ADENOID HYPERTROPHY: DEFINITION OF SOME RISK FACTORS

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Adenoids removed for airway obstruction and/or recurrent infections have been studied to identify a possible mechanism to explain chronicity. In this regard, macrophages may play a relevant pathogenic role as well as neutrophils during bacterial infections and eosinophils in allergic inflammation. Therefore, this study aimed at investigating some mediators as surrogate markers of inflammation in children who had to undergo to adenoidectomy. Globally, 67 children (25 females, 42 males, mean age 4.9 years), affected by persistent obstruction caused by adenoid hypertrophy were consecutively enrolled into the study. Blood samples were collected from patients and controls to determine serum CD163, Myeloperoxidase (MPO) and ECP. There were significant differences between patients and controls for serum CD163 (p<0.0001); MPO (p<0.0001); serum ECP (p<0.0001). This study demonstrated some risk factors for severe AH: apnoea, recurrent respiratory infections, and high serum CD163 levels.
Recently, there has been considerable interest in the relationship between allergic and autoimmune diseases. We evaluated the prevalence of thyroid autoimmunity in 566 children affected by atopic dermatitis (AD), urticaria, rhinitis, chronic cough, and asthma. Our results suggest that allergy and autoimmunity can be two potential outcomes of dysregulated immunity. It is tempting to speculate that NK Th2 cells can favour asthma onset and at the same time improve thyroid autoimmunity.
IMPAIRED SPIROMETRY MAY SUGGEST SENSITIZATION.

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The present study confirms that sensitization is very frequent in the general population and suggests that impaired FEF₂₅₋₇₅ may be a marker of sensitization. Therefore, when spirometry is abnormal, mainly concerning FEF₂₅₋₇₅, sensitization should be suspected.
IMPAIRED $\text{FEF}_{25-75}$ VALUES MAY PREDICT BRONCHIAL REVERSIBILITY IN ALLERGIC CHILDREN WITH RHINITIS OR ASTHMA.

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FEV$_1$ is considered an important parameter for asthma diagnosis and follow-up. However, it has been proposed that FEF$_{25-75}$ could be more sensitive than FEV$_1$ to detect slight airways obstruction. Bronchial reversibility defined by positive response to bronchodilation test. The aim of the present study was to define whether an impaired FEF$_{25-75}$ value (<65% of predicted) may be predictive for reversibility in a large cohort of allergic children with rhinitis or asthma. Six hundred allergic children were recruited: 300 with controlled asthma and 300 with allergic rhinitis. All of them were evaluated by performing spirometry, bronchodilation test, and skin prick test. Two predictors were significantly associated with bronchial reversibility: i) an impaired FEF$_{25-75}$ value (<65% of predicted), and ii) sensitization to perennial allergens. It was more relevant in children with rhinitis ($\text{OR}_{\text{Adj}}$: 8.9 and 2.2 respectively). In conclusion, this study, conducted in real life, could suggest that an impaired FEF$_{25-75}$ value (<65% of predicted) may be considered a reliable marker of bronchial reversibility, mainly in children with allergic rhinitis.
IMPAIRED FEF<sub>25-75</sub> MAY PREDICT HIGH EXHALED NITRIC OXIDE VALUES IN CHILDREN WITH ALLERGIC RHINITIS AND/OR ASTHMA.

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Allergic rhinitis and asthma are closely associated. Inflammation is a common pathological characteristic shared by both disorders. The measure of the fractional concentration of exhaled nitric oxide (FeNO) may be considered a surrogate marker for airway inflammation. Forced expiratory flow between 25% and 75% of vital capacity (FEF<sub>25-75</sub>) has been previously demonstrated to be able to predict BHR and bronchial reversibility. The aim of this study was to evaluate whether impaired FEF<sub>25-75</sub> values may be related to FeNO values in a pediatric cohort of allergic subjects. 850 children with allergic rhinitis, allergic asthma, or both, were evaluated. Bronchial function (FEV<sub>1</sub>, FVC, and FEF<sub>25-75</sub>), FeNO, and sensitizations were assessed. Bronchial function and FeNO were significantly different in the 3 groups (p<0.001). A strong inverse correlation between FeNO and FEV<sub>1</sub> was found in patients with rhinitis, asthma and asthma with rhinitis (r=-0.72, r=-0.70 and r=-0.70, respectively). Impaired FEF<sub>25-75</sub> values (such as <65% of predicted) were significantly associated with high FeNO levels (such as ≥ 34 ppb). In conclusion, this study provided evidence that FEF<sub>25-75</sub> is strongly and inversely related with FeNO and FEF<sub>25-75</sub> may predict high FeNO levels in children with allergic rhinitis, asthma or both.
AIRWAYS ALLERGIC INFLAMMATION AND *L. REUTERII* TREATMENT IN ASTHMATIC CHILDREN

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Recently, it has been hypothesized that the oral administration of specific live probiotic strains may have therapeutic potential in the treatment of allergic inflammation. The aim of this study was to evaluate the effect of the oral *L. reuteri* DSM 17938 administration (1X10⁸ CFU), in airways allergic inflammation in mild persistent asthmatic children. In this DBPC randomized study we selected 50 children (6-14 years old), affected by mild persistent asthma (GINA step 2) and allergic to HDM. At the run-in period (T-2), the children were submitted to medical examination, prick tests for the main respiratory allergens, spirometry and children asthma control test (C-ACT). We selected only the children with well controlled asthma (C-ACT >19 and FEV₁ > 80%). After two weeks (T0) the children were allocated into two groups, the FeNO was measured and the breath condensate was collected. Group A children were treated with the placebo (5 drops per day) and Group B children with *L. reuteri* (10⁸ CFU =5 drops per day) for 60 days. After the treatment period (T1), all patients were evaluated by medical examination, C-ACT, spirometry, FeNO measurement and exhaled breath condensate analysis. The FeNO values showed a significant reduction (p=0.045) in *L. reuteri* group but not in the placebo group at the end of the treatment (T1). Furthermore, the cytokines exam showed an increase in IL-10 levels (p<0.05) and a significant reduction in IL-2 levels (p<0.05) only in *L. reuteri* group at T1. No significant differences in FEV₁ values and C-ACT score were found in both groups. In conclusion, these data showed that *L. reuteri* (10⁸ CFU) was effective in reducing bronchial inflammation in asthmatic children. No significant effect was found on FEV₁ values and C-ACT score, probably because we selected children with well controlled asthma.
Asthma is traditionally defined as a chronic disease characterized by bronchial hyper-responsiveness and lung inflammation. The airway inflammation and remodelling together likely explain the clinical manifestations of asthma. The mechanisms by which the external environmental cues, together with the complex genetic actions, propagate the inflammatory process that characterizes asthma are beginning to be understood. There is also an evolving awareness of the active participation of structural elements, such as the airway epithelium, airway smooth muscle, and endothelium, in this process; these structural elements within the lung and the bone marrow serve as reservoirs for and the source of inflammatory cells and their precursors. Although often viewed as separate mechanistic entities, so-called innate and acquired immunity often overlap in the propagation of the asthmatic response. This review examines the newer information on the pathophysiological characteristics of asthma and focuses on the role of airway epithelium in the exacerbation of the disease.
A potential role of Helicobacter Pylori (HP) infection in several extra-intestinal pathologies has been recently suggested. The aim of our study was to assess the role of serology positive for HP in atopic and non atopic infants and children affected by atopic dermatitis, urticaria, rhinitis and asthma. We included 615 children affected by atopic diseases. According to prick test positivity and age, we divided the patients into two groups: atopic or non-atopic patients and infants (0-2 years) or children (2-12 years). The serum levels of antibodies for H. pylori immunoglobulin G were measured by using an ELISA test. We found a not significant difference between group 1 and group 2 about atopy. There was a significant higher frequency of HP positive serology in older children. As for infants, a higher significant prevalence of HP positive serology was found in non-atopic patients. HP positive serology was significantly higher only in non-atopic infants affected by atopic dermatitis and urticaria than in atopic. In group 2, non atopic children shown a significant increase in the prevalence of HP serum positivity than atopic children. As for asthma, there was an higher prevalence of HP serology positive in non atopic asthmatic children group than in atopic asthmatics. On the contrary, the prevalence of positive HP serology was not significantly different between atopic and non atopic children affected by dermatitis, urticaria, and rhinitis. The present data confirm an inverse association between HP positive serology and atopy in both groups. However, the higher prevalence of positive HP serology was observed in non atopic asthmatics children than in atopic asthmatics. We could speculate that HP infection can favour non atopic asthma onset.
Asthma is characterized by airway inflammation that is controlled by a complex cytokine network. The Th1/Th2 imbalance has been well documented in the pathogenesis of allergic asthma. Recently, Th17 cells and regulatory T (Treg) cells have been found to participate in the pathogenesis of allergic asthma. This study aimed at verifying whether anti-inflammatory treatment could change serum IL-4, IL-10 and IL-23 in asthmatic children. Globally, 78 children (40 males and 38 females, median age 9.3 ± 3.7 years), with asthma and monosensitized to house dust mites, were evaluated. Lung function (such as FEV₁) and serum IL-4, IL-10 and IL-23 levels were measured at baseline (T0), after 4 weeks (T1) and after 12 weeks (T2) of inhaled corticosteroid (ICS) treatment. The control group consisted of 40 healthy children (22 males and 18 females) age matched. At baseline, IL-4 and IL-23 levels were higher in severe asthmatics than in control group (p < 0.001), while serum IL-10 levels were significantly lower in group of asthmatic children as compared to healthy control group (p < 0.001). At T2, IL-4 and IL-23 significantly diminished (p < 0.001), while IL-10 significantly increased. There was significant relationship between FEV₁ and IL-4, IL-10 and IL-23 at T0 (r = -0.784; r = -0.735 and r = -0.787, respectively). Moreover, there were correlations between FEV₁ and IL-4, IL-10 and IL-23 in patients at T1 (r = -0.563; r = -0.539 and r = -0.583, respectively) and at T2 (r = -0.549; r = -0.428 and r = -0.393, respectively). The present study provided evidence that: i) serum IL-23 was up-regulated also in asthmatic children, ii) ICS treatment was able of reducing IL-23, and iii) IL-23 change well related with lung function improvement. Thus, it is presumable that IL-23 could be a suitable marker of allergic inflammation in asthma.
The aim of the present work was to assess the prevalence of early cardiac involvement in children with celiac disease (CD), and the impact of a gluten free diet (GFD) on this issue. Sixty CD children was compared with a control group of 45 healthy children by an echocardiographic examination. CD patients were re-evaluated 1-year after 1-year GFD. Main outcome measures were ejection fraction (EF), fractional shortening (FS), left ventricular end-diastolic diameter (LVDD), left ventricular end-systolic diameter (LVSD), any regurgitating valve lesions. Mild cardiac involvement was found in 13 CD children and in one control (21.7% vs. 2.2%; p=0.003), and was secondary to regurgitation of mitral valve, aortic valve, pulmonary and tricuspid valve, or to impaired ejection fraction. CD children as compared to controls had significantly lower contractility indices, and higher left ventricular dimensions. In patients adhering to the GFD all valve regurgitations resolved, and the echocardiographic parameters significantly improved. Subclinical cardiac involvement in CD children is quite frequent, and GFD may exert a beneficial effect on the overall cardiac performance.
PROBIOTICS AND HELICOBACTER PYLORI INFECTION IN CHILDREN

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Approximately 50% of the world population is infected with Helicobacter pylori (H. pylori), with the highest prevalence rates in developing countries. The current guidelines suggest the use of triple therapy as first choice treatment of Helicobacter pylori infection, although the eradication failure rate is more than 30%. Current interest in probiotics as therapeutic agents against Helicobacter pylori is stimulated by the increasing resistance of pathogenic bacteria to antibiotics, thus the interest for alternative therapies is a real actual topic. Available data in children indicate that probiotics seems to be efficacious for the prevention of antibiotic associated side-effects, and might be of help for the prevention of Helicobacter pylori complications by decreasing Helicobacter pylori density and gastritis, and for the prevention of Helicobacter pylori colonization or re-infection by inhibiting adhesion to gastric epithelial cells. There is no clear evidence that probiotics may increase the Helicobacter pylori eradication rate.
Nasal polyposis is a chronic inflammatory disease affecting the nasal cavity and the paranasal sinuses. It is a relatively common disease, occurring in 1-4% of the general population, but it is rarely described in the pediatric population. Most of the published series include children presenting with other underlying systemic diseases, mainly cystic fibrosis. The aim of the present study was to describe the characteristics of the patients suffering from nasal polyposis, evaluated at the Pediatric Clinic of the University of Pavia (Italy) over the last 17 years. 56 consecutive pediatric patients referring to our Pediatric Department had a diagnosis of nasal polyposis over the last 17 years. All children underwent allergy evaluation, nasal endoscopy, CT scan of the paranasal sinus, and Functional Endoscopic Sinus Surgery. The mean age of the present cohort was of 11.8 years and most of the patients were male. 50% of the patients presented with unilateral, polyposis, mostly with a diagnosis of antrochoanal polyp. 4 patients presenting with bilateral polyposis suffered from cystic fibrosis. Main symptoms at diagnosis included nasal obstruction, snoring and rhinorrhea 32% of the patients presented at least a positivity to skin prick test, for major inhalant and food allergens. Nasal polyposis in children could represent an alert sign for other underlying systemic diseases. Nasal endoscopy should therefore be prescribed when a diagnosis is suspected. To properly treat a patient presenting with nasal polyposis, it is necessary to integrate medical and surgical skills through a multidisciplinary approach.
MUCOSAL IMMUNITY AND SUBLINGUAL IMMUNOTHERAPY IN RESPIRATORY DISORDERS

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The increasing prevalence of allergy and its impact on individual quality of life underline the need of an improvement of the treatment options in order to modify the natural course of allergic diseases. In this context, specific sublingual immunotherapy (SLIT) represents an approach currently available to redirect inappropriate immune response in atopic patients. The immunological mechanism that underlies SLIT has only started to be investigated. Oral mucosal tissue displays high permeability for allergens. It is conceivable that the sublingual administration route might induce immunological tolerance towards allergens involving cells and mediators specific of oral and intestinal mucosa. Recent literature data stated the presence in oral mucosa of dendritic cells (DCs) which express the high-affinity receptor for immunoglobulin (Ig)E (FceRI). Moreover some studies indicated that the mechanism of immunotherapy might be based on the increase of number and activity of regulatory T cells. Accumulating evidences suggest that the generation of T regulatory cells in periphery is orchestrated by a particular subset of DCs. It seems that repeated stimulation of naïve CD4 T cells with allogenic immature DCs induce Tr1 cells maturation. Nevertheless other cells are involved in this process, such as TLR, MHC of I and II class and costimulatory molecules such as CD40, CD 80/B7.1 and CD 86/B7.2. An increase of serum IgG4 and IgA, a reduced number of inflammatory cells infiltrating target organs, as well as a reduction of eosinophilic cationic protein and a very heterogenous influence on T cells in the peripheral blood in terms of T cell suppression also occur with SLIT. All these molecules orchestrate the immune response within the regional immune system, recreating a favourite environment for the induction of tolerance operated by SLIT.
The aim of the study was to evaluate fasting levels of glucose, insulin, leptin, total ghrelin, and obestatin in a group of prepubescent obese children before and after weight loss. We enrolled 64 prepubescent obese children, but only 35 completed the study (mean age 7.6 ± 0.9 years, 19 females) and 20 normal-weight prepubescent children as controls. Fasting plasma concentration of glucose, insulin, Homeostasis Model assessment for insulin resistance (HOMA-IR), and leptin, total ghrelin, and obestatin levels were measured at baseline and after a 6-month lifestyle intervention (i.e. improved nutrition and increased physical activity). At baseline, obese children showed significantly (p<0.001) higher leptin and obestatin levels, and lower total ghrelin concentrations than control subjects. Weight loss significantly (p<0.001) diminished plasma leptin and insulin levels and increased ghrelin and obestatin concentrations. Weight loss in prepubescent children is associated with a significant change in leptin, ghrelin and obestatin concentrations. These results confirm the hypothesis that levels of these hormones are closely associated with obesity in childhood and might take part, as consequence but not as a cause, in glucose, fat, and energy metabolism.
PTX3 behaves as an acute-phase response protein as its blood levels rapidly and dramatically increase during endotoxic shock, sepsis, and other inflammatory and infectious conditions. Therefore, this study was designed to investigate a possible role of PTX3 in children with Atopic Dermatitis (AD). One-hundred-and-thirty-six patients (37 females, 99 males, mean age 10.4 years) were enrolled in the study. One hundred patients (74%) had only respiratory symptoms (allergic rhinitis and/or bronchial asthma); thirty-six patients (26%) showed dermatitis associated with respiratory allergy (allergic rhinitis and/or bronchial asthma). PTX3 levels were higher in children with AD and there was a significant correlation between serum PTX3 levels and SCORAD index (p-value=0.0001, rho=0.658). Therefore, this study may show that PTX3 might be a reliable marker for the severity of AD in children with respiratory allergy.
PENTRAFIN 3 IN CHILDREN SUFFERING FROM ALLERGIC RHINITIS

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Allergic disorders are typically characterized by an inflammatory response to allergen exposure. PTX3 behaves as an acute-phase response protein as there is a relationship between PTX3 plasma levels and disease severity. Therefore, this study was designed to investigate a possible role of PTX3 in children with allergic rhinitis. One hundred patients (28 females, 72 males, median age 11 years) were enrolled in the study. All patients were monosensitized: 43 (43\%) to seasonal allergens (Graminaceae), 57 (57\%) to perennial allergens (house dust mites, cat and dog epithelium, alternaria tenuis). Patients’ blood samples for assessing serum PTX3 levels were performed during the spring. Children with rhinitis had higher PTX3 levels and there was a significant relationship between symptom severity and serum levels. Therefore, this study shows that PTX3 serum levels could be a reliable marker for symptom severity in children with allergic rhinitis.
Hypersensitivity reactions after immunization with tetanus toxoid are occasionally observed in atopic and non-atopic individuals. High IgE levels in infancy may predict subsequent allergy. The aims of this study were: i) to evaluate the role of specific IgE to tetanus toxoid in children in response to tetanus immunization and the possible factors associated with specific IgE levels, and ii) to investigate the correlation between specific IgE levels to tetanus toxoid and the late development of allergy (up to 12 years). Initially, 278 healthy infants (152 males and 126 females, aged 12 months) living in an urban city were screened for serum total IgE and specific IgE to tetanus toxoid, after having obtained informed consent from parents. After 12 years, 151 children could be evaluated. Total IgE summed with tetanus specific IgE were significantly associated with allergy at 12 years. In conclusion, this study demonstrates that serum total IgE and tetanus specific IgE may be predictive of subsequent allergy onset.
Sinusitis is frequently associated with asthma. The diagnosis and management of patients with asthma associated with sinusitis are often challenging, though sometimes unsatisfactory. Detection and treatment of sinusitis in asthmatics may lead to a better control of asthma symptoms. Most of the studies regarding the relationship between sinusitis and asthma have been conducted in adults. The aim of the present study was to evaluate the presence of sinusosal comorbidity in children with un-controlled asthma both clinically and through nasal endoscopy after the first 6 months of treatment. The present study included 294 consecutive asthmatic children (97 males, mean age 7.3 years). Asthma diagnosis, severity assessment and treatment were performed according to GINA guidelines. Twenty-one patients with non-controlled asthma presented with endoscopic features of sinusitis, but without any clinical sign or symptom. We defined such condition occult sinusitis. Not only overt sinusitis, but also occult sinusitis could be a significant comorbidity in asthmatic patients. For this reason, it may be beneficial to determine the presence of sinus inflammation in children with non-controlled asthma, even when they don’t present clinical signs or symptoms of upper airways involvement.
TETANUS TOXOID IGE MAY BE USEFUL IN PREDICTING ALLERGY DURING CHILDHOOD

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Hypersensitivity reactions after immunization with tetanus toxoid are occasionally observed in atopic and non-atopic individuals. High IgE levels in infancy may predict subsequent allergy. The aims of this study were: i) to evaluate the role of specific IgE to tetanus toxoid in children in response to tetanus immunization and the possible factors associated with specific IgE levels, and ii) to investigate the correlation between specific IgE levels to tetanus toxoid and the late development of allergy (up to 12 years). Initially, 278 healthy infants (152 males and 126 females, aged 12 months) living in an urban city were screened for serum total IgE and specific IgE to tetanus toxoid, after having obtained informed consent from parents. After 12 years, 151 children could be evaluated. Total IgE summed with tetanus specific IgE were significantly associated with allergy at 12 years. In conclusion, this study demonstrates that serum total IgE and tetanus specific IgE may be predictive of subsequent allergy onset.