RESULTS. Twenty-eight percent of participants had vitamin D levels of <30 ng/mL, which is the lower limit of the normal range. Each 1-log unit increase in vitamin D level was associated with decreased odds of any hospitalization in the past year (odds ratio [OR]: 0.05 [95% confidence interval [CI]: 0.004–0.71]), use of inhaled corticosteroids and/or leukotriene inhibitors in the past year (OR: 0.18 [95% CI: 0.05–0.67]), and increased airway hyperresponsiveness (OR: 0.15 [95% CI: 0.024–0.097]). In multivariate analysis, increasing serum levels of vitamin D were associated with lower total serum IgE levels, peripheral eosinophil counts, and dust mite–specific IgE levels.

CONCLUSIONS. Vitamin D deficiency is relatively frequent in Costa Rican children, and lower levels are associated with increased markers of allergy and asthma severity.

REVIEWER COMMENTS. Maternal vitamin D intake during pregnancy has been inversely associated with asthma symptoms in early childhood. However, no study has examined the relationship between measured vitamin D levels and markers of asthma severity in childhood. This study found an association between reduced vitamin D levels and increased markers of allergy and asthma severity in a population of Costa Rican children with asthma. Additional study of this topic using an unscreened birth cohort, a case-control approach, or a clinical trial of vitamin D supplementation would be a preferable next step. Also of note, although the authors used the current standard “normal” lower threshold to define vitamin D deficiency, there is substantial debate about what the appropriate lower limit should be.

TH17 Cells Mediate Steroid-Resistant Airway Inflammation and Airway Hyperresponsiveness in Mice


PURPOSE OF THE STUDY. To investigate the function of T-helper 17 (TH17) cells in the context of antigen-induced airway inflammation.

METHODS. The authors examined the role of TH17 cells in asthma by using a mouse model in which severe combined immunodeficient (SCID) mice were challenged with ovalbumin. On day 0, ovalbumin-specific TH2 or TH17 cells were adoptively transferred into the SCID mice. The SCID mice were challenged with ovalbumin for 3 consecutive days after cell transfer. Mice were treated with dexamethasone or phosphate-buffered saline (control) before cell transfer on day 0 and before ovalbumin challenge on day 2. In a separate experiment, wild-type mice and interleukin 17 (IL-17) receptor-null mice underwent the same protocol.

RESULTS. Transfer of ovalbumin-specific TH2 or TH17 cells into the SCID mice, followed by ovalbumin challenge, resulted in specific cellular influx into the airways and airway hyperreactivity (AHR). TH2 cell reconstitution resulted in airway inflammation that consisted mostly of eosinophils and lymphocytes and was sensitive to dexamethasone. TH17 cell reconstitution resulted in a primarily neutrophilic airway response that was resistant to dexamethasone. Adoptive transfer of ovalbumin-specific TH2 or TH17 cells, followed by ovalbumin challenge, resulted in AHR in both cases, but the AHR was sensitive to dexamethasone in the mice reconstituted with TH2 cells and not in the mice reconstituted with TH17 cells. The inflammatory and cellular responses associated with TH17 cell transfer were mediated primarily by IL-17, because IL-17 receptor-knockout mice did not develop airway neutrophilia after adoptive transfer of ovalbumin-specific TH17 cells, followed by ovalbumin challenge.

CONCLUSIONS. Reconstitution of SCID mice with TH17 cells in a model of antigen-induced airway inflammation leads to airway neutrophilia and AHR. TH17 cell–mediated neutrophil influx into the airways and AHR are resistant to dexamethasone treatment.

REVIEWERS COMMENTS. Asthma is a significant cause of morbidity and death in the pediatric population, and steroid-resistant asthma is a particularly challenging asthma phenotype to manage. This study provides insight into a possible mechanism of steroid-resistant asthma, involving neutrophil recruitment into the lung tissues by TH17 cells in an IL-17–dependent pathway. Future research should be directed at determining whether the findings in this mouse model are applicable to humans and identifying patients with this asthma phenotype. If these findings prove applicable to humans, then TH17 cell– and IL-17–specific therapies may prove useful for patients with steroid-resistant asthma.

DIAGNOSIS AND MANAGEMENT

Wheezing and Bronchial Hyper-responsiveness in Early Childhood as Predictors of Newly Diagnosed Asthma in Early Adulthood: A Longitudinal Birth-Cohort Study

PURPOSE OF THE STUDY. To estimate the contributions of gender and early life factors to newly diagnosed and persistent asthma in young adults.

STUDY POPULATION. The study evaluated 849 enrollees of the Tucson Children’s Respiratory Study who had adult data at 22 years of age.

METHODS. The cohort was derived from all healthy infants born in Tucson, Arizona, between 1980 and 1984. Shortly after birth, the parents completed a questionnaire on demographic data and were instructed to see a collaborating pediatrician at the first sign of lower respiratory illness. Physician-diagnosed asthma or wheezing was assessed at 2, 3, 6, 8, 11, and 16 years of age. At 6 years of age, allergy skin-prick tests were performed for all participants, and cold air bronchial challenge was performed for participants with a history of lower respiratory illness. At 22 years of age, an in-depth evaluation was performed with questionnaires on asthma symptoms, asthma medication use, and smoking history. Allergy skin-prick tests and spirometry were performed for participants still living in the Tucson area.

RESULTS. Subjects with adult data at 22 years of age were more likely to have nonsmoking, nonminority parents with higher levels of education than were those without adult data. Of the 849 participants, 255 (30%) had asthma diagnosed at some time in their lives, 181 (22%) had active asthma, and 224 (26%) reported current smoking. Participants with inactive asthma had pre- and postbronchodilator spirometry results comparable to those of participants who never had asthma. Participants with newly diagnosed asthma had lower forced expiratory volume in 1 second/forced vital capacity ratios, which were not bronchodilator responsive. Factors associated with newly diagnosed asthma, chronic asthma, or shortness of breath with wheezing at 22 years of age included female gender, parental asthma, late-onset (>3 years of age) wheeze, persistent wheeze, Alternaria mold sensitivity at 6 years of age, cold air bronchial hyperresponsiveness, and reduced air flow rates at 6 years of age. Seventy percent of participants with current asthma and 63% with newly diagnosed asthma reported episodes of wheeze before 6 years of age. Male gender was a significant indicator of asthma remission by early adulthood. The combination of Alternaria sensitivity and cold air bronchial hyperresponsiveness at age 6 years and persistent wheeze at age 6 years were strong predictors of chronic asthma at age 22 years.

CONCLUSIONS. Children with transient early wheezing were at much less risk for chronic asthma that persisted through childhood or reappeared more intensely in early adult life, compared with children with persistent or late-onset wheezing. Women were twice as likely to have new asthma diagnosed between 16 and 22 years of age.

PURPOSE OF THE STUDY. To identify symptoms and other factors that may be predictive of an asthma exacerbation in children 2 to 5 years of age.

STUDY POPULATION. Children 2 to 5 years of age who participated in a previous, double-blind, randomized, multicenter, parallel-group, placebo-controlled, 12-week study of 4 mg of monteleukast for the treatment of persistent asthma.

METHODS. A posthoc analysis was performed with data collected on 689 patients. Caregivers provided twice-daily answers in a validated, asthma-specific, diary record of daytime symptoms (cough, wheeze, difficulty breathing, and activity limitation), nighttime cough symptoms, β2-adrenergic receptor agonist use, and medical visits for worsening asthma. Scoring for daytime symptoms used a 6-point scale from 0 (no symptoms or limitations) through 5 (very severe symptoms or limitations) for every severe symptom or limitation) and scoring for nighttime cough used a 5-point scale from 0 (no nighttime cough) through 4 (coughed all night and disturbed the caregiver’s sleep). To identify the predictors of an exacerbation (worsening symptoms that led to oral corticosteroid use, an unscheduled visit to a physician or emergency department, or hospitalization), information was analyzed by using general estimating equations with an exchangeable, within-subject, log-rithmic odds ratio regression structure.

RESULTS. A total of 196 (28%) of the 689 patients enrolled had ≥1 asthma exacerbation during the study period, and 235 exacerbations occurred overall. Each of the
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