152. Dilemmas and progress in understanding childhood asthma

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WITHDRAWN

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More airway smooth muscle in preschool children increases risk of future asthma

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Introduction: Accurate prediction of future asthma in preschool wheezers is not possible. Reticular basement membrane (RBM) thickness and airway smooth muscle (ASM) are increased in school-aged asthmatic children [Regamey AJRCCM 2008], but nothing is known about ASM changes in preschool wheezers, or the relationship of early airway pathology to future asthma.
Aims: 1)To measure RBM thickness and ASM in severe preschool wheezers and age-matched controls; 2)To relate preschool RBM thickness and ASM to school age asthma
Methods: Endobronchial biopsies (EBx) were obtained from preschool wheezers (n=47, median age 26 months) and non-wheezers (n=21, median age 15 months) undergoing clinically indicated bronchoscopy between 2002-2005 [Saglani AJRCCM 2007]. 5μm sections were stained with haematoxylin & eosin. ASM was expressed as a proportion of the subepithelial area. ASM and RBM thickness were quantified using computer analysis. Children were followed up age 6-11 years to determine asthma status.
Results: At preschool age, RBM thickness was increased in wheezers (n=37, median 4.3μm) compared to controls (n=16, median 3.6μm), p=0.01. ASM was similar between preschool wheezers (n=28, median 0.08) and controls (n=14, median 0.077), p=0.97. 51/68 (75%) children were followed up at school age. School age children with and without asthma had similar RBM thickness in their preschool EBx, p=0.23. However, children with asthma (n=8, median age 9.1 years) had increased preschool ASM (median 0.12) compared to those without asthma (n=24, median age 7.3 years, median ASM 0.066), p=0.007.
Conclusion: Preschool children whose EBx had a higher proportion (>10%) of ASM had a 10 fold increased risk of asthma at school age.

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Remodelling in the bronchial mucosa in very young children with high risk for developing asthma

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Remodelling of the bronchial wall was thought to be a typical characteristic for asthma and the result of chronic inflammation. Structural changes were documented in bronchial mucosa of preschool children treated for asthma. We have very limited knowledge about the onset of these changes in small children. The course of wheezing disorders in young age cannot be reliably predicted, so it is difficult to identify the most probable candidates for developing asthma.
The aim of our study is to identify abnormalitites in the bronchial wall in children with high-risk of developing asthma. We examined endobronchial biopsies from 23 children under 4 years of age undergoing flexible bronchoscopy for clinical reasons others than recurrent wheezing. Twelve children fulfiled the criteria of Asthma Predictive Index, eleven children were in the control group. Thickness of the basement membrane was significantly higher in the high risk group than in the controls (on the average 4.14 μm vs. 3.53 μm respectively). On the other side, there seems to be no significant difference in the presence of neutrophil leucocytes and myofibroblasts between the two groups. This may correlate with the fact that all the patients were suffering from chronic or repeated respiratory problems for which they were indicated to bronchoscopy. However we suggest that first signs of remodelling like thickening of the basement membrane can be already present in children with high-risk of developing asthma in very early age. This may help us to improve therapeutic interventions in these children to prevent further development of irreversible morphological changes in later age. Supported by IGA MH CR No. NT 11444 and NT 11459.

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Airway inflammation, lung function and wheezing phenotypes in preschool children

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Background: Wheeze is a common symptom in preschool children. Currently, it is difficult to predict whether wheezing symptoms will pass or will persist and develop into asthma in later childhood.
Aim: To prospectively study whether inflammatory markers in exhaled breath condensate (EBC) and pre- and post-bronchodilator interrupter resistance (Rint) assessed at preschool age, are able to predict wheezing phenotypes at five years of age.
Methods: Children (N=227) from the ADEM study [1] were included. At preschool age (median (IQR): 3.3 (2.8-3.8) years), pre- and post bronchodilator Rint was assessed. EBC was collected using a closed-glass condenser system. Inflammatory markers ((Interleukin (IL)-2, IL-4, IL-8, IL-10, sICAM) were measured using multiplex immunoassay. Wheezing phenotypes were determined at five years of age via annual questionnaires.
Results: Children were classified as; never- (n=47), early-transient- (n=89), intermittent- (n=46), and persistent wheezers (n=45) [2,3]. Children with persistent- and intermittent wheeze had elevated levels of all interleukins compared with never wheezers ($p<0.05$). Moreover, children in the never- and transient wheeze group had slightly lower levels of baseline Rint compared with persistent wheezers (Median (IQR) 1.3 (1.1-1.7) and 1.4 (1.2-1.6) vs. 1.5 (1.3-1.9) kPa·s/L, $p<0.10$).
Conclusions: Children of the intermittent- and persistent wheeze group at age 5 years already had elevated inflammatory markers at preschool age, indicating augmented airway inflammation in these children.
References:
[1] van de Kant et al. BMC Public Health 2009; 9:210.
[2] Martinez FD et al. N Engl J Med 1995; 332:133-8.
[3] Sears MR et al. N Engl J Med 2003; 349:1414-22.

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Airway inflammation is a continuous trait in children regardless of asthma symptoms

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Rationale: Elevated fractional exhaled nitric oxide (FeNO) and bronchial hyperresponsiveness are used as surrogate markers of asthma.
Objective: To investigate the association between FeNO and bronchial responsiveness in a population of high risk children including the full spectrum from asymptomatic children to children with intermittent asthmatic symptoms and children with persistent asthma.
Methods: An unselected group of 196 six-year-old children were included from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort born of mothers with asthma. Bronchial responsiveness was assessed as the relative change in specific airway resistance after cold dry air hyperventilation. FeNO measurements were performed prior to the hyperventilation test. The association between FeNO and bronchial responsiveness was assessed by generalized linear models.
Measurements and main results: Bronchial responsiveness and FeNO exhibited a significant and linear association. A doubling of FeNO corresponded to an 8.4% increase in airway resistance after challenge (95% CI; 3.7-13.1; p=0.0006). There was no evidence of interaction with current asthma and stratified analyses showed similar associations in children with and without asthma.
Conclusion: FeNO and bronchial responsiveness are associated and continuous traits in the population regardless of asthma. This suggests bronchial inflammation may be present subclinically, and cautions against the use of these surrogate markers for a dichotomized approach to asthma diagnosis. Childhood asthma remains a clinical diagnosis and surrogate markers may only be used cautiously as supportive evidence.

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Randomized placebo-controlled study of ciclesonide in preschool children with recurrent wheeze and a positive asthma predictive index or atopy

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Rationale: To assess the efficacy and safety of ciclesonide, *versus* placebo, in preschool children with recurrent wheeze and a positive asthma predictive index (API) or atopic sensitization.
Methods: Children 2–6 yrs with recurrent wheeze episodes were eligible if they had a positive API, or were sensitized to aeroallergens. Children with exclusive episodic viral wheezing were excluded. After a 2–4-week baseline period, patients with ongoing symptoms/rescue medication use were randomised to once-daily ciclesonide 40, 80, 160 μg or placebo for 24 weeks.
Results: The number of wheeze exacerbations requiring systemic steroids was unexpectedly low in all groups: 25 (10.2%) in placebo group, as compared to 11 (4.4%), 18 (7.3%), and 17 (6.7%) in ciclesonide 40, 80, and 160 μg, respectively. The difference in exacerbation rates between the placebo group and the pooled ciclesonide groups was significant (p=0.03). Large and significant ($p<0.0001$) improvements in symptom scores and rescue medication use occurred in all groups, including placebo. Improvements in FEV_1 and FEF_{25-75} (measured in 284 4-6 yr olds) were larger in the ciclesonide than in the placebo group. No differences in safety parameters (adverse events, height growth, serum and urinary cortisol levels) between ciclesonide and placebo were observed.
Conclusions: In preschool children with recurrent wheeze and a positive API, ciclesonide modestly reduces wheeze exacerbation rates and improves lung function. A large placebo response and patient-selection issues may have affected outcomes, highlighting the limitations of current classification system of preschool wheezing disorders.

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Oposite effect of endotoxin exposure with different *MD-2* genotypes on asthma in children

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Background: Endotoxin exposure may play an important role in the development of asthma. MD-2 is a glycoprotein that assembles with TLR4 to form functional signalling receptor for endotoxin. We hypothesised that genetic variations in *MD-2* may modify the relationship between endotoxin exposure and asthma.
Methods: Study population comprised 423 children with physician-diagnosed asthma and 414 non-asthmatic controls (age 6-18 years) recruited from the general hospital in Slavonski Brod, Croatia. We collected mattress dust sample and measured endotoxin content using kinetic limulus assay. We genotyped 9 haplotype-tagging SNPs in *MD-2* (Sequenom). Correction for multiple comparisons was carried out using Benjamini-Hochberg's False Discovery Rate (FDR) method.
Results: In the whole population, endotoxin exposure was associated with a decreased risk of asthma (aOR 0.75, 95%CI 0.58-0.98, p=0.03). None of the *MD-2* SNPs was associated with asthma after FDR correction. For three SNPs we identified a significant interaction between genotype and endotoxin exposure (rs7822054, rs7822407 and rs11786591; $p_{int} \leq 0.02$), in that increasing endotoxin load was protective against asthma in some genotype groups, but the association tended to be in the opposite direction amongst children with other genotypes. For example, for rs7822054, amongst children carrying A allele endotoxin exposure was protective (aOR 0.71, 95%CI 0.46-1.00), but amongst G allele homozygotes it increased the risk of asthma (aOR 2.64, 95%CI 1.09-6.38; FDR corrected $p_{int}=0.03$).
Conclusion: The effect of endotoxin exposure on asthma may differ among children with different variants of the *MD-2* gene.

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Lessons learned from the epidemiology and natural history of asthma: Outcomes and treatment regimens (TENOR)

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Rationale: Patients with severe or difficult-to-treat asthma are an understudied population. The primary objective of The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study is to characterize the natural history of disease in the largest cohort of severe or difficult-to-treat asthma patients. We highlight the main findings of 25 research articles.
Methods: TENOR was a 3-year, multicenter, observational cohort study of N=4,756 patients (n=3,489 adults ≥18 years; n=627 adolescents 12-17 years; n=637 children 6-11 years). Data was collected semi-annually and annually.
Results: Regardless of age, patients demonstrated high rates of HCU, despite receiving multiple long-term controller medications. Uncontrolled asthma, per the NHLBI guidelines, is highly prevalent and predictive of future asthma exacerbations in children and adolescents/adults. Children have an increased exacerbation risk and asthma burden compared with adolescents/adults. Increased weight is associated with worse asthma related outcomes. Aspirin sensitivity is associated with increased asthma severity and possible remodeling of both the upper and lower airways. Also, the phenotypes of persistent airflow are described. IgE and allergy play an important role in severe or difficult-to-treat asthma. Quantitative results not listed due to space constraints.
Conclusions: Patients with severe or difficult-to-treat asthma demonstrate an unmet need. The characterization of this cohort has improved our understanding of asthma control and exacerbations.