

Role of immunisations and infections for the development of atopy

E. VON MUTIUS

MOTS-CLÉS. Asthme. – Virus. – Th1/Th2 – Vaccinations. – Mycobactéries.

KEY-WORDS. Asthma – Viruses. – Th1/Th2. – Vaccines. – Mycobacteria

Up to 70% of wheezing episodes in the first year of life have been shown to relate to viral respiratory infections [1, 2]. In earlier studies virus isolation rates were relatively low and varied significantly between studies (9.8%-48.6%) depending on different approaches in sampling and processing of the different materials [3-12]. These proportions were, however, higher in cases than in controls. RSV, rhinovirus and parainfluenza virus were the most frequent isolates in wheezy children [3, 5-8, 10]. In studies closely following children over months [13] coronaviruses and influenza viruses were also found in a significant proportion of wheezing episodes. A recent study using PCR techniques in addition to conventional methods yielded much higher virus identification rates. Johnston and coworkers [14] detected viruses in 80% of nasal aspirates of asthmatic episodes taken in 108 schoolage children over a 13 months period. In most of the episodes rhinoviruses were found. During asymptomatic control periods, the identification rate of rhinoviruses amounted to 12%.

Two major hypotheses have been proposed to explain the association between viral infections and wheezing [15]. One hypothesis states that viral infections early in life damage the growing lung or alter host immune regulation. The second hypothesis holds that respiratory infections are more severe in infants and children with some underlying predisposition. In this case, the symptomatic viral infection is merely an indicator of an otherwise silent condition, whereas viral infections were causal risk factors if the first hypothesis holds true. These two arguments are not mutually exclusive. It is conceivable that severe viral lower respiratory tract infections occur primarily in infants and children with an inherent predisposition, and that both the infection and the predisposition contribute to the development of wheezing illness or other long-term respiratory abnormality.

There is still an ongoing debate about a potential causal role of infection with respiratory syncytial virus (RSV) for the subsequent development of childhood asthma and atopy. RSV infections are

Journée Parisienne d'Immuno-Allergologie Infantile, Paris, samedi 20 novembre 1999.

University Children's Hospital, MUNICH (Germany).

Tirés à part: Dr E. Von Mutius, adresse ci-dessus.

VON MUTIUS E. – Role of immunisations and infections for the development of atopy. *Rev. fr. Allergol.*, 1999, **39** (8), 649-652

very common in the first year of life. According to Long and coworkers [15] 80% or more of all infants are infected with RSV in the first year of life, but lower respiratory tract illness is also evident in about 40% of these children. Thus, a significant proportion of children undergo inapparent RSV infections in the first years of life suggesting that host factors exist which determine the manifestation of bronchiolitis after an RSV infection.

Several investigators have followed children with proven RSV bronchiolitis into later childhood. Most authors [16-18] reported reductions in pulmonary function and increased frequency of airway hyperresponsiveness in cases as compared to controls. These results are, however, also consistent with the notion of an underlying premorbid respiratory abnormality rather than a subsequent damage of the airways through the RSV infection. Pullan and coworkers (18) for example followed 130 infants and compared them with matched controls. Of the RSV group 6.2% were wheezing at the age of 10 years as compared to 4.5% of the control group. A slightly increased prevalence of repeated mild episodes of wheeze was found during the first 4 years of age (38% vs 15%), but no increased rate of atopic sensitization.

When considering the second hypothesis, several risk factors associated with an underlying predisposition to wheeze may be relevant. If wheeze is a nonspecific symptom of airway narrowing then either underlying abnormalities of lung and airway structure which result in smaller airway calibers, or a propensity to obstruct the airway lumen by mechanisms such as airway hyperresponsiveness may be relevant. There is some evidence that asthmatics may be more susceptible to acquire viral infections than healthy non-asthmatic children [19, 20]. For example, Minor and coworkers [19] observed that asthmatic children experienced significantly more viral respiratory tract infections than their nonasthmatic siblings. Rhinoviruses use receptors on the cell surface for cellular attachment. The most common receptor is ICAM-1 [21] which has been shown to be expressed more frequently in epithelial cells of asthmatics than of normal subjects [22].

In contrast to the studies discussed above, other studies have reported an inverse relation between asthma and the overall burden of infections. In Papua New Guinea Anderson observed that respiratory infections were more common among young children in the Highlands, where the asth-

ma prevalence was exceedingly low, than in the coastal regions of the country, where asthma occurred more frequently [23]. In the Fiji Islands, Flynn and coworkers [24] reported that in the indigenous children with frequent respiratory infections and a high hospital admission rate for pneumonia, the prevalence of asthma and airway hyperresponsiveness was lower than in less exposed children. Likewise, a higher prevalence of bronchitis and respiratory infections was found in East European countries, whereas atopic sensitization, hay fever, asthma and BHR were all significantly lower than in Sweden or West Germany [25, 26].

There is also increasing evidence that sibship size contributes to the expression of atopy in families. Many authors have shown that the number of siblings is inversely related to the prevalence of self-reported inhalant allergy, hay fever, atopic eczema, skin test reactivity and the presence of specific IgE antibodies in the serum [27] in children, adolescents and adults. Most reports which were large enough to allow a separate analysis of the influence of older and younger siblings found a stronger relation with the presence of older siblings than with younger brothers and sisters. David Strachan who first described the phenomenon in 1989 [28] proposed that «infection in early childhood, transmitted by unhygienic contact with older siblings, or acquired prenatally from a mother infected by contact with her older children» may prevent the development of allergic diseases. The strong inverse relation between sibship size and the expression of atopy in families may, however, also be attributable to other mechanisms. The number of older siblings might be a surrogate measure for multiple pregnancies in which feto-maternal immune responses may change with each pregnancy. If this notion were correct then not only the number of older siblings but also the number of pregnancies including miscarriages should be related to the occurrence of atopic diseases in the offspring.

Yet, the results of other recent studies substantiate the potential protective effect of infections early in life on the development of mainly atopy and to a lesser extent on asthma in later childhood. In Guinea-Bissau, West Africa, Shaheen and colleagues followed children at the age of 0-6 years into young adulthood [29]. The subjects with childhood measles had about half the rate of atopic sensitization defined as skin prick test positivity to aeroallergens than those who had been vaccinated and did not acquire measles (12.8% vs 25.6%). A recent report from Southern Italy

showed that military students who were sero-positive for hepatitis A as a potential indicator of hygiene had a significantly lower prevalence of atopic sensitization to common aeroallergens and a lower prevalence of atopic diseases as compared to their peers who did not have antibodies to hepatitis A [30]. In a recent study from East Germany the development of allergy at the age of 5-14 years was significantly reduced if a child from small families entered day nursery between 6-11 months of age as compared to 12-23 months of life or after the second birthday (15.7% vs 21.8% vs 27%) [31]. In the prospective Tucson Cohort Study, children who had non-wheezing lower respiratory tract illnesses such as pneumonia and tracheobronchitis in their first three years of life had subsequently reduced skin test reactivity and depressed levels of total serum IgE at the age of 6 years [32]. A potential protective effect of parasitic infections e.g. in areas of the Developing World has not yet been explored sufficiently.

Recent immunologic findings add biologic plausibility to the hypotheses inferred from these epidemiologic studies. In simplistic terms, two T helper cell phenotypes develop from a common ancestor cell. Different patterns of cytokine release are produced by these different T-helper cells. Th2-like T-cells produce among other mediators interleukin 4 (IL-4) and interleukin 5 (IL-5) and thereby increase the production of IgE and attract eosinophils to the lung. In contrast, Th1-like T-cells produce among other cytokines interleukin 2 (IL-2) and interferon gamma [33] which is produced in the course of infectious diseases and inhibits the production of IgE [34]. Thus, a predominant activation of Th1-like T-helper-cells in the course of recurrent viral or bacterial infections may prevent the proliferation of Th2-clones and the development of allergic disease [33].

These findings have prompted investigators to speculate about a potential harmful effect of vaccinations and antibiotic use. This discussion was further fueled by a recent paper by Shirakawa and colleagues [35] who reported that, amongst BCG immunized Japanese schoolchildren, asthmatic symptoms and several indices of atopy were significantly less likely in positive tuberculin responders as compared to negative responders, and that remission of atopic symptoms between the ages of 7 and 12 years was much more likely in

positive tuberculin responders. The interpretation of these findings has been debated intensively. The inverse association between allergic status and tuberculin reactivity may simply reflect the imbalance of Th1/Th2 responsiveness characteristic of atopic individuals who have been shown to express smaller delayed type hypersensitivity skin reactions to recall antigens than non-atopic subjects [36]. This imbalance may relate to genetic or other constitutional factors rather than to exposure to Mycobacteria. Such an interpretation is supported by findings of a Swedish group showing that a single immunization for BCG after birth does not affect the prevalence of atopic diseases at schoolage [37].

Likewise, the role of vaccination for measles has been questioned. The generalisability of the findings from Guinea-Bissau, West-Africa, to western populations must, however, be called in question. In fact, several studies were unable to detect an adverse effect of childhood immunizations on the development of allergic diseases [37, 38]. Moreover, there is no evidence to date to suggest that the use of antibiotics may causally be related to the inception of childhood asthma or allergies. A recent retrospective study by Hopkin and coworkers [39] showing a positive association between antibiotic use and asthma must be interpreted with great caution since a potential severe bias by reverse causation, *i.e.* children with preexisting symptoms of asthma may receive more antibiotics because of their disease, cannot be excluded.

Therefore, a subject's overall burden of continuing infections early in life and throughout childhood which may be respiratory or gastrointestinal may direct the immune response towards a predominant Th1-like response by suppressing the Th2 pathway. A suppressed Th2 response may then reduce the risk to develop atopy and asthma. To date there exists no rationale to withhold vaccinations or antibiotics where necessary, to prevent the development of atopy or childhood asthma. Infections by some respiratory viruses such as RSV and rhinoviruses at certain stages of lung maturation may unmask the manifestation of asthma in a predisposed host. Again, it seems very unlikely that avoidance of day care centres will reduce the incidence and prevalence of childhood asthma.

★

★ ★

REFERENCES

1. Wright A.L., Holberg C.J., Martinez F.D., Morgan W.J., Taussig L.M. – Breast feeding and lower respiratory tract illness in the first year of life. *Br Med J.* 1989, 299: 946-949.
2. Duff A.L., Pomeranz E.S., Gelber L.E., Price G.W., Farris H., Hayden F.G. *et al.* – Risk factors for acute wheezing in infants and children: viruses, passive smoke, and IgE antibodies to inhalant allergens. *Pediatrics*, 1993, 92: 535-540.
3. Horn M.E., Brain E.A., Gregg I., Inglis J.M., Yealland S.J., Taylor P. – Respiratory viral infection and wheezy bronchitis in childhood. *Thorax*, 1979, 34: 23-28.
4. Jemmings L.C., Barns G., Dawson K.P. – The association of viruses with acute asthma. *N Z Med. J.* 1987, 100: 488-490.
5. Horn M.E., Reed S.E., Taylor P. – Role of viruses and bacteria in acute wheezy bronchitis in childhood: a study of sputum. *Arch Dis Child*, 1979, 54: 587-592.
6. Henderson F.W., Clyde W.A. Jr., Collier A.M., Denny F.W., Senior R.J., Sheaffer C.I. *et al.* – The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. *J. Pediatr.* 1979, 95: 183-190.
7. Mitchell-Inglis H., Inglis H., Simpson H. – Viral infection in wheezy bronchitis and asthma in children. *Arch Dis Child*, 1976, 51: 707-711.
8. Carlsen K.H., Orstavik I., Leegaard J., Hoeg H. – Respiratory virus infections and aeroallergens in acute bronchial asthma. *Arch Dis Child*, 1984, 59: 310-315.
9. Horn M.E., Bram E., Gregg I., Yealland S.J., Inglis J.M. – Respiratory viral infection in childhood. A survey in general practice, Roehampton 1967-1972. *J Hyg Lond.* 1975, 74: 157-168.
10. Disney M.E., Matthews R., Williams J.D. – The role of infection in the morbidity of asthmatic children admitted to hospital. *Clin Allergy*, 1971, 1: 399-406.
11. Glezen W.P., Loda F.A., Clyde W.A. Jr., Senior R.J., Sheaffer C.I., Conley W.G., Denny F.W. – Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. *J. Pediatr.* 1971, 78: 397-406.
12. Tyrerell D.A.J. – A collaborative study of the aetiology of acute respiratory infections in Britain 1961-4. A report of the Medical Research Council Working Party on acute respiratory virus infections. *Br Med J.* 1965, 2: 319-326.
13. Roldaan A.C., Masural N. – Viral respiratory infections in asthmatic children staying in a mountain resort. *Eur. J. Respir Dis*, 1982, 63: 140-50.
14. Johnston S.L., Pattemore P.K., Sanderson G., Smith S., Lampe F., Josephs L. *et al.* – Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. *Br Med J.* 1995, 310: 1225-1229.
15. Price J.F. – Acute and long-term effects of viral bronchiolitis in infancy. *Lung*, 1990, 168 Suppl: 414-421.
16. Long C.E., McBride J.T., Hall C.B. – Sequelae of respiratory syncytial virus infections. A role for intervention studies. *Am. J. Respir. Crit. Care Med.*, 1995, 151: 1678-1681.
17. Sims D., Downham M., Gardner P., Webb J., Weightman D. – Study of 8 year old children with a history of RSV bronchiolitis in infancy. *Br Med. J.*, 1978, 1: 11-14.
18. Pullen C.R., Hey E.N. – Wheezing, asthma and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J.*, 1982, 284: 1665-1669.
19. Minor T.E., Baker J.W., Dick E.C., DeMeo A.N., Ouellette J.J., Cohen M., Reed C.E. – Greater frequency of viral respiratory infections in asthmatic children as compared with their non-asthmatic siblings. *J. Pediatr.* 1974, 85: 472-477.
20. Bardis P.G., Johnston S.L., Pattemore P.K. – Viruses as precipitants of asthma symptoms. II. Physiology and mechanisms. *Clin Exp Allergy*, 1992, 22: 809-822.
21. Rowlands D.J. – Rhinoviruses and cells. Molecular aspects. *Am. J. Respir. Crit. Care Med.* 1995, 152: S81-S85.
22. Vignola A., Campbell A., Chanez P., Bousquet J., Paul-Lacoste P., Michel F.B., Godard P. – HLA-DR and ICAM-1 expression on bronchial epithelial cells in asthma and chronic bronchitis. *Am. Rev. Respir. Dis.* 1993, 148: 689-694.
23. Anderson H.R. – The epidemiological and allergic features of asthma in the New Guinea Highlands. *Clin. Allergy*, 1974, 4: 171-183.
24. Flynn M.G.L. – Respiratory symptoms, bronchial responsiveness, and atopy in Fijian and Indian children. *Am. J. Respir. Crit. Care Med.* 1994, 150: 415-420.
25. Braback L., Breborowicz A., Julge K., Knutsson A., Riikjarv M.A., Vasar M., Bjorksten B. – Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. *Arch. Dis. Child*, 1995, 72: 487-493.
26. Von Mutius E., Martinez F.D., Fritzsche C., Nicolai T., Roell G., Thiemann H.H. – Prevalence of asthma and atopy in two areas of West and East Germany. *Am. J. Respir. Crit. Care Med.* 1994, 149: 358-364.
27. Von Mutius E. – The influence of birth order on the expression of atopy in families: a gene-environment interaction? (Editorial). *Clin. Exp. Allergy*, 1998, 28: 1454-1456.
28. Strachan D.P. – Hay fever, hygiene, and household size. *Br Med J.* 1989, 299: 1259-1260.
29. Shaheen S.O., Aaby P., Hall A.J., Barker D.J.P., Heyes C.B., Shiell A.W., Goudiaby A. – Measles and atopy in Guinea-Bissau. *Lancet*, 1996, 347: 1792-1796.
30. Matricardi P.M., Rosmini F., Ferrigno L., Nisini R., Rapicetta M., Chionne P. *et al.* – Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *Br Med J.* 1997, 314: 999-1003.
31. Kramer U., Heinrich J., Wjst M., Wichmann H.E. – Age of entry to day nursery and allergy in later childhood. *Lancet*, 1998, 352: 450-454.
32. Martinez F.D., Stern D.A., Wright A.L., Taussig L.M., Halonen M., GHM Associates. – Association of non-wheezing lower respiratory tract illnesses in early life with persistently diminished serum IgE levels. *Thorax*, 1995, 50: 1067-1072.
33. Romagnani S. – Human TH1 and TH2 subsets. Regulation of differentiation and role in protection and immunopathology. *Int. Arch. Allergy Immunol.*, 1992, 98: 279-285.
34. Parronchi P., De Carli M., Manetti R., Simonelli C., Sampaio S., Piccinini M.P. *et al.* – IL-4 and IFNs exert opposite regulatory effects on the development of cytolytic potential by TH1 or TH2 human T cell clones. *J. Immunol.*, 1992, 149: 2977-2983.
35. Shirakawa T., Enomoto T., Shimazu S., Hopkin J.M. – The inverse association between tuberculin responses and atopic disorder. *Science*, 1997, 275: 77-9.
36. Strannegard I.L., Larsson L.O., Wennergren G., Strannegard O. – Prevalence of allergy in children in relation to prior BCG vaccination and infection with atypical mycobacteria. *Allergy* 1998, 53: 249-254.
37. Alm J.S., Lilja G., Pershagen G., Scheynius A. – Early BCG vaccination and development of atopy. *Lancet*, 1997, 350: 400-403.
38. Henderson J., North K., Griffiths M., Harvey I., Golding J. – Pertussis vaccination and wheezing illnesses in young children: prospective cohort study. The Longitudinal Study of Pregnancy and Childhood Team. *Br Med. J.* 1999, 318: 1173-1176.
39. Farooqi I.S., Hopkin J.M. – Early childhood infection and atopic disorder. *Thorax*, 1998, 53: 927-932.

