study and the West Virginia University Institutional Review Board approved the experimental protocol.

The control group included 10 children whose parents signed informed consent for tonsillectomy and adenoidectomy as well as biopsy of sinus tissue for pathologies other than CRS, including recurrent streptococcal pharyngitis and adenotonsillar hypertrophy. These patients did not have CT scan to document absence of CRS, as it would have been unethical to expose them to x-rays. Instead, all parents completed a preoperative sino-nasal symptoms score questionnaire (SN-5) and patients were excluded from the control group if their SN-5 score was >3.5. SN-5 is a validated symptom score questionnaire for the evaluation of CRS in children that consists of five domains: infection symptoms, nasal obstruction, allergy

symptoms, emotional distress, and activity limitations¹⁶. The SN-5 score was found to highly correlate with CT scan diagnosis of sinusitis in children, with a score of >3.5 being highly indicative of true sinus disease.¹⁶

Demographic and historical data recorded from all subjects included age, sex, history of previous adenoidectomy, and nasal steroid use. Diagnosis of asthma was based on the guidelines published by the Global Initiative for Asthma (GINA), using medical history and spirometry data interpreted by a board-certified pediatric pulmonologist. Specific serum IgE levels were measured by ImmunoCAP® Fluorezyme Immunoassay (FEIA, level of >0.35 kU/L was considered positive) or a standard prick skin test for aeroallergens was used to confirm a diagnosis of allergic rhinitis.

Sinus tissue samples were removed from the middle meatus region under endoscopic guidance using a biting or cutting forceps. Adenoid tissue was removed via the oropharynx with a biting or cutting forceps prior to adenoidectomy. All specimen were immediately snap frozen with liquid nitrogen and then stored at -80°C. Each sample was homogenized in 1X protein lysis buffer, homogenized twice for 30 s each, and centrifuged to remove debris.

Mucosal expression of inflammatory cytokines and chemokines was measured using the Luminex™ 100 System (Luminex, Austin, TX) and a Milliplex kit (Millipore, Billerica, MA) following the manufacturer's specifications. Each mediator was normalized to total protein tissue content measured with the Precision Red Advanced Protein Assay (Cytoskeleton, Denver, CO). The 40 cytokines and chemokines tested included: EGF, eotaxin, FGF-2, Flt-3 ligand, fractalkine, G-CSF, GM-CSF, GRO, IL-10, IL-12 (p40), IL-12(p70), IL-13, IL-15, IL-17, IL-1 α , IL-1 β , IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, INF- α 2, INF- γ , IP-10, MCP-1, MCP-3, MDC, MIP-1 α , MIP-1 β , PDGF-AA, PDGF-AB/BB, RANTES, sCD40L, sIL-2Ra, TGF- α , TNF- α , TNF- β , and VEGF.

Data were analyzed using the Student's t-test for continuous variables or the Chi-Square test for nominal variables. Differences with a p-value <0.05 were considered statistically significant.

RESULTS

The 10 control subjects did not have CRS (based on clinical score), asthma, or allergic rhinitis. Their average age was 4.5 years and 7 of them were female (Table 1). Four of them were being treated with nasal steroids at the time of surgery in an attempt to reduce the swelling of the adenoids. There was no statistically significant difference between demographic and clinical data obtained from the control subjects compared with 10 patients diagnosed with CRS only (i.e., without asthma or allergic rhinitis), except for the lower average SN-5 clinical score (p<0.0001).

Twenty-three of the 28 children with CRS resistant to maximal medical management also underwent adenoidectomy, and 11 of them (48%) had had a previous adenoidectomy (Table 2). Fifteen patients (54%) had asthma and 8 (29%) had allergic rhinitis. Eleven patients (39%) were female and average age at time of surgery of 6.6 years. Eighteen patients (64%) were taking a nasal steroid at the time of surgery for an average duration of 3 months. The

average SN-5 score was 4.59. There was no significant difference in sex, age, history of previous adenoidectomy, SN-5 score, or diagnosis of allergic rhinitis between the asthmatic and non-asthmatic groups. However, twice as many patients with CRS and asthma were treated with nasal steroids compared to CRS patients without asthma, and this difference was close to statistical significance ($p = 0.06$).

When sinus tissue of control patients was compared to sinus tissue of children with CRS, but no asthma or allergic rhinitis, 34 of the 40 inflammatory cytokines tested were increased in the CRS group (Figure 1), and the difference was significantly different for 7 cytokines, including TNF- β ($p=0.046$), MCP-3 ($p=0.042$), IL-7 ($p=0.023$), IL-12(p70) ($p=0.015$), IL-12(p40) ($p=0.044$), Flt-3 ligand ($p=0.007$), and EGF ($p=0.033$). Similarly, when adenoid tissue of control patients was compared to adenoid tissue of children with CRS, but no asthma or allergic rhinitis, 36 of the 40 cytokines tested were increased in the CRS group (Figure 2), and the difference was statistically significant for 16 of these cytokines, including VEGF ($p=0.018$), TNF- β ($p=0.028$), MCP-3 ($p=0.027$), INF- γ ($p=0.041$), IL-6 ($p=0.024$), IL-5 ($p=0.006$), IL-15 ($p=0.0007$), IL-12 (p70) ($p=0.003$), RANTES ($p=0.008$), PDGF-AB/BB ($p=0.036$), MIP-1 β ($p=0.028$), MDC ($p=0.033$), GRO ($p=0.023$), fractalkine ($p=0.014$), Flt-3 ligand ($p=0.0007$), and FGF-2 ($p=0.012$).

When compared to non-asthmatic children with CRS, the sinus tissue of asthmatic children with CRS showed increased levels for 27 of the 40 inflammatory cytokines tested (Figure 3), but the increase was statistically significant only for TNF- β ($p=0.009$). In the adenoid tissue, 39 of the 40 cytokines tested were higher in asthmatic children compared to non-asthmatic children (Figure 4), and the increase was statistically significant for 5 of these, including EGF ($p=0.018$), eotaxin ($p=0.037$), FGF-2 ($p=0.013$), GRO ($p=0.037$), and PDGFAA ($p=0.049$).

Table 3 summarizes the statistical significance of the differences of cytokine expression in sinus tissue measured between the control group and the CRS-only group (i.e., no asthma or allergic rhinitis) and between the asthmatic and non-asthmatic CRS groups. All cytokines that were significantly increased in the CRS-only group compared to the control group were also increased in the asthmatic CRS group compared to the non-asthmatic CRS group. TNF- β was the only cytokine that was significantly increased in the asthmatic CRS group compared to the non-asthmatic CRS group, and was also significantly increased in the CRS-only group compared to the control group.

Table 4 summarizes the statistical significance of the differences of cytokine expression in adenoid tissue measured between the control group and the CRS-only group (i.e., no asthma or allergic rhinitis) and between the asthmatic and non-asthmatic CRS groups. Fifteen of 16 cytokines that were significantly increased in the CRS-only group compared to the control group were also increased in the asthmatic CRS group compared to the nonasthmatic CRS group. FGF-2 and GRO were significantly increased in both the CRS-only group compared to the control group and in the asthmatic CRS group compared to the nonasthmatic CRS group. Fractalkine and IL-12(p70) were significantly increased in the CRS-only group compared to the control group and approached significance in the asthmatic CRS group compared to the non-asthmatic CRS group.

DISCUSSION

This study shows that the inflammatory response in the sinus and adenoid tissues of children with CRS is qualitatively similar but quantitatively amplified in the setting of a concomitant diagnosis of asthma. Specifically, the cytokines and chemokines that were significantly increased in the CRS-only (i.e., no asthma or allergic rhinitis) group compared to the control group were almost universally expressed at higher levels in the asthmatic CRS group compared to the non-asthmatic CRS group. While this evidence is consistent with previous epidemiologic and clinical observations^{17, 18} our study is the first confirming this pathophysiological model with direct measurement of mucosal inflammation in children.

In the sinus tissue, TNF- β was the only cytokine whose increase reached statistical significance in the asthmatic CRS group compared to the non-asthmatic CRS group. This cytokine was also significantly increased in the CRS-only group compared to the control group. In the adenoid tissue, FGF-2 and GRO were significantly increased in both the CRS-only group compared to the control group and in the asthmatic CRS group compared to the non-asthmatic CRS group. Fractalkine and IL-12(p70) were significantly increased in the CRS-only group compared to the control group and approached significance in the asthmatic CRS group compared to the non-asthmatic CRS group.

These inflammatory patterns can inform the future use of specific cytokines as biomarkers, and also identify specific targets for biological therapies using humanized anti-cytokine antibodies. Indeed, the results of our study suggest that new therapeutic strategies are necessary, considering the strong inflammatory response found in the tissues of CRS patients with asthma despite the use of nasal steroids by most of them. As the bioavailability of nasal sprays is not effort- or maneuver-dependent, it is plausible that the sinus and adenoid tissues examined in this study had been exposed to significant concentrations of potent topical corticosteroids, raising some concern about the actual anti-inflammatory potency of these drugs *in vivo*. As the children included in this study had failed medical management, it is possible that they represent a distinct subpopulation with particularly severe inflammation or steroid resistance, or perhaps less compliant with therapy.

Furthermore, our data provide insight about the relationship between CRS and asthma. Specifically, our data support the hypothesis that children with asthma and CRS have a similar, but more severe form of the same inflammatory process as children with CRS but without asthma. It is possible that this pattern of cytokines expression is a manifestation of the “united airways” hypothesis, i.e., that the inflammatory process associated with atopy is homogeneous across contiguous upper and lower segments of the respiratory tract. But it is also possible that lower airway disease in patients with both CRS and asthma is driven, at least in part, by a more severe inflammatory process in the upper airway. This may be the result of postnasal secretions seeding the lower respiratory tract, or rather derive from the systemic absorption of inflammatory mediators synthesized in the upper airways. More likely, a neurogenic link based on cholinergic-mediated naso-sino-bronchial reflexes and/or noncholinergic, non-adrenergic axon reflexes fits best the pathophysiological models developed in animals and other experimental systems. In all scenarios outlined above, the

present data strongly support the practice of aggressively treating sinus disease in children with asthma in order to achieve better or full control of asthma symptoms.

Among the limitations of this study, the most important is the relatively small sample size. However, the collection of samples in a pediatric population is always problematic, especially when the samples need to be obtained from asymptomatic controls. Although it is likely that a larger sample size would increase the number of differences reaching statistical significance, power analysis suggests that this would be prohibitive in terms of time and costs. One limitation directly related to the small sample size is the inability to determine the potential influence of allergen sensitization and exposure on the cytokine levels. The same is true for the use of topical corticosteroids, which have been shown to significantly reduce adenoid tissue^{19,20} and treat the rhinosinusitis²⁰. We could have observed significant statistical differences had we obtained the samples after a period of washout of topical steroids. However, this would have been unethical. Randomization would have contributed to the quality of the study, but it would have also prevented access of part of the patients with severe symptoms to therapies proven to be effective. Finally, the SN-5 score used to exclude CRS in control patients is not as accurate as a CT scan of the sinuses, but it would have been unethical to irradiate asymptomatic children.

Compared to CRS children without asthma, CRS children with asthma had significantly higher sinus levels of TNF- β and adenoid levels of EGF, eotaxin, FGF-2, GRO, and PDGF-AA. Although, to our knowledge, TNF-beta expression has not been studied in sinus or adenoid tissues in CRS or asthma, there have been reports demonstrating high prevalence of TNF-beta polymorphisms in chronic sinusitis²¹ and in asthma²². A recent study demonstrated increased T-cell activation markers in the adenoids of children with CRS. This study also showed that CRS severity was associated with the levels of activated cells and cytokines in adenoid tissues²³. Therefore, our findings suggest that TNF-beta may be one of the major players in the mechanism of CRS and asthma. However, more studies are needed to explore this possibility.

The current investigation did not permit the precise identification of the cellular origin or role in pathogenesis of these cytokines. Such investigations would be complicated by the well-known cytokine characteristics of redundancy and pleiotropy (multiple cell sources, ability to exert more than one action, often on multiple cell types). Therefore, confirmation of a causal role for any of these cytokines in pathophysiology will require the conduct of a controlled clinical trial using a specific blocking agent. Not surprisingly, these cytokines are involved in stimulation of cell growth, proliferation, and differentiation, and a number of key processes linked with allergy and asthma, such as chemo-attraction of inflammatory cells (e.g. eosinophils) and tissue remodeling^{24,25}. Also, more differences were observed in the adenoids compared to the sinuses, perhaps reflecting the major role of the adenoids in regulating immune function.

Our research focused on sinus and adenoid tissue in children, but other investigators have conducted studies in children with otitis media²⁶⁻²⁹. A recent study demonstrated higher IL-5 and TNF- α production in stimulated cells from hypertrophic adenoids of pediatric patients with otitis media with effusion (OME) than in children without OME²⁹. Sobol et

al²⁶ assessed middle ear fluids for cells by immunocytochemistry and for expression of cytokines by in situ hybridization in twenty-six patients with otitis media with effusion undergoing myringotomy and ventilation tube placement. Compared to non-atopic children, there was a predominance of eosinophils, T lymphocytes, and T(H)2 mediators (IL-4 and IL-5) in the middle-ear effusions of atopic children. In a follow-up study using middle ear biopsy specimens from 7 children with persistent otitis media with effusion and 7 controls²⁷, there were statistically significant increases in the expression of CD3, major basic protein, and IL-5 in the atopic population. Our study also assessed IL-5 and there were significant differences between CRS-only and controls in adenoid tissue (Table 4), but not between CRS-with versus without asthma and not in sinus tissue.

In summary, our data show that the inflammatory response in the upper airway mucosa of asthmatic children with CRS is similar, but more severe, compared to that of nonasthmatic children with CRS. This observation is consistent with the hypothesis that asthma in these patients is caused or exacerbated by severe upper airway disease, and may provide a basis for the observation that asthmatic children are at risk for worse surgical outcomes after sinus surgery and/or adenoidectomy compared to non-asthmatic children⁴. Our findings support the concept that treating sinus disease is paramount in the management of chronic asthma in children. In addition, this study provides specific and direct information on inflammatory profiles critical for the future validation of biomarkers and identification of targets for biological therapies of pediatric CRS and asthma.

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Figure 1.

Expression of inflammatory cytokines and chemokines in sinus tissue of children with chronic rhinosinusitis (CRS) only (i.e., without asthma or allergic rhinitis) vs. control children without CRS, asthma, or allergic rhinitis. Seven of the cytokines tested were significantly increased in the CRS group (marked in red). Data are mean concentrations in ng per μg of total tissue protein. *p<0.05; **p<0.01 = significantly different from control.

Figure 2.

Expression of inflammatory cytokines and chemokines in adenoid tissue of children with CRS only (i.e., without asthma or allergic rhinitis) vs. controls without CRS, asthma, or allergic rhinitis. Sixteen of the cytokines tested were significantly increased in the CRS group (marked in red). Data are mean cytokine concentrations in ng per μg of total tissue protein. *p<0.05; **p<0.01; ***p<0.001 = significantly different from control.

Figure 3.

Expression of inflammatory cytokines and chemokines in sinus tissue of children with CRS and asthma vs. children with CRS without asthma. Only TNF-β was significantly increased in asthmatic children (marked in red). Data are mean cytokine concentrations in ng per μg of total tissue protein. **p<0.01 = significantly different from children with CRS without asthma.

Figure 4.

Expression of inflammatory cytokines and chemokines in adenoid tissue of children with CRS and asthma vs. children with CRS without asthma. Five of the cytokines tested were significantly increased in asthmatic children (marked in red). Data are mean cytokine concentrations in ng per μg of total tissue protein. * $p < 0.05$ = significantly different from children with CRS without asthma.

Table 1

Comparison of demographic and clinical data of control subjects (no CRS, asthma or allergic rhinitis) vs. patients with chronic rhinosinusitis (CRS) only (without allergic rhinitis or asthma).

	Control (N = 10)	CRS-only (N = 10)	p-value
Female (%)	7 (70%)	5 (50%)	
Mean Age (years)	4.5	6.5	0.08
Nasal Steroid	4 (40%)	3 (30%)	0.65
Revision Adenoidectomy	0 (0%)	2 (20%)	0.14
Mean SN-5 score	2.02	4.33	<0.0001
Allergic Rhinitis	0 (0%)	0 (0%)	0
Asthma	0 (0%)	0 (0%)	0

Table 2

Comparison of demographic and clinical data of patients with chronic rhinosinusitis with vs. without asthma.

	Asthma (N = 15)	No-Asthma (N = 13)	p-value
Female (%)	5 (33%)	6 (46%)	
Mean Age (years)	6.87	6.38	0.67
Nasal Steroid	12 (80%)	6 (46%)	0.06
Revision Adenoidectomy	7 (47%)	4 (31%)	0.39
Mean SN-5 score	4.77	4.34	0.23
Allergic Rhinitis	5 (33%)	3 (23%)	0.59

Table 3

Summary of statistical significance of the differences in cytokines and chemokines expression in sinus tissue.

	CRS-only vs. Controls	CRS with vs. without asthma
EGF	p=0.0325	p=0.1466
Flt-3 ligand	p=0.0072	p=0.1212
IL-12(p40)	p=0.0440	p=0.2547
IL-12(p70)	p=0.0151	p=0.2546
IL-7	p=0.0233	p=0.2210
MCP-3	p=0.0417	p=0.3128
TNF- β	p=0.0455	p=0.0095

Note: Statistically significant differences ($p < 0.05$) are marked in **bold**.

Table 4

Summary of statistical significance of the differences in cytokines and chemokines expression in adenoid tissue.

	CRS-only vs. Controls	CRS with vs. without asthma
FGF-2	p=0.0121	p=0.0133
Flt-3 ligand	p=0.0007	p=0.4566
Fractalkine	p=0.0141	p=0.0581
GRO	p=0.0227	p=0.0368
IL-12(p70)	p=0.0029	p=0.0676
IL-15	p=0.0007	p=0.5948
INF- γ	p=0.0409	p=0.3711
MCP-3	p=0.0266	p=0.1770
MDC	p=0.0328	p=0.2602
MIP-1 β	p=0.0275	p=0.2318
PDGF-AB/BB	p=0.0356	p=0.6515
RANTES	p=0.0082	p=0.7540
TNF- β	p=0.0282	p=0.2674
VEGF	p=0.0175	p=0.7050
IL-5	p=0.0063	p=0.4207
IL-6	p=0.0243	p=0.3437
EGF	p=0.0000	p=0.0183
Eotaxin	p=0.0891	p=0.0368
PDGF-AA	p=0.4355	p=0.0493

Note: Statistically significant differences ($p < 0.05$) are marked in **bold**.