Allergol Immunopathol (Madr). 2010;38(3):107–109

Allergologia et immunopathologia

www.elsevier.es/ai

EDITORIAL

# Respiratory tract infections and lung function in early life – "Cling together, swing together"

Early life occurrences in health and disease have become a major focus of interest, as the first years of life are being considered a most vulnerable period. Acute respiratory viral infections are the major cause of morbidity in infants. Severe early life viral infections, mainly with respiratory syncytial virus (RSV) or rhinovirus, have actually been alleged to divert the immune response towards an allergic phenotype bearing the risk of asthma development, even though this hypothesis is still a matter of debate.[1] Upon long-term follow-up, lower respiratory tract infections (LTRIs) in early life have been shown to be associated with reduced flow values, but normal lung volumes, at school age.[2] These data, however, were retrospective, and were not controlled for lung function before the index LTRI in early life. A recent study in a birth cohort in Oslo has prospectively addressed the question as to whether there is a causal relationship between LTRIs in early life, and reduced lung function later in childhood: even though reported bronchiolitis, bronchitis, and three or more LTRIs in the first 2 years of life were associated with reduced FEF50 (forced expiratory flow at 50% of forced vital capacity) at age 10 years, these associations were not causative, as they were no longer significant after adjustment for birth lung functions and other relevant parameters (such as maternal smoking during pregnancy).[3]

Conclusive evidence supports the association between viral respiratory infections and acute wheezing–as a consequence of airway narrowing–in infants, as well as in older children and in adults. When in a community-based birth-cohort study in Western Australia on 263 infants from birth until one year of age, detailed information on all acute respiratory illnesses (ARIs) were collected, two-thirds of the ARIs were upper respiratory tract infections (URTIs), and one-third were LTRIs; 29% of the LTRIs were associated with wheeze. Viruses were detected in 69% of the ARIs, predominantly rhinoviruses (48.5%) causing both URTIs and LTRIs[4]. In otherwise healthy adults and children, ages 2.5 to 16 years, when suffering from symptoms of URTIs on the day of testing, lung function abnormalities especially in forced expiratory parameters have been demonstrated.[5,6] Also, in adult asthmatics, experimental nasal inoculation with rhinovirus has been shown to cause airway obstruction as measured by FEV1, as well as an increase in airway hyperresponsiveness and augmented lower airway inflammation.[7,8] Other data suggest that in addition a variety of other viruses causing common colds can induce lower airway inflammation, to a greater extent in asthmatics than in otherwise healthy people.[9]

In infancy, a subgroup of children suffer from recurrent asthma-like clinical symptoms, i.e. recurrent wheezing. When these infants contract URTIs, will these mild infections also have an impact on the infants' pulmonary function, and maybe do long-term harm to the infants' respiratory system? In this issue of Allergologia et Immunopathologia, Mallol et al. present their data from their study on 28 infants (ages, 54–75 weeks) with a history of recurrent wheezing (three or more previous episodes of physician-diagnosed wheezing).[10] Spirometric lung function was assessed in these infants when they suffered from an URTI, defined as the presence of a runny nose, sneezing, nasal obstruction, and eventually cough (but no signs of respiratory distress, nor fever), plus the history of a close contact person with recent similar symptoms. These "URTI lung function data" were compared to lung function data assessed in the same infants when they had been asymptomatic for at least 4 weeks. Even though the infants were not wheezy during URTI, lung function showed significant decreases in all forced expiratory parameters, most evident for FEF50%, FEF75%, and FEF25–75%. Lung function was abnormal in 50% of patients during URTI. The good news is that lung function returned to normal when infants were asymptomatic. So, there may apparently be some degree of bronchial hyperreactivity resulting in airway narrowing during URTIs in these infants, but there is no evidence of chronic, irreversible lung

0301-0546/$ - see front matter 
doi:10.1016/j.aller.2010.02.001

function impairment following these URTIs. Normal lung functions have already been demonstrated in otherwise healthy teenagers after a recent mild acute respiratory infection. It is reassuring that unscathed withstanding the (mild) insults to the respiratory tract caused by viral URTIs in the long run also holds true for infants with recurrent wheezing.

We have to keep in mind that the study by Mallol et al. included only a specific subset of infants, namely infants with recurrent wheezing who probably have a predisposition to react to viral infections with airway narrowing. Neither family history of asthma nor tobacco exposure during pregnancy were risk factors for a higher degree in airway narrowing during URTI. So, how can we explain these findings of significant decreases in spirometric parameters during URTIs in these infants, how can a common cold lead to lower airway obstruction? Of course, it cannot be ruled out that viruses may have reached the lower airways, e.g. after aspiration of nasal contents, and may have caused subclinical pathology in the lower airways – without typical clinical LTRI symptoms. Experimental data on adult patients, however, are not in favour of this mechanism having a contributory effect on nasobronchial interaction.[11] Also, there is no experimental evidence for a nasobronchial reflex responsible for nasobronchial cross-talk.[12] An explanatory hypothesis that appears much more attractive, is the concept of the ''united airways'',[13] with the mucosal membranes and their inflammatory responses of the upper and lower airways to be considered as a functional unit. This concept has been developed for allergy, and it defines allergic asthma and allergic rhinitis as two different manifestations of the same disease. From allergy studies, we know that after nasal challenge in patients with allergic rhinitis, mucosal inflammation is not restricted to the challenged organ only, but extended throughout the whole airway. The current hypothesis suggests that nose and bronchi are linked through the systemic circulation, with inflammatory cells and cytokines as mediators.[13] Viral infection of the nasal mucosa results in vasodilation and increased vascular permeability, which in turn cause nasal obstruction and rhinorrhoea – the main clinical symptoms of an URTI. Cholinergic stimulation leads to increased mucosal gland secretion and sneezing. Differences exist in the degree of epithelial destruction between various respiratory viruses. Extensive research into the role of inflammatory response of the host has produced evidence for increased concentrations of several inflammatory mediators, such as kinins, leukotrienes, histamine, interleukins 1,6, and 8, tumour necrosis factor, and RANTES in the nasal secretions of patients with common colds. The complex host response mechanisms triggered by the viral infection are, however, not resolved yet.[14] Still, adaptation of the ''united airways concept'' from allergic diseases to infection-induced inflammation appears to be a conceivable hypothesis.

In any case, routine lung function data should not be obtained from patients when they present with symptoms of URTIs. This has been shown for older children, and holds true for infants with recurrent wheeze also. Does this study also have therapeutic implications? Should we treat infants with recurrent wheezing with bronchodilators, even if they only suffer from an URTI? We do not know, as bronchodilator responses were not assessed in the study. Many parents may just start bronchodilators in their infants with a common cold, if they have a history of recurrent wheezing, from earlier experience that URTIs may finally result in another wheezy episode. On the other hand, why should infants be treated with a drug if they do not present with clinical signs showing that they will benefit from that ''reliever'' medication?

As a closing remark, though leading astray from the main intention of the study: once again, this study showed that tobacco exposure during pregnancy was significantly associated with lower expiratory airway flows in asymptomatic infants. Isn't it time to impose a sanction on smoking mothers who voluntarily do harm to their defenceless unborn children?

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A. Schuster
*Department of Paediatric Cardiology and Pneumology, University of Duesseldorf, Germany*
*E-mail address:* Schuster@med.uni-duesseldorf.de