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Nasal epithelium injury by chlorination products and other stressors predicts persistent sensitization to aeroallergens in young schoolchildren

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ABSTRACT

Background: Allergic sensitization during childhood is a dynamic process with a substantial rate of remission. Factors influencing this process are largely unknown.

Methods: We conducted a two-year prospective study among 121 schoolchildren (mean age, 5.8 years; 64 boys). We measured urea, club cell protein (CC16), β_2-microglobulin and albumin in nasal lavage fluid (NALF) and IgE to cat, pollen or house dust mite (HDM) in nasal mucosa fluid.

Results: Odds of persistent sensitization to any aeroallergen increased across baseline ascending tertiles of urea-adjusted β_2-microglobulin or albumin and descending tertiles of albumin- or β_2-microglobulin-adjusted CC16 (*P*-trend = 0.006, 0.02, 0.044 and 0.006, respectively). Persistent HDM sensitization also increased with baseline descending tertiles of raw or urea-adjusted CC16 (both *P*-trend = 0.007). Such strong associations were not observed with new-onset or remitted sensitization to any aeroallergen or with raw NALF concentrations of urea, albumin or β_2-microglobulin. At baseline, house cleaning with bleach and chlorinated pool attendance emerged among the strongest and most consistent determinants of NALF biomarkers, being both associated with higher urea and lower CC16 in NALF.

Conclusion: In young children, a defective nasal epithelium attributable to immaturity or stressors such as chlorination products is predictive of more persistent aeroallergen sensitization.

1. Introduction

Since the 1970s, the prevalence of allergic diseases such as asthma and hay fever has dramatically increased in affluent societies, affecting up to one third of the population (Muraro et al., 2016). While considerable advances have been made in understanding the mechanisms of allergies, much less is known about factors driving the epidemic of allergies. Initially, it was hypothesized that allergies were the consequences of Western hygiene practices, which by reducing microbial exposure during early life would shift the immune system towards a Th2 dominant response (Strachan, 1989). A more recent hypothesis proposes that the rise of allergies is primarily due to epithelial barrier defects caused by changes in lifestyle or environment (Holgate, 2011). There is growing evidence indeed that airway epithelium alterations play a key role in the development of allergic diseases, contributing to both the allergic sensitization and its clinical expression (Lambrecht and Hammad, 2012). Studies of patients with asthma or allergic rhinitis have revealed a number of structural or functional defects of the airway epithelium, including increased tight junction permeability, airway wall remodelling, club cell loss and goblet cell metaplasia (Holgate et al., 2000; Fedorov et al., 2005, Kim et al., 2010; Steelant et al., 2016). According to the epithelial hypothesis, some of these defects could promote allergic diseases by facilitating the transepithelial delivery of allergens to dendritic cells and/or by decreasing the secretion of mediators such as the club cell protein (CC16) down-regulating the Th2 differentiation and the inflammatory response (Hung et al., 2004, Johansson et al., 2007; Tokita et al., 2014).

The major challenge for epidemiological studies testing the epithelial hypothesis is to assess non-invasively the airway epithelium integrity. One possible approach consists of measuring the serum concentrations of lung-specific proteins (also named pneumoproteins), which are biomarkers reflecting the structural or functional integrity of the pulmonary epithelium (Hermans and Bernard, 1998, 1999). When for ethical reasons it is not possible to collect blood (e.g. in schoolchildren), an alternative approach is to use epithelial biomarkers measurable in nasal lavage fluid (NALF) (Sardella et al., 2012, 2013). Studies using these peripheral airway biomarkers have shown that various stressors including air pollutants, strenuous exercise or

Abbreviations: Alb, albumin; β_2-m, β_2-microglobulin; CC16, club cell protein; CPs, chlorination products; CPA, cumulative pool attendance; ELF, epithelial lining fluid; eNO, exhaled nitric oxide; HDM, house dust mite; IQR, interquartile range; NALF, nasal lavage fluid; OR, odds ratio

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endotoxin can cause acute or chronic damage to the airway epithelial barriers (Broeckaert and Bernard, 2000; Lagerkvist et al., 2004, Nanson et al., 2001; Michel et al., 2005). Among these stressors, chlorination products (CPs) are of particular interest because these strong oxidants linked to the hygiene of the developed world are well-known for their capacity to breach tight junctions (Bernard, 2007). In addition, epidemiological evidence suggests that exposure to CPs in swimming pools, especially during early life, may increase the risk of allergic sensitization or diseases (Bernard et al., 2003, 2008; Bougault et al., 2012, Voisin et al., 2014; Andersson et al., 2015). Supporting these findings, recent biomarker studies among school adolescents or children have demonstrated that the disruption of airway epithelium by CPs correlated with the risk of allergic sensitization, especially to house dust mite (HDM), and among sensitized subjects, with the risk of developing asthma or hay fever (Sardella et al., 2012, 2013; Bernard et al., 2015a, 2015b).

However, because of their cross-sectional design, biomarker studies conducted until now cannot be used to infer a causal relationship between allergic sensitization and loss of epithelial barrier function associated with environmental stressors. The reason is that the impaired barrier function can be also the consequence of the sustained Th2-mediated inflammation and/or of the proteolytic activity of aeroallergens from pollen, fungi or HDM (Vinhas et al., 2011, Leino et al., 2013; Wan et al., 1999). In an attempt to resolve these issues, we prospectively investigated in young children the associations between nasal epithelium defects and the risks of new-onset or persistent sensitization to most common aeroallergens. We evaluated the integrity of the nasal epithelium by measuring in nasal lavage fluid (NALF) CC16 as a marker of cell damage/dysfunction and plasma-derived albumin and β_2-microglobulin (β_2-m) as markers of epithelial permeability.

2. Materials and methods

Study participants were children (53% boys, mean age at baseline 5.8 years) who were recruited and examined in 30 schools in Belgium. As described in detail elsewhere (Voisin et al., 2010), a total of 430 children participated in the baseline examination. Two years later, among the 310 children still in schools, 236 (78.1%) participated to the examination and of them 121 could successfully perform all the tests, both at baseline and at follow-up. The ethics committee of the faculty of medicine of the catholic university of Louvain approved the study protocol. Children were examined with the signed informed consent of parents and their oral assent at time of examination.

2.1. Questionnaire

We used a parent self-administered questionnaire to collect data about the child's medical history, environment and lifestyle. For swimming practice, the questionnaire included specific questions to calculate the cumulative hours the child had spent in indoor and/or outdoor chlorinated pools (CPA, cumulative pool attendance), over lifetime and over the two years preceding baseline examination. Parents were also asked whether their child had ever been diagnosed as having asthma, hay fever or perennial allergic rhinitis.

2.2. Samples collection and analyses

We examined children in their schools between 9:00 A.M. and 3:00 P.M. The protocol comprised the measurement of height, body weight and exhaled nitric oxide (eNO, NIOX analyser, Aerocrine AB, Solna, Sweden) and a screening of specific IgE to cat dander, house-dust mite and grass (*anthoxantum odoratum*), weeds (*Parietaria officinalis*) or tree (*betula odorosa, Corylus avellana, Carpinus betulus, Alnus incana*) pollen. These specific IgE were measured in nasal mucosa fluid using the Rhinostick test, a non-invasive method with a similar sensitivity but a greater specificity than skin-prick tests (Marcucci et al., 2004). The Rhinostick test was calibrated with serum standards and considered positive at specific IgE $\geq$ 0.35 kIU/L. As described elsewhere (Sardella et al., 2012), NALF was collected by instilling two and a half ml of sterile physiological water at 37 °C into each nostril. The concentrations of CC16 and β_2-m were measured by non-isotopic immunoassays based on the agglutination of latex particles (Bernard et al., 1992; Hermans et al., 1998). Albumin and urea were quantified by the Beckman Synchron CX5 Delta Clinical System. Concentrations of biomarkers in NALF were expressed as raw concentrations or as concentrations adjusted to the median NALF concentration of urea (i.e. as the ratio to urea concentration multiplied by the median urea concentration at baseline or follow-up) in order to correct for variations in the epithelial lining fluid (ELF) recovery (Cavaliere et al., 1986). We similarly adjusted the NALF concentration of CC16 to the median NALF concentrations of albumin or β_2-m as indices integrating the decrease/dysfunction of CC16-secreting cells with the increased epithelial permeability. The use of β_2-m in addition to albumin as permeability biomarker presents theoretically two advantages. First, the adjustment with β_2-m, a plasma protein with a size close to that of CC16 (12 vs 16 kDa) should allow a more precise adjustment of CC16 levels in NALF for the transepithelial leakage of CC16 from plasma into the ELF. Second, because of its small size, β_2-m could detect slight enlargements of the paracellular pores that would pass unseen with albumin. All these biomarkers were determined in NALF collected from each nostril separately and the mean value was calculated for the statistical analyses.

2.3. Statistical analyses

Concentrations of biomarkers were reported as median with interquartile range (IQR) and were log-transformed to approximate normal distribution. Differences between baseline and follow-up values were assessed using the chi-squared test or the paired Student's *t*-test. We used Pearson's correlation analysis to evaluate the univariate associations between the different NALF biomarkers at baseline or follow-up as well as between levels of the same biomarker at baseline and at follow-up. Associations of NALF biomarkers with the risks of new-onset, remitted or persistent aeroallergen sensitization were assessed by logistic regression models in which children were categorized in tertiles of descending CC16 or ascending urea, β_2-m and albumin in NALF. We run these models by testing the raw or adjusted concentrations of NALF biomarkers and by considering various possible other predictors including gender, parental allergy or asthma, parental smoking, breastfeeding, day care attendance, chlorinated pool attendance or house cleaning with bleach. Although none of these other predictors was associated with the process of allergic sensitization, we decided to refine the odds ratios estimation by an a priori adjustment for gender and parental asthma/allergy, which are two well established predictors of allergic diseases. As there were less than 10% differences between crude and adjusted odds ratios, only the latter were reported in the Tables. Trends in odds across tertiles of NALF biomarkers were evaluated using the Cochran Armitage test. Factors influencing the baseline levels of NALF biomarkers were then traced by multiple regression analyses with variable selection based on the Akaike information criterion. We tested a total of 24 variables including age, gender, parental asthma or allergy, active or passive smoking, chlorinated pool attendance and a variety of other lifestyle- or environment-related factors (See Table S1 in Supplementary material for the complete list). Statistical analyses and graphs were made with the JMP 12.00 from SAS Institute. All *P*-values were two-sided with a level of statistical significance at $P < 0.05$.

3. Results

The cohort included 121 children (52.9% of boys) with a baseline mean age of 5.8 years. The characteristics of children are presented in Table 1 that combines both sexes as there were no significant gender

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