Have Recent Investigations into Remission from Childhood Asthma Helped in Understanding the Pathogenesis of this Disease?

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Source of support: Self financing

Studies show that a significant proportion of young people suffering from childhood onset asthma later recovered, usually in adolescence. In this article we argue that an understanding of the differences between children who recover from asthma and those who do not would contribute to increased understanding of the pathogenic mechanisms of the disease and could provide new clues about prevention and treatment. We note that some researchers have recently published results from these kinds of investigations. This paper reports results regarding genetic determinants, distorted mechanisms of inflammation, and mind/body relationships. We also try to integrate findings from these 3 areas to formulate general conclusions about the pathogenesis of asthma.

MeSH Keywords: Allergy and Immunology • Asthma • Remission Induction

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893575
Background

Most clinicians are convinced that many children with asthma “grow out” of it, or in other words, recover from this disease, and that this is not the case with adults with asthma.

In the paper subtitled “Asthma remission: does it exist?”, van den Toorn et al. concluded that “epidemiological work has demonstrated that a certain percentage of subjects with apparently outgrown atopic asthma remains asymptomatic without the need for therapy for the rest of their lives” and that “asthma remission does exist” [1]. Tot et al. followed a cohort of 34 216 children born in 1994 and diagnosed with asthma at age 6–12 years and found that 48.6% were in remission [2]. These early findings have been recently confirmed by large-scale population-based studies [3–5].

In 1996, Andersson et al. distributed a questionnaire to the parents of all children aged 7–8 years in 3 municipalities in northern Sweden [3]. Among 3430 responders, after medical evaluation, these authors identified 248 children as having asthma. These children were reassessed annually until age 19 years. Remission was defined as: no use of asthma medication and no wheezing during the 12 months prior to the endpoint of the surveys. At age 19, 21% were in remission, 38% had periodic asthma, and 41% had persistent asthma. Remission was more common among boys. These authors also found that a low probability of remission was related to sensitization to furry animals, and to the initial severity of asthma [3].

Cazzolethi et al. implemented a large longitudinal prospective study between 2000 and 2009 in Italy [4]. People age 21–47 years with current asthma were followed-up at 6 medical centers within the framework of the “Italian Study on Asthma in Young Adults” [4]. The survey began by sending a screening questionnaire focused on the presence of respiratory symptoms. The questionnaires were sent to random samples of people aged 20–44 years at the time of recruitment. All the subjects with self-reported physician diagnosis of asthma and who reported current asthma were invited to participate in the follow-up. Finally, 214 people participated in the study. The authors found that 29.7% of these subjects had recovered from asthma after about 10 years.

Wu et al. used another approach in their study, the so-called population-based study [5]. They distributed a questionnaire addressed to the parents of pupils at 94 elementary and middle schools. The self-administered questionnaire concerned the respiratory health of the parents of those children. The questions were focused on symptoms of the occurrence of and recovery from asthma. Using this methodology, the authors found that 860 of the 25 377 respondents reported ever having asthma. The highest incidences of the onset of this disease occurred at ages 0–12 and 36–40 years. In this Asian population, asthma occurrence showed a U-shaped age distribution with a prominent second peak in the 30s. The survey demonstrated that a high proportion of late-onset asthma sufferers persisted or relapsed in adulthood [5]. Javed et al. discussed 9 large population-based cohort studies [6]. The estimated remission rate varied from 22% to 65% [6].

It seems that if we could identify the phenomena occurring during the recovery period it would be possible to better understand the mechanisms of the pathogenesis of this disease and probably determine new ways to treat and prevent this disease. Some information on this topic could come from a comparison of the characteristics of children in whom remission has occurred compared to those children who have not experienced recovery. The researchers who compared the epidemiological and functional factors did not find essential differences [6, 7]. Javed et al. write that “Gender, socioeconomic status, smoking exposure, family history of asthma or atopy, breastfeeding history, peak flow meter availability, asthma action plan, and influenza vaccinations were not associated with remission” [6]. Covar et al. conclude, however, that sensitization and exposure to allergens, low lung function, and greater airway hyperresponsiveness decrease the probability of remission from asthma [7].

Some researchers have recently published the results of investigations into genetic, inflammatory and mind-body mechanisms observed in the period of recovery from childhood asthma [8–12]. It is worth considering whether this new data could be integrated to better define the nature of the disease. We attempt to present such considerations in this article.

Various Genetic Risk Scores in the Phenotypes of Differently Progressing Asthma

Belsky et al. presented the polygenic risk of the development of asthma on the basis of data gathered from a 4-decade longitudinal study [8]. These investigators took into account 15 genetic variants (so-called SNPs), which predispose to asthma and which have been found in recent genome-wide association studies (GWAS). Among these SNPs, 7 were related to locus 17q12-21 in the 17th chromosome. They proposed the concrete so-called “genetic risk score”. There is a published list of these SNPs [8]. This genetic score was monitored during the long-running Dunedin Multidisciplinary Health and Development Study in a cohort of 1037 subjects spanning the ages 9–38 years. Those cohort members with childhood-onset asthma with high genetic risk scores were more likely to develop life-long disease. The authors concluded that genetic risk assessments enable the prediction of which childhood-onset asthma will remit and which will become life-long. Belsky et al. also noted that the genetic score is related to different
phenotypes of asthma: eosinophilic, Th2-mediated, and non-Th2-mediated. The authors stress, however, that these phenotypes might also have their own individual genetic determinants and not reflect only the sum of SNPs detected in GWAS studies.

They concluded that future asthma therapies might be more effective when targeted at those particular phenotypes. Nevertheless, the authors admit that currently known genetic risk factors do not yet allow a confident prediction of the onset and course of asthma [8].

Asthma as an Inflammatory Disease with Differently Distorted Immunity

Wasserman et al. published the results of an investigation of local and systemic immunological parameters associated with the remission of asthma symptoms in children [9]. They examined the peripheral blood mononuclear cell cytokines and local mediator profiles in 3 groups of 12–18-year-old patients: (1) adolescents with continuing symptoms of asthma, (2) a group of patients who had persistent symptoms in early childhood but in whom these had resolved, and (3) a control group. The patients from the first group manifested elevated numbers of eosinophils and eosinophil cationic proteins and also increased IL-5 in sputum, which was not observed in the second group [9]. Peripheral blood mononuclear cell cytokine studies revealed increased production of type 1 cytokines IL-12, IFN-γ and TNF-α in the first group compared with the second group. The production of IL-4 and IL-5 was unchanged. These findings suggest that decreased expression of IL-12, IFN-γ and TNF-α as well as decreased eosinophilic inflammation is associated with the resolution of asthma symptoms.

Siegle et al. presented the results of experiments into blocking induction of T helper lymphocytes in a novel murine model of childhood asthma [13]. These authors assume that early-life respiratory viral infections are linked to subsequent development of asthma in children. The experiment in animals consisted of trials of the inhibition of induction of T helper type 2 lymphocytes by administration of neutralizing antibodies against interleukin IL-4 and IL-25 and assessment of development of the airway inflammation and remodeling. The authors concluded that in their new murine model of childhood asthma administration of anti-IL-4 or anti-IL-25 prevents the development of some key features of asthma. They suggested that suppression of the development of a Th2 response during the neonatal period or later in childhood could be effective for primary prevention.

Psychosocial Stress and Asthma

Gustafsson et al. studied the impact of family relationships and social support as salutogenic factors in children suffering from asthma [14]. The authors studied the role of psycho-social factors in the development of allergy prospectively in 82 infants with a family history of atopy. The investigation consisted of an assessment of the ability of the examined families to adjust to the demands of the situation (‘adaptability’), and to balance between emotional closeness and distance (‘cohesion’). These assessments were first performed when the children were 18 months old. The social network, life events, atopic symptoms, psychiatric symptoms, and socio-economic circumstances of the families were re-evaluated when the children were 3 years old. The children were classified as atopic (asthmatic symptoms or eczema) or as non-atopic. The authors concluded that psychosocial factors, family interaction, and a supportive social network played a significant role in the development of atopic illness in the early childhood. The authors were convinced that measures which enhance family interaction and the social network could positively influence the course of the disease [14]. Klinnert et al. also concluded that the data obtained during their prospective study “provide support for the possible contribution of psychosocial factors to asthma onset and persistence into childhood” [15].

Recently, Rosalind J. Wright discussed the role of stress in the expression of asthma [16]. She is convinced that psychological and social factors interact throughout the life-course in the development of this disease. These interactions include also in utero environment. She suggests that maternal stress, starting in pregnancy, influences programming of neuroendocrine and immune systems of offspring. She postulates that psychological, behavioral, and physiological correlates of stress should be taken into account in studies of the development of asthma. She discusses indicators of so-called constraining communities and associations between early family stress and the development of asthmatic phenotypes in early childhood. She writes that the influences of stress on gene-environment interactions and epigenetic mechanisms of gene expression have been sparsely examined in relation to pathophysiology of asthma [16].

Neurotypes and neural circuitry involved in brain-asthma linkages were discussed recently by Rosenkranz et al. [17,18] and Busse et al. [19].

The Attempt to Integrate Recently Acquired Data Related to the Pathogenetic Mechanisms Characteristic for the Period of Remission from Childhood Asthma

Genetic component

The most important conclusion from the work of Belsky et al. can be seen in the confirmation of the existence of a specific...
set of genetic variants characteristic of the childhood-onset asthma phenotype [8]. According to these authors, the genetic risk assessment will enable the prediction of whether a child will recover from the disease in the future. However, these authors say that such predictions are as yet “not sufficiently sensitive or specific to support immediate clinical translation”. This imperfectness of contemporary possibilities for distinguishing just this phenotype of childhood-onset asthma, which will predispose to recovery, is probably caused by the current simplified formulation of the genetic risk score. This is based on the sum of interactions of SNPs, but the various genetic phenotypes of asthma are probably also determined by some additional influences.

For instance, Yoshikawa et al. are convinced that the mechanisms of the genetic conditioning of asthma will be explained more effectively by so-called “epistatic analyses” [20]. They note that, contrary to Mendel’s classical law of heredity in which each gene locus exerts an independent effect on a single phenotype, it has been proven that 2 different gene loci can affect the same phenotype. A circumstance when 2 loci jointly affect a phenotype is classically defined as ‘epistasis’ [20]. In our recently published letter to the editor, we tried to highlight the fact that the concept of the so-called ‘missing heritability’ is therefore particularly important in relation to asthma [21].

The formation of phenotypes, which predispose to asthma, may also be caused by the polymorphism of genes responsible for the expression of cytokines involved in the pathogenesis of asthma [22].

There is also the regulation of genetic information at the gene-expression level through several mechanisms. Environmental factors may alter gene expression by DNA or histone modification [23]. Thus, the epigenetic regulation can evoke the particular asthmatic phenotype without a changed gene sequence [23]. The important environmental factors include allergenic exposure, pollutants (especially particulates), tobacco, aerosol exposure, viral infections, and exposures to endotoxin [24–28].

Since the pathogenetic process of asthma is ongoing at the interface between external surroundings (polluted air) and the airway epithelium, the gene-environment interactions should be precisely integrated into the theory of this particular chronic disease [25,27].

**Inflammatory component**

Asthma is conceived as an inflammatory disease with distorted immunity. Both pathogenic mechanisms are influenced by genetic variants. It is known, for example, that the genes encoding IL-13 and the beta-chain of the IgE Fc receptor-R1 contribute to susceptibility to asthma [26]. It is also known that genes for the cytokine IL-18 and its receptor, IL18-R1, as well as TNF-α are implicated in the pathogenesis of asthma [26].

Recent progress made in functional studies in human subjects and mouse models of allergic airway disease indicate the important role of IL-33 in driving TH2 inflammation, which is central to eosinophilic allergic asthma. IL-33 acts on cells of both the adaptive and innate immune systems. Recently, it has been found that type 2 innate lymphoid immune cells produce hallmark TH2 cytokines, such as IL-5 and IL-13 [29].

Against this background of generally agreed conclusions related to the influences of genetic diversity and altered immune responses in asthma, it is easier to interpret the findings of Waserman et al. [9]. These researchers emphasize that the distinguishing features of children who experienced remission is their low cellular eosinophilic response and the relatively low expression of the so-called first-type cytokines (IL-12, IFN-γ, TNF-α). It should be noted that type 1 cytokines include those that enhance cellular immune responses. Therefore, the relatively low level of type 1 cytokines predisposes to low eosinophilia.

The meaning of the data obtained by Waserman et al., who examined children remitted from asthma, can be supported by data obtained in adolescents and adults who are in remission from asthma.

Arshad et al. write that sputum examination of adolescents who remitted from asthma showed the lowest sputum eosinophils count within the remission group and the lowest eosinophils/neutrophils ratio [11].

This is confirmed by Volbeda et al. who applied the AMP provocation test in adult patients [12]. The administering of S’monophosphate (AMP) in patients with bronchial hyperresponsiveness (BHR) usually augments sputum eosinophilia. These authors demonstrated that the examined patients with complete asthma remission showed no AMP-induced sputum eosinophilia [12].

Boulet et al. evaluated the profile of peripheral blood regulatory T cells in adult patients with complete remission of asthma after the adenosine monophosphate and methacholine provocation test [10]. They found, despite remission of asthma, a decreased suppressor function of regulatory T cells.

Summarizing data resulting from observations of children who grow out of asthma and data obtained from examinations of adolescents and adults who remitted from asthma, the recovery is characterized by a low cellular immune response.

This is not in contradiction with the results of the experiments conducted by Siegel et al. in animals, discussed above [13].
These researchers blocked the induction of T helper type 2 lymphocytes (Th2) and this prevented the sustaining of asthma. The proliferated inflammatory cells in asthmatic airways are regulated by a network of Th2 cytokines, such as IL-4, IL-5, and IL-13. Th2 cells mediate adaptive immune responses and, therefore, their neutralization has a preventive effect.

The observations of Siegle et al., based on the results of experiments in animals, also have an additional value, because these authors draw attention to the specific mechanism of induction of asthma in children. These researchers point out that, in the etiopathogenesis of this disease in children, there is a sequence of events involving the early infection by respiratory syncytial virus (RSV) followed by sensitization to the allergen of ovalbumin [30].

The same team of researchers generalized their findings and highlighted that these early toxic allergens can be traffic-related particulate pollutants, especially diesel exhaust particulates [31].

The importance of such a sequence of events may be associated with the insights of Lambrecht and Hammad [32]. They emphasized in their recent review paper that “barrier epithelial cells are being increasingly more implicated in disease pathogenesis than previously thought” [32]. They remark that these cells sense exposure to allergens via pattern recognition receptors that activate conventional and inflammatory dendritic cells (DCs) and other innate immune cells. Early infant infection by respiratory syncytial virus (RSV) can probably dysregulate the so-called “barrier immunity”.

Mind-body influences

It is known that the onset and exacerbation of asthma symptom often occur during times of increased psychological stress [33,34].

Early studies from the 1990s, such as the publications of Gustafsson et al. or Klinnert et al., presented arguments for the influence of distorted family relationships, mood disorders, anxiety, and psychological stress on the course of asthma in childhood, and were formulated on the basis of the methodology of psychological investigations [14,15].

Rosalind J. Wright emphasized recently the importance of so-called “constricting communities” characterized by the presence of a number of stressors, including poverty, unemployment, limited social capital or social cohesion, and high crime or violence exposure rates. She maintains that there is increased asthma prevalence among children in such communities [16]. She also examined the influence of events in the so-called “Fragile Families” on asthma onset in children.

She maintains that “factors leading to the onset, remission, or persistence of asthma across the life-course may be influenced by social experiences and physical exposures beginning in utero, a series of social and biologic experiences initiated by early childhood exposure, or cumulative exposure to toxic biologic or social factors over critical periods of development” [16].

Recently, some authors have published papers presenting the results of research conducted using functional brain imaging [17,18,35], showing in a more objective manner that stress contributes to maintaining the inflammation manifested by increased eosinophilia. Discussing these findings, Buss states that “stress may not cause inflammation but enhances its expression when it develops to a second signal” [19]. Thus, it becomes more understandable why psychological stress may contribute to the development of chronic asthma.

Conclusions

1. There are genetic determinants of a specific asthma phenotype, which enable the prediction of recovery from this disease with a high level of probability. However, insufficient knowledge about the gene-environmental interactions does not allow a definite or completely certain prediction of recovery from childhood-onset asthma.
2. Genetic pathogenic variants are responsible for distorted immunity in childhood-onset asthma. The distinguishing features of children who experienced remission are their low cellular eosinophilic response and the relatively low expression of the so-called “first type” cytokines (IL-12, IFN-γ, and TNF-α). Thus, these children have specific mechanisms to secure low cellular immune response.
3. Prolonged psychological stress can disturb the process of recovery from childhood-onset asthma and may contribute to the development of chronic asthma.
4. Today, knowing that a genetic phenotype of childhood onset asthma exists, which predisposes to remission, we can infer its existence relying on the specific characteristics of the inflammatory process and we can strive to improve prevention and treatment by suppressing the abnormal cellular immune responses and improving the psychosocial circumstances of the patient.
5. The presented considerations suggest seeking new ways to suppress abnormal cellular immune responses.
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