POINT OF VIEW

Prognostic bases of asthma. Natural history?

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Received 29 July 2010; accepted 30 July 2010
Available online 22 September 2010

Abstract
Different causes of asthma have been established. The most common cause is conditioned to a genetic predisposition towards atopy (atopic asthma), although other factors can also give rise to bronchial inflammation, such as over-exposure to environmental irritants (occupational asthma), altered arachidonic acid metabolism (aspirin-induced asthma) and also exercise – in which different thermal and osmotic mechanisms are known to intervene. The prognosis of these different variants of asthma depends on the severity of the condition; patient age at onset of the disease; patient age at the time of diagnosis; the treatment provided; and adherence to therapy. The concept of “natural history” refers to the spontaneous evolution or course of the disease process in the absence of pathogenic or etiological treatment, with the provision of only symptomatic treatment. In order to gain increased certainty regarding the course of these patients, the study groups must present similar baseline characteristics in terms of the start and severity of the condition; the start of treatment; compliance; and the clinical and functional control findings.

Although asthma is considered to be a chronic disorder, i.e., of indefinite duration and therefore posing difficulties for influencing the course of the disease (which may be referred to as its “natural history”), the clinical reality of asthma may in fact be more optimistic, depending on the genetic and environmental characteristics and on the adequacy of the diagnostic and treatment interventions. Thus, in order to assess the evolution of the disease, a series of aspects must be taken into account.

Two basic elements are implicated in the pathogenesis of asthma: increased bronchial smooth muscle contractility, i.e., bronchial hyperresponsiveness, and inflammation secondary to regular or frequent stimulation by exogenous irritants such as environmental contaminants and/or allergens. The intervention of one or other of these elements gives rise to the different types of asthma, and bronchial remodelling plays an important role in defining the evolution or course of the disease (GINA).3

Depending on the severity and chronology of the process, the dominant symptomatology (dyspnea, wheezing, cough) may prove common (of different intensity and frequency) or episodic – with manifestation in the form of acute exacerbations or attacks. These symptoms may have a genetic basis which on one hand determines bronchial hyperresponsiveness and on the other, conditions an anomalous immune response (with a predominance of Th2 activity) to potentially allergic environmental elements.2,4 This
predisposition underlies the concept of atopic asthma, which is the most common form of the disease.

In other patients, bronchial inflammation and consequent hyperresponsiveness appear as a result of exposure to environmental irritants almost always related to professional or occupational activities. Such occupational asthma is late in manifesting, following a period of professional activity, although it may also appear earlier as a result of exposure to the causal irritants in the home (domestic industries) or smoking.\(^5\)

Other processes which sporadically manifest with similar symptoms, included within the controversial concept of “asthma syndrome”,\(^6\) are exercise-induced asthma and aspirin (or acetylsalicylic acid, ASA)-induced asthma – the etiopathogenic bases of which differ from those of the asthma variants described above.

In any case, the evolution or course of the disease will depend on the patient predisposition, the establishment of an early and correct diagnosis, and on adequate treatment.

**Prognosis conditioning factors**

**Atopic asthma**

Genetic predisposition is the basis of allergic diseases in general, involving transmission through a series of genic alterations (polygeny) which prove variable from one individual to another. Alterations of certain genes on the one hand condition host immune response to allergens, and on the other give rise to bronchial responsiveness. The penetrance or individual predisposition to develop asthma is conditioned by the large number of implicated genes, as well as by the degree of predisposition of the parents. The alteration only of immune response (atopy), without alterations in bronchial lability, may exclusively cause rhinitis or allergic rhinosinusitis, but also eosinophilic bronchitis – characterised by the presence of bronchial mucosal inflammation but with no bronchoconstriction. In such situations the patient presents dry, persistent cough as the exclusive or dominant clinical manifestation.\(^7\)

The different phenotypes depend on the mentioned predisposition (genotype) and on exogenous environmental factors, which in turn may differ from one location to another. Patient age at asthma onset is largely dependent upon the mentioned antecedents. In this sense, the disease manifests earlier in the presence of a high familial incidence and more adverse environmental conditions. The severity of the disease process likewise depends on both of these factors. Genetic predisposition causes most cases of asthma to manifest in childhood, particularly in preschool and schoolchildren.\(^8\) In adolescents and young adults, allergic predisposition is likewise the most common cause of asthma, though other environmental factors such as smoking may also exert an influence.\(^9\) The prevalence of atopic asthma in older age groups is variable, with clear differences among publications, due to the incidence of a range of factors.\(^10\)

The evolution of allergic asthma is particularly dependent on a correct diagnosis based on the clinical manifestations and allergological study findings. Such evaluations are typically carried out once there is a manifest suspicion of asthma – in most cases in early childhood. After confirming the diagnosis, early treatment is essential in order to ensure a good patient course. Pathogenic management aims to prevent or reduce the inflammation (anti-leukotrienes, inhalatory corticosteroids) although, as in all diseases, the primary concern should be treatment of the underlying cause (i.e., etiological treatment). Additional priority concerns are the reduction of the environmental presence of allergens and irritants, and particularly the application of immunotherapy, which is well known to be effective in correcting the host immune response.\(^11\) However, certain circumstances (severity of the process, polysensitisation), not patient age\(^12\), may advise a delay in immunotherapy or contraindicate such therapy. Lastly, regular patient control and good adherence to therapy are also critical elements.

**Occupational asthma**

Occupational or professional asthma can manifest in atopic patients in whom the familial incidence of allergic diseases is low, but it can also manifest in patients who suffered asthma in childhood, were correctly treated and proved asymptomatic in adult life – since immunotherapy corrects immune dysfunction but not bronchial hyperresponsiveness.\(^13\) Thus, although patients can be freed of their symptoms, long-term relapse is possible if certain recommendations are not taken into account, such as the avoidance of smoking or the choice of an appropriate professional activity in which the patient is not exposed to environmental irritants. Regular exposure to allergens in the occupational setting (animals, latex, soya, etc.) is the cause of asthma in such individuals. However, in non-atopic individuals, regular exposure to irritants may produce bronchial inflammation, which in turn gives rise to hyperresponsiveness and thus to the generation of bronchial spasms during exposure – with improvement during rest days or holidays. Accordingly, and apart from anti-inflammatory treatment, the prognosis of such cases will depend only on the avoidance of these irritants – changing occupational activity or adopting protective measures, where possible.\(^14\)

**Aspirin-induced asthma**

It has been estimated that 30–70% of all patients who do not tolerate aspirin (acetylsalicylic acid, ASA) have previously suffered allergic rhinitis and asthma that worsened at a certain age (between 30–40 years) on using analgesics – not only aspirin but also other non-steroidal anti-inflammatory drugs (NSAIDs). All such patients show nasal mucosal hypertrophy, and many also present nasal polyps, in what is known as the “aspirin triad” (rhinosinusitis, polyps, bronchial asthma). Some cases are also characterised by the association of ocular, skin (urticaria, angio-oedema) or gastrointestinal symptoms. The cause of such aspirin intolerance is inhibition of the cycloxygenase-(COX-1) enzyme, which intervenes in the metabolism of arachidonic acid, originating from mast cell activation. This results in depression of the system that stabilises prostaglandin E\(_2\) (PGE\(_2\)) activity, giving rise to an increase in the production of cysteiny1-leukotrienes (Cys-LT) and thus to activation of the cells that intervene in inflammation.\(^15\) Treatment in such cases involves avoidance of the non-tolerated anti-inflammatory drugs, although desensitisation can also
be achieved through the daily administration of an aspirin dose (300 mg) – giving rise to tolerance and even the reduction or elimination of the nasal polyps and symptoms. The prognosis is largely dependent upon these therapeutic measures, although atopic patients must continue their regular treatment for asthma, which in these situations is usually severe.

Exercise-induced asthma

It has been estimated that as a result of the persistent bronchial inflammation, up to 90% of all atopic asthmatic individuals suffer dyspnoeic episodes during physical exercise – the intensity of dyspnea being dependent upon the severity of asthma in each case, and on the particularities of the physical exercise. The prognosis is tied to the aforementioned characteristics of asthma, its treatment, and adherence to therapy.

The above-described dyspnoeic episodes differ from the dyspnea experienced by non-atopic individuals during exercise (apparently observed in 5–20% of the general population and in 30–70% of athletes) – the severity of the condition in this case depending on the type of physical activity involved and on the climate in which it is carried out. The pathogenesis of this variant (which has been suggested to correspond to exercise-induced bronchospasm rather than asthma), where bronchial inflammation is predominantly neutrophilic, has not been fully established. Mechanical, thermal and osmotic stimuli are known to intervene, along with hyperventilation and changes in airway physiology; giving rise to mast cell activation, with the release of proinflammatory mediators such as histamine, leukotrienes and chemokines. The management measures in these cases are limited to preventing dyspnea when exercise is to start, based on prior warm-ups and the use of certain drugs (salbutamol, cromoglycate, nedocromil) inhaled 30–60 min before exercise – with good protective effects. To date, reversibility of this type of dyspnea has proved elusive, and the long-term prognosis therefore depends only on the cessation of sports activities.

Natural history

The natural history of asthma, i.e., spontaneous evolution of the disease without any etiopathic treatment (only symptoms management), would certainly imply the poorest prognosis, with the progressive deterioration of respiratory function. This would have a negative impact on patient quality of life and ultimately could lead to fatal complications. In reasonably well-developed countries these situations are not found, although for a number of reasons the evolution of the disease is not always as desired. Undoubtedly, the known personal and environmental risk factors are decisive for the evolution of the disease process, depending on their intensity, since they clearly contribute to the persistence of inflammation and consequent bronchial remodelling. The evaluation of these factors is of predictive, but not evolutive usefulness. The existing treatment options exert a positive influence upon the evolution of the disease, provided they are correctly applied. Under the concept of the natural history of asthma, the studies designed to assess patient condition over the long term usually fail to specify the treatments used or the other factors upon which the prognosis normally depends. The percentages of patients included in the studies are grouped according to their condition after a given duration of follow-up, but the treatments received by these patient groups are not usually commented. In general, reference is made to anti-inflammatory and bronchodilating therapy, i.e., pathogenic treatment, but not to etiological treatment (immunotherapy). While the inflammation improves with treatment, it also tends to recur if the triggering elements persist (i.e., allergens in the case of atopic asthma).

In the case of asthma induced by aspirin and NSAIDs, the course is less certain. Patients who already suffered atopic asthma in the past, despite desensitisation, show a torpid and more severe course, requiring oral and even intravenous corticosteroids to deal with the most important attacks. On the other hand, about 15% of the patients do not associate their attacks to analgesic use, and are reluctant to undergo provocation tests despite the fact that in 6% of these cases the illness is of a familial nature, with a more problematic natural history of the disease.

Conclusions

In order to firmly define the non-spontaneous evolution of asthma in the context of applied treatment measures, the patient groups studied must have common characteristics, in order to assess the true efficacy of therapy, taking into consideration the following:

1. Patient age at the start of the symptoms and at the time of the study.
2. Familial antecedents of atopy.
3. Environmental characteristics: urban, rural, home, work, smoking.
4. Association to regular, sporadic or seasonal contact with or exposure to certain elements: animals, pollen, environmental contaminants, smoking, aspirin.
5. Severity based on the clinical picture and associated allergic pathology (rhinitis, eczema, etc.). Results of the allergological study. Respiratory function.
6. Treatment: etiopathic (anti-inflammatory drugs), etiological (immunotherapy). Patient age at disease onset, follow-up, adherence, variations over the years.
7. Frequency of clinical and respiratory function controls.

References