sample size of 23 children. Although preoperative survey results are used for comparison in each child, there is no control group. Ideally, the same survey would be given to a group of children/parents with sinusitis treated without surgery, to assess the effects of natural history or nonsurgical therapy. Comparison with this control group would more fully quantify the benefits of surgery. It is not clear how these 27 children were selected for study. Were they part of a larger surgical group, with some patients excluded from study? Was this a series of consecutive patients undergoing FESS for defined surgical indications? These issues affect how we can generalize the conclusions of this report. It is unlikely that we will see a randomized, prospective trial of FESS in children. Outcome studies such as this one, measuring symptom scores and quality of life changes, give support for the use of FESS in children with refractory sinus disease.

Austin S. Rose, MD
David E. Tunkel, MD
Baltimore, MD

Correlation Between Presumed Sinusitis-Induced Pain and Paranasal Sinus Computed Tomographic Findings


Purpose of the Study. Sinusitis is typically a clinical diagnosis based on history and symptoms. This study investigated the correlation between clinical symptoms of facial and/or head pain and actual localized findings consistent with a sinusitis on sinus computed tomographic (CT) imaging.

Study Population. Two hundred patients with a clinical history of sinusitis that were referred by their internist or otolaryngologist for CT imaging of the paranasal sinuses.

Methods. Before the CT scanning, each patient was asked to complete a sinus questionnaire that inquired about pain in 8 different areas of the head and neck, the duration of illness, use of allergy medications, smoking, pets, and seasonal variation of pain symptoms. All CT scans were independently scored by 3 radiologists who were blinded to the patients’ questionnaire responses. The scores were then averaged.

Results. Eighty-two percent reported having some form of facial pain or headache; the right temple/forehead was the most commonly reported site. Six percent were considered to have acute sinusitis, 14% had a history of sinus surgery, 12% were smokers, and 55% owned pets. Nine percent had no abnormalities on the CT scan. The maxillary sinus was the most frequently (68%) involved sinus. No correlation could be found between the reported sites of pain and findings on CT. Furthermore, no relationships were found between the sinus CT findings and smoking, owning a pet, or duration of pain symptoms. Similar numbers of sites of pain (5.45 and 5.88) were reported between patients with and without CT findings.

Conclusions. This study demonstrated that there was a lack of correlation between reported site of pain and CT findings. Two key points the author stated are 1) symptoms of pain alone may not be sufficient to diagnose sinusitis and 2) the limited value of CT scans for evaluating patients with facial pain/headaches only or patients with a low suspicion for sinusitis.

Reviewers’ Comments. Most clinical diagnoses of sinusitis involve more than facial pain or headache alone. The diagnosis is based on a compilation of symptoms that may include fever, facial swelling/tenderness, purulent drainage, cough, malodorous breath, and nasal congestion. It is not clear that these patients had more than facial pain alone, which would not be sufficient for clinical diagnosis. Although these patients were referred by internists and otolaryngologists for imaging of their paranasal sinuses, the specific indications for the CT scan are not clear. For example, CT scans may have been ordered after antibiotic treatment to rule out structural abnormalities. Overall, this article does make an important point that facial pain does not equate with sinus disease.

Sally H. Joo, MD
Robert A. Wood, MD
Baltimore, MD

Asthma

Pathophysiology

Viral Induction of a Chronic Asthma Phenotype and Genetic Segregation From the Acute Response


Purpose of Study. To address the role of persistent infection and cytokine bias in the development of the chronic asthma phenotype after paramyxoviral infection.

Methods. The investigators used a mouse model of paramyxoviral bronchiolitis with acute pathology similar to the human condition. Wild-type C57BL/6J, same-strain interferon gamma (IFN-γ)-null mice and same-strain interleukin-1 (IL-1)–null mice were maintained under pathogen-free conditions for study at 7 to 9 weeks of age. Mice were inoculated with mouse parainfluenza virus type 1 (Sendai virus; SeV Fushimi strain) or ultraviolet (UV)-inactivated SeV. Histology of the mouse lung, bronchoalveolar lavage fluid analysis, and airway reactivity measurements to aerosolized methacholine were performed. In addition, allergen challenges were performed with ovalbumin using sensitized and nonsensitized C57BL/6J mice.

Results. Following a single paramyxoviral infection of mice (C57BL6/J strain), the investigators demonstrate that not only does this produce acute bronchiolitis, but also a chronic lung response with airway hyperreactivity and goblet cell hyperplasia lasting at least 1 year after complete viral clearance. During the acute response to virus, same-strain ICAM-1-null mice are protected from airway inflammation and hyperreactivity despite similar viral infections; however, the chronic response proceeds despite ICAM-1 deficiency. Neither response is influenced by IFN-γ deficiency, but the chronic response is at least partially prevented by glucocorticoid treatment. In contrast to viral infection, allergen challenge caused only short-term expression of asthma phenotypes.

Conclusions. Paramyxoviruses cause both acute airway inflammation/hyperreactivity and chronic airway remodeling/hyperreactivity phenotypes. These 2 phenotypes can be segregated by their dependence on the ICAM-1 gene and so depend on distinct controls that appear critical for the development of lifelong airway diseases such as asthma. These findings raise the possibility that asthma not only resembles a persistent antiviral response, but also may be caused by such a response. These data may help
provide a link between paramyxoviral infections in infancy with subsequent asthma in later in life.

**Reviewer’s Comments.** This is a very provocative study that strikes at the core of the ongoing debate regarding the specific role of acute viral lower respiratory tract illnesses and the predisposition to chronic asthma. Previous investigations have demonstrated that paramyxoviral infections and asthma may activate a network of epithelial immune-response genes that are part of the innate immune response. The current investigation provides strong evidence to support this concept and provides new insight into how paramyxoviral infections may lead to chronic airway changes in structure and function, which are typical of asthma. Additional studies will be needed to identify the genes responsible for epithelial remodeling and chronic hyperresponsiveness in response to this type of viral infection. Furthermore, additional investigation will be needed to confirm and further elucidate this type of a viral pathway, which is distinct from an allergen-driven pathway that may lead to chronic airway dysfunction manifested in asthma.

**John James, MD**  
Fort Collins, CO

**ASSOCIATION OF THE ADAM33 GENE WITH ASTHMA AND BRONCHIAL HYPERRESPONSIVENESS**


*Purpose of the Study.* To identify novel genetic polymorphisms associated with bronchial hyperresponsiveness (BHR) in asthma.

*Study Population.* Four hundred sixty white affected sib-pair families from the United States and the United Kingdom with current asthma.

*Methods.* A genetic linkage analysis was performed for current asthma and BHR. Case-control, transmission disequilibrium, and haplotype analyses were conducted to identify the gene(s) most commonly associated with asthma. Novel genes of interest were identified by a combination of public data mining, complementary DNA (cDNA) library screening, direct cDNA selection, and reverse transcriptase-polymerase chain reaction (RT-PCR).

*Results.* Positional cloning revealed a novel genomic region of interest on chromosome 20p13. Ultimately, polymorphisms in the ADAM33 gene were linked to asthma and BHR. ADAM 33 is a complex metalloproteinase with numerous diverse functions that is expressed in lung fibroblasts and bronchial smooth muscle, but not bronchial epithelial cells. The alleles in ADAM 33 that were associated with an increased susceptibility to asthma were common, ranging from 20% to 95%.

*Conclusions.* Allelic variation in the ADAM33 gene may underlie lower airways dysfunction in asthma, including BHR and airway remodeling.

**Reviewers’ Comments.** What are the genetic predispositions to asthma? In this study, current asthma and BHR were linked to a new category of molecules. ADAM proteins are a subfamily of matrix metalloproteinases. They have diverse posttranslational cellular functions, capable of regulating myogenic fusion, proteolysis, cell adhesion, and cell signaling. Their proteolytic functions include the shedding of cell-surface cytokine and cytokine receptors that are involved in inflammation, cell proliferation, and cell death. How the linkage of the ADAM33 gene to asthma and BHR and its expression in human lung fibroblasts and bronchial smooth muscle relates to asthma is not clear. It is speculated that ADAM33 expression may be a primary cause of fibroblast proliferation, and their differentiation into myofibroblasts and smooth muscle, leading to subepithelial fibrosis, smooth muscle hyperplasia and increased matrix deposition, underlying BHR, and airway remodeling. For more information on this subject, please see a brief editorial, titled “Inherit the Wheeze” by Drazen and Weiss, that accompanies this article on pages 383–384 of the same issue, and a review article, titled “ADAM-33 Surfaces as an Asthma Gene,” by Shapiro and Owen in the New England Journal of Medicine (2002;347:936–938).

**Akaluck Thatayatikom, MD**  
Andrew H. Liu, MD  
Denver, CO

**SEQUENCE VARIANCE IN THE FceRI ALPHA CHAIN GENE**


*Purpose of Study.* A known relationship exists between immunoglobulin E (IgE) levels and expression of high-affinity IgE receptors (FceRI). Sequence variants in the IgE-binding alpha chain of FceRI, which may affect IgE binding, were examined in asthmatic and nonasthmatic subjects to look for a relationship to IgE levels.

*Study Population.* The study subjects were 389 patients with asthma treated only with inhaled albuterol and with an average forced expiratory volume in 1 second (FEV1) of 62.3% of predicted, and 341 patients without a history of asthma or atopy by questionnaire.

*Methods.* DNA was extracted from peripheral blood and screened for mutations in the core promoter and exons of the FceRI alpha chain gene by single-strand conformational polymorphism using radiolabelled primers. The most common site of polymorphism, the T/C −335 locus, was genotyped by restriction fragment length polymorphism. For stratification analysis, subjects were genotyped at 40 unlinked candidate single nucleotide polymorphisms, selected from a database. IgE levels were measured for each subject. For subjects in the highest and lowest quartile of IgE, stratification analysis was performed to look for genetic polymorphisms occurring at high or low frequency.

*Results.* Three single nucleotide polymorphisms were detected in the 5’ flanking region of the FceRI alpha chain gene, although no variants were detected in the gene itself. The most common was a T/C translocation at −335 base-pairs before the translational start site, whose frequency differed significantly between whites and blacks (P < 0.001). In the entire cohort of white asthmatic patients, the T/C translocation was not associated with IgE levels, but a lower proportion of the CC genotype was found in whites in the highest quartile of IgE. In black asthmatics, the same trend was not observed.

*Conclusions.* Homozygosity for the C allele at locus −335 of the IgE-binding alpha chain of FceRI may lead to lower IgE binding.

**Reviewers’ Comments.** This study population may have been biased toward milder or undertreated asthmatics, because no patients on medications other than inhaled albuterol met the selection criteria. Although this study suggests a possible connection between IgE levels and T/C translocation at the −335 locus of the FceRI alpha chain promoter region, the overall lack of association between the IgE level and CC genotype at this locus raises additional questions about the relationship of this translocation to IgE binding. Future studies including a more represen-
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John James

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