Chapter 3

Meaning of Endotype-Phenotype in Pediatric Respiratory Pathology

Francisco Muñoz-López

Additional information is available at the end of the chapter

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Abstract

Respiratory processes that take place in childhood (preschool and adolescence) have a predominant frequency, especially rhinitis and asthma. Family predisposition and the environment define the characteristics of the endotype and the phenotype. Heritage, both of the genes related to bronchial hyperresponsiveness and those related to atopy (production of specific IgE against allergens and hypereosinophilia) are the fundamental basis of those processes that begin at preschool age and continue into adulthood if they do not receive early and etiological treatment. The physiological vagal hyperresponsiveness of the infant; the environment in which it develops, even from the prenatal phase (pregnant smoker); and viral infections are responsible for frequent bronchial processes in the early years that, sometimes, also extend into adolescence. In summary, the coordination of the endotype and the phenotype has led to the acknowledgement and acceptance of these three tracheobronchial processes: transient early wheezing, non-atopic wheezing, and atopic wheezing/asthma.

Keywords: children, phenotype, endotype, bronchospasm, wheezing, asthma

1. Introduction

The phenotype is defined as "observable characteristic with no direct relationship to a disease process, including physiology, triggers and inflammatory parameters" and the endotype as "distinct disease entities which may be present in cluster of phenotypes, but each defined by a specific biological mechanisms." [1, 2].

The variability of bronchopulmonary processes that take place in childhood makes it difficult to establish the criteria for the definition of asthma and, therefore, the phenotype. Age is one

of the most important determinants of the phenotype in early childhood and adolescence, including determinants from genetics to the environment. In early childhood, airway development, the environment (especially pregnant smoker), and frequent viral infections, without a doubt, have a decisive influence to establish the phenotype. Symptomatology and lung function (especially the specific airway resistance, atopy, and airway hyperresponsiveness (AHR) at age of 3–5 years) identify several groups of variants: only wheeze, wheeze with irritants, chest congestion and cough, wheeze with allergens that correlate to atopy, and AHR. Asthma that began at those ages, usually preceded by rhinitis, usually lasts until adolescence, if an adequate treatment was not carried out, especially based on the etiology (immunotherapy). In some cases, at that age, the causality may be different, environment and acquired habits (especially smoking) that lead to inflammation of the airways, similar to what occurs in adults (occupational asthma). Three variants have been proposed based on the endotypes: mild to intermittent asthma, asthma with severe exacerbations and multiple allergens, and severe obstructive asthma with neutrophilia [2, 3].

Allergic diseases can be predicted taking into account the key factor in their onset, genetic predisposition, since it is inherited as autosomal dominant trait. Knowledge that at least one of the parents suffers from an allergic disease is a factor to consider. In fact, it is the most reliable indicator for predicting predisposition, although not sufficient to predict it accurately. If both parents are allergic, and even more if they are asthmatic, the risk of allergic respiratory disease can be predicted even better. Although the existence of first-degree relatives suffering from allergic disease is considered the most valuable data, among many others that have been studied, the degree of reliability can be specified as 50% of cases.

2. Genetic predisposition: chromosomes and genes involved

The allergic predisposition (atopic) is of a polygenic nature, that is to say, the genes that support the polymorphisms that give rise to the body's abnormal response to substances (allergens) that are well tolerated by most people and which originate the production of specific IgE antibodies (reagins) against proteins with antigenic capacity contained therein. Even with no atopic predisposition, at any age, excessive exposure to allergens equally can cause specific IgE production, with consequent clinical translation.

The genetic basis of asthma is not unique, but depends on a complex polymorphism, and it is not strange that the involvement of the various genes that are supposed to be implicated is not yet known. The allergic reaction is linked to the predominance of Th2 lymphocyte activity and the subsequent increase in specific IgE. Chromosome 11 (11q13) was the first to identify genes involved in its production; in it lies the synthesis of the β chain of the high-affinity IgE receptor.

It is estimated that at least 100 genes are involved in the pathogenesis of atopy and asthma. Some 30 loci on various chromosomes have been linked on the one hand with the function of the airways and another on the production of IgE [4, 5]. Chromosome 5 (5q31-q33) contains the genes that modulate the production of interleukins secreted by Th2 lymphocytes, such as IL-4 and IL-13, responsible for the atopic response when involved in the secretion of IgE by

B lymphocytes (plasma cells), as well as other interleukins (IL-3, IL-5, IL-9) which also intervene. In addition, in the same gene, the protocadherin-1 (PCDH1) that could alter the integrity of the bronchial epithelium, the first line of defense against inhalation of environmental substances, has been identified [6]. On the other hand, the onset of asthma in the pediatric age has linked to chromosome 17q21, the main genetic determinant of the ORMDL3 gene that encodes endoplasmic reticulum proteins, and has also been associated with poor outcome in children exposed to environmental irritants, especially tobacco smoke [7, 8].

Logically, genes related to the allergic reaction are common to other allergic processes, such as those caused by food or drugs mainly, which may be the cause of dermatological (eczema, urticaria), digestive, or anaphylactic processes. Sometimes, because of the same, there is allergic rhinitis, but it must be taken into account that it is not always an exclusive manifestation of the allergy but at the same time, the genes involved in the pulmonary function (airway hyperresponsiveness) can intervene. In these cases, rhinitis precedes asthma, as in many cases eczema manifests itself early in infants who later suffer from asthma.

Based on these data, the respiratory processes of allergy cause are rhinitis, tracheobronchitis, and asthma.

3. Respiratory processes

3.1. Rhinitis

The respiratory mucosa shows structural and functional homogeneity in all areas where it is found with the exception of greater vascularization in the nasal area. Its specific function lies in providing a defense against the noxious agents that so abundantly penetrate through the airways. The entire inner layer of the airway participates in the ciliary defense system with which the epithelial cells are endowed, in addition to the various mucosal glands and cells of the immune system, present in the subepithelial layer throughout the mucous membrane. Likewise, it can present a unified response, although in different ways, against allergens in individuals with an atopic disposition. For this reason, allergic disease is commonly manifested by symptoms that affect the entire mucosa (rhinitis, asthma, rhinosinusitis, rhinoconjunctivitis), although frequently only a partial stretch is affected, with symptoms exclusive to the upper airway.

In most asthma cases, children display rhinitis or rhinopharyngitis during some time prior to symptoms at lower levels of the respiratory tract. Even at birth or in the first months of life, children can display symptoms of allergic rhinitis, although at that age specific sensitization can hardly be demonstrated. The symptoms that can precede the onset of asthma are hydrorrhea, nasal congestion, and sneezing. Later, when asthma is treated correctly and symptoms disappear, rhinitis symptoms—albeit mild—tend to remain as an aftermath.

3.2. Tracheobronchitis

If the concept of asthma is based on the occurrence of dyspnea (shortness of breath is preponderant), episodes of coughing and breathing noises can also lead to an asthma diagnosis.

In many cases (at any age) coughing is productive, and low wheezing is detected by auscultation, sometimes due to tracheobronchial obstruction by mucus secretion or by some degree of constriction of the smooth bronchial muscle. Asthmatic children sometimes display these same symptoms, alternating with dyspnea episodes (**Table 1**).

3.3. Asthma

Even under proper treatment conditions, asthma is usually persistent. Patients experience unexpected relapses, although most children experience clear and progressive improvement, both in terms of seizure frequency and intensity. The speed of improvement largely depends on the prognostic outlook. Many children stop having attacks shortly after starting hyposensitization treatment, and in these cases, a positive prognosis is highly likely. However, another non-negligible group in the framework of undeniable improvement displays a greater tendency to relapse, sometimes as a result of seemingly banal respiratory processes caused by epidemic viral infections or nonspecific triggers, such as change in the weather, overexertion, or exposure to environmental contaminants. In general terms, without a solid underlying statistical basis, it has been estimated that in 75% of cases, childhood asthma is benign and subject to good prognosis, 20% of asthmatic children suffer from a mild form, and the remaining 5% suffer from severe asthma. Children in this 25% group are therefore most likely to suffer from asthma in adulthood [4, 5]. In any case, we must bear in mind that wheezing is a common symptom in other processes which should be considered (**Table 2**).

Cough	Whistling rales	Dyspnea	Expectoration
Rhinopharyngitis	Tracheobronchitis	Wheezing bronchitis	Chronic bronchitis
Sinusitis	Foreign body	Bronchiolitis	Bronchiectasis
Adenoiditis	Mucoviscidosis	Gastro-oesophageal reflux	Pneumonia
Whooping cough	Bronchiectasis	Extrinsic allergic alveolitis	Mucoviscidosis
Tracheobronchitis	Hemosiderosis	Extra-tracheobronchial:	Hemosiderosis
Laryngitis	Lymphadenopathy	• Pleuritis	COPD
Bronchitis	Pulmonary cysts	• Pneumonia	
Bronchiectasis	Immotile cilia syndrome	• Tuberculosis	
Foreign body	Lobular emphysema	• Pulmonary edema	
Gastrooesophageal reflux	Tracheoesophageal fistula	• Etc.	
Inhalation of irritating gases	Eosinophilic bronchitis		
Eosinophilic bronchitis			
COPD			
Psychogenic			

Table 1. Common tracheobronchial symptoms and more frequent processes (other than asthma).

Common	Asthma
	Gastroesophageal reflux
	Infections: bronchiolitis, bronchitis, pneumonia, upper respiratory
Uncommon	Bronchopulmonary dysplasia
	Foreign body aspiration
Rare	Bronchiolitis obliterans
	Congenital vascular abnormalities
	Cystic fibrosis
	Immunodeficiency diseases
	Mediastinal masses
	Primary ciliary dyskinesia
	Tracheobronchial anomalies
	Vocal cord dysfunction

Table 2. Causes of wheezing in children.

Several follow-up studies over several years reach different conclusions in the numbers of asthma persisting in adulthood. These differences can be explained by the different criteria taken into account for estimating the persistence of the disease, in addition to the different conditions of patients' lives, such as the workplace, smoking, climate, urban or rural living, etc. It is known that broncholability (airway hyperresponsiveness) persists indefinitely, although with proper and early treatment it can decrease significantly. This weakness can be displayed in unfavorable situations, such as a viral infection and excessive exposure to environmental pollutants, with the onset of sporadic respiratory symptoms (wheezing) which should not be labeled as asthma and much less be interpreted as asthma relapse.

It is difficult to establish a prognosis beforehand, although some data are available to evaluate it. The immune system matures throughout childhood, so most infections occur in the early years of life. Depending on their environment, children may experience up to a hundred infections in their first 8 or 10 years of life, i.e., an average of one infection per month, so that the immune system receives sufficient stimuli for maturation. While they do not always appear with a very striking clinical picture, these respiratory tract infections can trigger bronchial obstructions of varying intensity. This can result in the false diagnosis of asthma, without the existence of a hypersensitivity reaction or inflammation that leaves permanent side effects. As the defense system matures when a child is between 6 and 8, the child stops experiencing bronchial obstruction, and these "false asthma patients" will be the ones who heal spontaneously.

Some endocrine system maturational factors (still undetermined) in some children boost an improvement around puberty, more evident in boys than in girls. But this improvement is only apparent. In most cases it is not uncommon for more or less mild symptoms to appear sporadically, sometimes during physical exercise, in addition to other minor symptoms such as rhinitis or eczema, when present. The typical physical and psychological changes during

this age make asthma patients often underestimate their symptoms and abandon treatment. However, spirometry tests often reveal impaired respiratory function, to varying degrees, predominantly affecting peripheral bronchi ("small airways"), evidenced by the reduced mid-expiratory flow.

To make a prognosis, the location of bronchial obstruction must be determined, and it is not detectable when the respiratory function is checked only by measuring the peak expiratory flow (PEF). The obstruction of peripheral bronchi is an indicator of poor outcome. It has even become established that this data may have prognostic value, so that 7-year-old children without asthma are more likely to develop asthma in the following 6 years if their average expiratory flow is lower than normal. Expanding on this concept, the reduction of mean flow at that age also predicts the persistence of asthma in adults, 25 years later.

3.3.1. Pathogenesis

Asthma is a disease whose onset in childhood has, in most cases, a genetic factor of not only allergic predisposition (production of specific IgE against allergens and eosinophilia) but also factors responsible for airway hyperresponsiveness (AHR). In other cases, especially of later onset, bronchial inflammation, with initial involvement of the respiratory mucosa, asthma is a consequence of environmental irritants or viral infection, in which case neutrophilic is the dominant.

In the pathogenesis of asthma, bronchospasm occurs first aided by the AHR, and it is what characterizes the initial phase of asthma attack. Airway smooth muscle contraction involves the formation of actin-myosin cross bridges with the rate of formation dependent upon the activity of myosin light chain kinase and myosin light chain phosphatase. Subsequently, the release of various proteolytic enzymes of eosinophils (ECP, MBP, EPO, EPX) and phospholipid metabolites (LT, PG, TX) triggers the inflammatory reaction, which is responsible of the prolongation of the crisis as well as the chronicity of the process. Congenital AHR is the consequence of several mutations in the genes encoding β_2-adrenergic receptors of the bronchial smooth muscle, related to the greater sensitivity of the same in the people affects due to the mutation. The consequence of this mutation is the α-adrenergic (constrictor)/β-adrenergic (relaxant) imbalance. In addition, mast cells have been demonstrated in the bronchial smooth muscle of these patients, which undoubtedly have a predominant role in the hyperresponsiveness when the mediators responsible for bronchial smooth muscle constriction and the attraction of eosinophils and neutrophils (histamine, tryptase, chymase) and later those involved in the inflammatory reaction (leukotrienes, prostaglandins, thromboxanes) are relapsed [1, 2].

Genetic predisposition (endotype) can be based either in the mutation that leads to congenital AHR or the multiple factors affecting atopic. The coincidence to both genetic backgrounds determines the early onset of rhinitis/asthma which has led to the conception of different phenotypes. Family atopy is a key factor for the onset of allergic disease in infancy, but the absence of AHR, sometimes, is manifested by skin, digestive, or anaphylactic (food, drug) reactions. If the family atopic predisposition is absent, the AHR that can be secondary to environmental factors will also be basic in the pathogenesis of asthma that in these cases, the onset will be later.

The AHR is responsible for acute and sporadic bronchospasm (episodes of dyspnea). The other symptoms, not sporadic, but habitual of greater or less intensity depending of the gravity, environment, and treatment, are mainly due to the inflammation that accompanies the process, whose cause differs in different circumstances [5–10].

Dominant symptoms, age of onset, persistence, and causes (viruses, allergens, environmental irritants) are the factors that influence the variability of phenotypes, not always persistent from childhood to adulthood, which undoubtedly differentiate the process at the different stages of life.

3.3.2. Prognostic criteria

The beforehand assessment of disease progression can be established based on the following data: family history, child-dependent factors, environment, disease characteristics, and early and correct treatment. The sum of unfavorable data worsens prognosis.

Family genetics, especially parental, increases the risk proportionally to the acuteness of the allergic process (asthma, eczema). Moreover, immunodeficiencies must be taken into account. They favor respiratory infections, especially selective IgA deficiency, which is present very often due to hypersensitivity reactions, perhaps due to an immune compensation mechanism. Within the environment, both the location of the home and the atmosphere within the home may have a significant influence. In terms of age of onset, it should be noted that in the first 2 or 3 years of life, episodes of shortness of breath may occur due to various anatomical-physiological causes (immune immaturity, bronchial constriction, vagal tone) which result in narrowing of the bronchial lumen in various circumstances. This should not be labeled as asthma. Thus, it is estimated that between 45 and 85% of these children in a few years will no longer exhibit symptoms. They are considered "false asthma patients" who will heal spontaneously. The possibility exists for the child to suffer from rhinovirus-induced bronchiolitis leading to significant desquamation of bronchial epithelium and inflammatory reaction which facilitates the passage of pneumo-allergens leading to sensitization, even in the absence of prior atopic predisposition.

Sensitization to multiple allergens is another cause of poor outcome, especially if these involve a fungus. These microorganisms result in a type of asthma which is more difficult to control. With regard to an atopic predisposition, suffering from several allergic diseases is another cause of poor outcome. Atopic eczema is the most influential, in direct proportion to how extensive and stubborn it is.

3.3.3. Evolutionary criteria

Not all children with wheeze at early age will have asthma later; the sex also influences the natural evolution of the process with a shift in severity and prevalence biased toward women after puberty (**Table 3**).

In summary, the evolution of the process can be summarized as follows:

Good evolution: decrease in the number of asthma attacks in 1 year to half or less than the previous year, respiratory function within normal limits.

	Age (year)		
	<5	**5–11**	**12–18**
Prevalence by sex	M > F	M > F	Before puberty: M > F After puberty: F > M
Predominant effector cell	Neutrophil Eosinophil	Eosinophil	Eosinophil
Reticular basement membrane	Begins after the first birthday	Not as thick as adults	Thickening approaches that are seen in adults
Lung function	Measures difficult to obtain	Changes associated with duration of asthma symptoms	Deficits present in those patients who began wheezing before age 3 but might not present in those who began wheezing in later childhood
Incidence of exacerbations	++++	+++	++

Taken from Szefler et al. [11].

Table 3. Pathophysiologic changes of asthma by age.

Moderate evolution: decrease in the number of attacks in 2 years to at least half of the previous year at the start of treatment, improving the intensity of attacks and maintaining an acceptable respiratory function.

Poor evolution: the number and intensity of attacks do not change, and the respiratory function does not improve but actually tends to worsen, with FEF_1 between 70 and 80% of predicted and $FMF_{25–75}$ between 40 and 60% of forecast.

Deterioration: aggravation of the crisis in frequency and/or intensity, with impaired respiratory function: $FEV_1 < 80\%$ and $FMF_{25–75} < 60\%$ of forecast.

3.3.4. Healing criteria

Atopic genetic predisposition is not modified by any therapeutic measure, but clinical signs can be suppressed in a large number of patients with appropriate preventive measures and early treatment, targeting primarily causal aspects (immunotherapy can partly correct the altered immune response).

The clinical criterion is possibly the most valuable with regard to how long the child must be free of symptoms, particularly dyspnea, since sometimes children unexpectedly relapse after a long time of being symptom-free. A widely accepted period of time is 2 years without an attack.

In parallel to the absence of subjective clinical symptoms, the objective assessment of the respiratory function (spirometry tests) is another data factor that must unavoidably be taken into account. This is because children cannot be considered asthma-free if bronchial obstruction persists, although they may be free from obvious symptoms. Certainly, a child with alterations in spirometric values cannot be considered risk-free.

Chronological	2 years without crisis
Functional	Absence of signs of bronchial obstruction (large and small airways)
Airway hyperresponsiveness	Decreased response to allergen inhalation
	Decreased response to methacholine or histamine inhalation
	Decreased response to physical exercise
Immunoallergics	Decreased response to prick test
	Decrease of total IgE
	Increase of IgG (IgG_1–IgG_4)
	Increase of Th1 lymphocytes
	Decrease of basophil degranulation (decrease of histamine release)

Table 4. Asthma healing criteria.

Table 4 shows the different data to be assessed after the etiological treatment (immunotherapy), the results of which will depend on the asthma cure criteria. This brings changes in the immune response (reduction of IgE, increase in IgG_1-IgG_4, and increase in Th1 lymphocytes), together with the decrease in histamine. Bronchial hyperresponsiveness, however, is maintained, although reduced by elimination or reduction of bronchial inflammation, which in itself does not represent a risk of relapse, as it is verified after an average of 10 years after the medical discharge [12].

4. Preschool children

Some anatomo-physiological characteristics of the airways of infants and young children predispose to the occurrence of processes that lead to narrowing or bronchial obstruction, which are manifested by common symptoms, such as cough, dyspnea, and noise or wheezing.

The smaller bronchial caliber is a basic fact that facilitates the obstruction, as a consequence of the inflammation of the mucosa, of the constriction of the smooth muscle or of the increase of the secretion of the tracheobronchial mucous glands. Also known is the physiological vagal tone of the infant, which lasts during the first years of life. Pathologically, bronchial hyperresponsiveness is a fundamental fact in the pathogenesis of asthma. This AHB, by stimulation of the bronchial smooth muscle, is usually secondary to the inflammatory reaction that takes place in various circumstances in the bronchial mucosa, but it is also a characteristic of individuals with atopic predisposition, since there are certain abnormalities in the protein chain of the β-receptors of the smooth muscle.

In relation to the infectious bronchopulmonary disease, so frequent in the first years of life, there is the well-known immaturity of the immune system, which in some children last for several years (transient immunodeficiency of the infant), facilitating the appearance of bronchial inflammatory processes, which they manifest with symptoms partly common to other

tracheobronchial processes. The inflammation of the small airways is correlated with the existence of exhaled nitric oxide (FeNO) whose values have been proposed for the diagnostic confirmation of asthma, even up to school age because it is considered as a potential biomarker to distinguish endotypes. However, despite its strong correlation with atopy, it seems that it can only be considered as a biomarker for transient wheezing but not for persistent wheezing phenotypes.

Viral infections (respiratory syncytial virus (RSV) and rhinovirus (RV)) are a frequent cause of respiratory processes in young children, often transient (bronchiolitis), although in some cases the persistence of chronic inflammation, disrupted epithelium, and airway remodeling can condition the major bronchoconstrictor response to environmental irritants and, especially, to allergens, causing asthma [13].

With this background, it is not uncommon for processes of different causality to manifest clinically with similar symptoms, which can lead to erroneous diagnoses, if the knowledge of differential signs is not in-depth, such as genetic background, habits, and family environment, among others (**Table 5**).

Dominant symptom: cough	Maxillary sinusitis
	Adenoid vegetations
	Rhinopharyngitis
	Whooping cough
	Primary ciliary dyskinesia
Pseudoasmatic symptoms	Infectious pathology
	• Immunodeficiencies
	• Bronchiolitis
	• Bronchitis obliterans
	Tracheobronchial foreign body
	Cystic fibrosis of the pancreas
	Gastroesophageal reflux
	Mediastinal tumors and adenopathies
Less frequent processes	Congenital anomalies
	• Laringo and tracheomalacia
	• Vascular rings
	Alpha-1 antitrypsin deficiency
	Hypersensitivity pneumonitis
	Pulmonary hemosiderosis
	Alveolar proteinosis
	Eosinophilic lung

Table 5. Most outstanding processes for differential diagnosis.

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In a large study (8310 mothers) in which the presence of respiratory symptoms that took place between 6 and 81 months after birth was investigated, the authors reached this conclusion:

1. Sixty-eight percent of the children never had episodes of wheezing .
2. Ten percent had them sporadically, with a prevalence between 18 and 42 months.
3. Eight percent presented them for a long time, between 30 and 69 months.
4. In 2% the prevalence was low until 19 months, increasing after 18 months.
5. Late onset in 5% of the children, in which the prevalence of sibilance lasted up to 42 months in 50% of them.
6. Persistent wheezy (7%) with 65% prevalence at 6 months and approximately 90% prevalence thereafter [14].

In a more recent study, the same authors analyze the need to assess the exhaled nitric oxide fraction (FeNO) together with the respiratory function, family history, and environment in which the child lives, in addition to the treatment received, facts that may condition the persistence of the process for a longer time [15].

A study carried with the purpose of knowing if the different respiratory processes in young children could be related to breastfeeding and its duration finds above all a possible protection against viral infections, but it has not been possible to establish its participation in the establishment of phenotypes related to other respiratory processes.

It is really difficult to establish a certain diagnosis of asthma in the first years of life, since in many cases it is the evolution of symptoms over the years that allows confirming the diagnosis with support of the appropriate immuno-allergological study. The diagnosis of asthma will be reached by previously excluding other possible causes of dyspnea or wheezing. As a more frequent diagnostic alternative, "wheezing bronchitis" would be characterized by single or repeated episodes of dyspnea or wheezing and/or noisy breathing, of variable intensity, which may be febrile, which begin in the first year of life and do not continue more than the third year. In summary, in preschool children this respiratory episodes can be classified as (a) occasional, one episode every 4–6 weeks or less; (b) frequents, more of one episode in 4–6 weeks, isolated intercrisis symptoms, mild; (c) moderate persistence, very frequent exacerbations, symptoms that interfere with daily activities and sleep; and (d) severe persistent, daily or almost daily symptoms, with frequent episodes of dyspnea.

Coinciding with these concepts, different phenotypes of bronchospasm pathology in children have been differentiated, distinguishing asthma and transient bronchitis (wheezy bronchitis) that encompassed various processes suffered by a group of children that after preschool age do not have bronchospasm, a consequence of the predisposing factors. However, it is not always easy to determine the phenotype of a certain patient, and it may even be that over time, as it evolves, there is a need to change the criteria. Hence the need to pay attention to the characteristics of the symptoms and their evolution, in addition to a whole series of

circumstances, such as the suffering other allergic processes by the same child (eczema, milk protein allergy), early onset of the clinic, or the existence of similar pathology among siblings, parents, or other close relatives, environmental contaminants, climate, etc. The lack of family history in approximately 20% of cases adds another obstacle to the diagnosis.

In most children, asthma begins in the first 5 years of life. Different studies indicate that between 15 and 35% of preschool children have had some episode of respiratory difficulty, accompanied or not by wheezing or other respiratory sounds (wheezing bronchitis); however, 60–65% of those children will not suffer a crisis after the third year.

Apart from asthma and wheezing bronchitis, many other bronchopulmonary diseases have an early start, with a symptomatology that may recall those processes, as more frequent, sinusitis, adenoiditis, mucoviscidosis, ciliary dyskinesia, various malformations, gastroesophageal reflux, etc., to be taken into account in all cases.

Physiological factors (reduced bronchial caliber, physiological vagal tone, immune immaturity) tend toward normalization, while pathological factors (familial atopy, congenital or acquired bronchial hyperresponsiveness) depend on their incidence and decrease or increase depending on the circumstance.

5. School age and teenagers

The asthmatic adolescent presents particular characteristics, in part conditioned by the teenager's personality but also, possibly, because this illness has a different expression than in other ages. It is a fact that an undetermined percentage of children improve when reaching adolescence, even being free from symptoms in some asthma cases qualified as mild or moderate. Nevertheless no cases of severe asthma disappear totally at this age. Some undetermined factors, possibly hormone-related, might influence this improvement in males. It should be clarified if this improvement is real and *definitive. Many* children at this age, with sporadic and mild symptoms more or less frequent (coughing, mild dyspnea after exercise), get used to their illness and say they feel well, although it is not rare listen to whistling of different intensity. Even in asymptomatic cases, with normal auscultation, the spirometry presents disturbances that show bronchial obstruction.

The persistence of respiratory processes that begin at preschool age can occur if the phenotype corresponds to the existence of atopic predisposition or, also, in some children infected by rhinovirus (RV) [16]. At these ages, asthma derives predominantly from atopy in relation to Th2 lymphocytes (IgE), eosinophilia, and airway inflammation. Early initiation of adequate treatment avoids the persistence and/or severity of asthma at these ages, especially in cases in which asthma was considered mild or moderate. However, no case of severe asthma stops manifesting at this stage of life and may become chronic due to the persistence of obstruction of the airways, manifesting recurrently serious or episodic, when predisposing factors are scarce. The persistence of asthma in these ages may be due to the intensity of the atopy (association of atopic eczema) and the AHR; the process self-control, failure to comply or the abandon treatment and inadequate medication in the crisis; and family or work environment, smoking, powder, animals, etc.

Some undetermined factors, possibly hormonal, must influence the improvement and also the inversion that occurs at this age, in terms of frequency by sex, with predominance in the female, predominant in adulthood. In some cases in which the symptomatology is very sporadic, however, spirometry can show alterations that reveal bronchial obstruction that will condition the subsequent evolution. However, in milder cases, it is possible that spirometry remains within normal limits, so the methacholine or histamine test can help demonstrate the hyperresponsiveness.

Four phenotypes related to responsible allergens (especially fungi) and AHR have been distinguished: [1] later sensitization to indoor allergens, [2] multiple early sensitization, [3] early sensitization to outdoor allergens (especially *Alternaria*) and later sensitization to indoor (including *Aspergillus*), and [4] early sensitization to indoor allergens and later sensitization to outdoor allergens [17, 18]. In some cases, asthma begins in adolescence, possibly due to the low familial predisposition of atopy (only uncles or grandparents) and only slight bronchial hyperresponsiveness, which is why it is possible that the environment or the beginning of smoking is responsible for its start [19].

At these ages, coming from the smallest ones or beginning in them, the following phenotypes and endotypes of asthma can be distinguished that usually extend until the adult age:

1. Eosinophilic: allergic, by aspirin, severe hypereosinophilic of late onset, and allergic bronchopulmonary mycosis
2. Prone to exacerbations: allergic, by aspirin, severe hypereosinophilic of late onset, wheezing from a younger age, exacerbation by virus, and premenstrual syndrome
3. Related to obesity: obstruction of air flow, severe steroid dependence, severe hypereosinophilic of late onset
4. Overexertion: athletes, wheezing from preschool age.
5. Fixed airflow limitation: noneosinophilic (neutrophilic)
6. Scarce response to steroids: neutrophilic, eosinophilic, obesity—airflow obstruction [1]

In cases of severe asthma, different clinical pictures can be distinguished, conditioned by the phenotype: [1] persistent chronic symptoms, [2] recurrent severe asthma exacerbations, [3] persistent airflow obstruction, and [4] brittle asthma: type 1 (persistent wild swing in peak flow) and type 2 (sudden acute deteriorations). In some of these variants, the aforementioned viruses (RSV) may be responsible.

One of the main problems at this age in the no compliance of medication. This feeling of well-being makes the adolescent to stop it, using the drugs only when not feeling well and, frequently, in an uncontrolled way and not using the proper medication. Mortality in teenager asthma has been related to self-management of severe crisis, with insufficient or inappropriate medication.

6. Resulting processes

Summarizing the concepts presented, the coordination of the endotype and the phenotype are the basis for the establishment of these currently accepted tracheobronchial processes:

1. Transient early wheezing: no family or analytical history of atopy; early onset and disappearance between 3 and 5 years; decreased lung function, but recovered before 6 years of age; no bronchial hyperreactivity (normal methacholine test); and eosinophilia or high levels of IgE. Possible predispositions: prematurity, genetic (congenital reduction of functional residual capacity (V_{max} FRC)), or environmental (smoking mother, irritants).
2. Non-atopic wheezing: beginning before 3 years of age, the majority (73% of cases) after viral infections (RSV, para-influenza, others), although infection by RSV before 3 years of age has been associated with the risk of persisting wheezing episode till 10 years of age. In general, there is no family history of atopy or clinical or analytical signs of it in the same patient: decreased lung function after infection and progressive normalization with maximum persistence of the process up to 13 years of age.
3. Atopic wheezing/asthma: in which there is no lack of familial atopic predisposition, it starts before 6 years (80%); early sensitization to pneumo-allergens; positive specific IgE and skin tests; frequent coincidence with associated allergic processes (rhinitis, eczema, urticaria); progressive deterioration of lung function and bronchial hyperreactivity; persistence that may reach adulthood, if adequate treatment is not carried out at an early stage (especially immunotherapy when indicated, anti-inflammatory, bronchodilators); and environmental measures [4, 20–23].

7. Controversies

Despite the evidence of the different ways of presenting the bronchospastic processes in the pediatric age, the evidence of the aforementioned predisposing factors has been questioned because there are several respiratory processes with similar symptoms but varying in the age of onset, persistence, family history, and coexistence or not with other processes of allergic cause (cutaneous, digestive). Likewise, the different coincidence of wheezing, atopy, or AHR can condition the different respiratory processes, based on the different uses of the term phenotype, such as:

1. Any observable trait (partial phenotype) includes signs, symptoms, measurements, and biological markers.
2. Clinically useful grouping defines groups that differ with respect to features of interest, e.g., risk factors, response to treatment, and prognosis.
3. Hypothesized disease entity defines a condition that is thought to represent a distinct disease entity.

These factors are the basis for doubting the reality of the phenotypes whose definition is also debatable, requiring a better definition of the term and its possible relationship with the aforementioned respiratory processes. “In the meantime, we should treat phenotypes as exactly that the best current working hypothesis” how the authors of the work finish [24].

Author details

Francisco Muñoz-López

Address all correspondence to: 5314fml@comb.cat

Department of Pediatric Immunoallergology, Faculty of Medicine, University of Barcelona, Clínic Hospital-Sant Joan de Déu Hospital, Spain

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