Clinical remission of asthma

Clinical remission of asthma: what lies beyond?

S Guerra

Further evidence suggests that ''complete'' remission of childhood asthma may be the exception rather than the rule

Asthma can be a debilitating disease with a major impact on quality of life and an increased risk of developing severe airway remodelling and non-fully reversible airflow obstruction. In the last decades, effective pharmacological treatments and management strategies have been developed for this disease. Yet, at the present time, asthma remains a treatable but not a curable disease.

It is not therefore surprising that much effort is being put into studying the risk factors associated with the inception and progression of asthma, since understanding these factors represents the first necessary step for developing effective prevention strategies. In this respect, the increase in the incidence and prevalence of asthma over the last decades has not only produced a general awareness of the public health burden associated with the disease, but it has also provided the scientific rationale for expecting a major role of environmental factors in its development. However, the epidemiological identification of these disease determinants has not proved to be an easy task. While profiles of risk factors for asthma have been identified, the exact mechanisms by which they operate are far from being fully understood for many (or most) of them. In addition, many of these factors are likely to be involved in complex gene-by-environment interactions and to be differentially linked to different asthma phenotypes. This complexity has limited the implementation of effective interventions to reduce the incidence of asthma and, to date, there is no conclusive programme of primary prevention for this disease.

To complicate things even more, remarkable paradoxes have emerged from recent research. Factors that are known to exacerbate or trigger asthma, such as exposure to endotoxin[1] or pets,[2] appear to be somewhat protective if they occur early in life. Similarly, while allergen avoidance is undoubtedly a beneficial and essential part of management strategies in atopic asthma, it does not appear to be as effective in protecting against onset of new asthma. Taken together, these observations strongly suggest that factors that determine the inception of asthma may differ from those that affect its progression, and reinforce the unique importance of studies that follow subjects with asthma over time. Observational and intervention studies on selected cohorts of asthmatics have indeed provided critical contributions to our understanding of the factors influencing the clinical course of the disease, and this evidence has affected to a large extent the way we currently treat and manage asthma.

Studies on asthmatic cohorts can also help to elucidate the natural history and long term outcomes of the disease. From a clinical standpoint, this is not an issue of secondary importance. Asthma is a variable disease that can persist, remit conclusively, or present any possible combination of remissions and relapses over time. Clearly, the long term sequelae of the disease on lung health are likely to be quite different across these different patterns. In this framework, longitudinal studies assessing the outcome of childhood asthma into adult life hold particular interest for two main reasons. Firstly, in the vast majority of cases asthma has its onset in childhood. Therefore, even though adult onset asthma is frequently associated with severe and difficult to treat forms of the disease, asthma initiated in childhood continues to have a greater public health impact at the population level. Secondly, asthma may lead in the long term to severe airway remodelling and, possibly, to the development of chronic airflow obstruction. These observations raise critical questions on whether this course is more likely to occur in the persistent forms of asthma, whether subjects predisposed to this progression can be identified at early stages of their disease, and whether optimal asthma management can be beneficial against disease progression. Longitudinal studies following cohorts of participants over a wide age span between childhood and adulthood represent our best tool to answer these questions.

In a recent issue of *Thorax* Vonk *et al*[3] reported evidence from such a cohort of 119 allergic asthmatic children (age 5–14 years) enrolled in an outpatient clinic in the late 1960s and re-evaluated in a follow up visit approximately 30 years later (age 32–42 years). Although the relatively small sample size suggests caution in interpreting these data, this study provides cogent findings that are consistent with those from previous longitudinal studies and may have important implications for the search of optimal management strategies in asthma.

Firstly, childhood asthma appeared to remit clinically (no reported active symptoms and no use of inhaled corticosteroids) in adult age ''only'' in approximately 50% of the cases. In interpreting these results, the selective nature of this cohort of outpatients should be kept in mind. It is known that children with asthma selected in the clinical setting are likely to differ from population based samples of asthmatics in many respects, particularly in terms of increased severity of the disease—a known risk factor for persistence of symptoms into adulthood. Rates of asthma persistence are therefore expected to be higher in clinic based than in population based cohorts.

Consistently, findings from several long term longitudinal cohorts[4–7] indicate that, in the general population, among subjects who had episodes of wheezing in childhood, approximately one third report active asthma symptoms when surveyed in their young to mid adult life. However, this proportion is remarkably higher, even in population based studies, among subjects whose childhood asthma was severe or characterised by frequent wheezing episodes. This concept is best illustrated by data from the Melbourne Asthma Study[8] in which several groups of school age children were enrolled based on their wheezing/asthma history and followed over time into their adulthood. At age 42, 15% of controls reported wheezing episodes in the last 3 years compared with 40% of the subjects who, during childhood, had wheezing associated with bronchitis or respiratory tract infection. However, wheezing episodes were reported by up to 70% and 90% of subjects who during childhood had fulfilled the criteria for asthma and severe asthma, respectively.

All evidence considered, it appears plausible to conclude that most children with moderate to severe forms of asthma will experience clinically active disease at least in some periods of their adult life. This important conclusion becomes even more striking when we consider a second finding from the

study by Vonk *et al*[3]: most cases of asthma in clinical remission (in that study, up to 57%) still show bronchial hyperresponsiveness and/or reduced lung function. This finding supports a clear distinction between clinical remission of asthma (that is, absence of symptoms and medication use) and complete remission of asthma. The implications of this distinction are quite relevant, given that the simple absence of symptoms is the most commonly used criterion for defining asthma remission in epidemiology and it is also used to a large extent in clinical algorithms for managing the disease.

Does the presence of bronchial hyperresponsiveness and reduced lung function among these apparently remitting asthma cases represent structural sequelae of the disease? Or does it represent an underlying inflammatory process still active in the airways? There are arguments to support both these scenarios. Most likely, in many cases of clinical remission of asthma an ongoing airway inflammation is present which can interact with—and possibly enhance—airway remodelling and structural changes of the lungs. Recent studies[9–11] have shown that, when compared with healthy controls, children and adolescents who have apparently outgrown their asthma related symptoms do show increased markers of airway inflammation. Eosinophils and interleukin (IL)-5 in bronchial biopsy tissue, the percentage of eosinophils in bronchoalveolar lavage fluid, exhaled nitric oxide levels, and bronchial responsiveness to adenosine-5′-monophosphate all appear consistently higher in subjects with remitting asthma than in controls.[9–11] This evidence raises the question whether a long term anti-inflammatory treatment should be considered in these cases of subclinical asthma. At the present time we do not have a conclusive answer to this question. However, the accumulating evidence on inflammation and airway remodelling in remitting asthma strongly argues for at least monitoring patients with asthma in clinical remission over time, possibly with periodic assessments of lung function, bronchial hyperresponsiveness, and other markers of inflammation.

Another interesting finding from the study by Vonk and colleagues[3] is that reduced lung function in childhood was a significant risk factor for the persistence of asthma and airflow limitation into adulthood, an association described quite consistently across previous large longitudinal studies.[5 6] Early deficits in lung function among children with asthma may be related to several factors, including early airway remodelling or impaired lung growth. Regardless of the nature of these factors, the fact that these deficits track over time implies that children with persistent asthma will be most often destined to have lower lung function than their peers in adult life. In addition, among subjects with long term asthma, these deficits in lung function may eventually lead to a non-fully reversible airflow obstruction—a key functional feature for the definition of chronic obstructive pulmonary disease (COPD).[12] The co-existence of asthma and COPD diagnoses in the same subject appears quite frequently in adults[13] and appears to be associated with increased mortality.[14] It is debatable whether subjects with asthma are at increased risk for COPD as a result of the clinical progression of the disease (that is, long term sequelae of the airway inflammation and remodelling associated with asthma) or as a result of an increased susceptibility to lung damage by noxious agents.[15] This is a vital question in terms of optimal prevention, treatment, and management of patients with co-existing signs of asthma and COPD. The scenario of a clinical progression of asthma into COPD is supported by a large body of evidence, including the reported correlation among asthmatics between the degree of airway remodelling associated with the disease and the presence of COPD-like functional signs such as irreversible airflow obstruction.[16 17] However, it is tempting to speculate that the tracking of reduced lung function over time shown by subjects who had severe childhood asthma may also play an important role in increasing the susceptibility of these subjects in adult life to noxious agents including cigarette smoking, and in lowering their threshold for a clinically relevant lung damage in response to these agents. At the present time this remains a largely unsolved question.

In this framework, the results on asthma persistence provided by Vonk and colleagues[3] reinforce the clinical relevance of understanding the long term sequelae of this disease. New evidence from longitudinal cohorts of asthmatic children entering their mid adult life will contribute to determining the structural and functional consequences of persistent asthma on the lungs and dissecting further the long hypothesised link between childhood asthma and COPD in adulthood.[18 19]

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Correspondence to: Dr S Guerra, Arizona Respiratory Center, University of Arizona, 1501 N. Campbell Ave, P O Box 245030, Tucson, AZ 85724-5030, USA; sguerra@arc.arizona.edu

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