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Allergic rhinitis and asthma

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The measurement of exhaled nitric oxide in routine practice

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Key words

Exhaled nitric oxide, asthma, inflammation, diagnosis, control, treatment

Summary

Exhaled nitric oxide (NO) is considered the most easily available clinical test to indirectly assess the level of eosinophilic airway inflammation in asthma, and to predict the efficacy of anti-inflammatory treatment with inhaled corticosteroids (ICS). It is possible to measure the level of exhaled NO using online or offline methods. The most widely used online method employs techniques that enable NO in exhaled air to be measured in a single exhalation, calculating the value at the end-expiratory plateau. Because of the correlation between the level of exhaled NO with the level of eosinophilic inflammation in the airway of asthmatic patients, it has been proposed as a clinical marker in the practice of respiratory and allergy physicians with differing targets. In particular it is considered to be highly effective in the diagnosis of allergic asthma, to be capable of identifying those patients with a higher response probability to inhaled corticosteroids, and to a lesser extent, to be of value in contributing to the management of the disease. The possibility of easily taking measurements of FeNO in an office setting even by relatively young children, and the availability of a portable device, opens a significant perspective for the routine use of FeNO evaluation in daily practice.

Introduction

Though asthma is an inflammatory disease of the airways, requiring regular treatment with inhaled corticosteroids in most cases, control of the disease is mainly based on symptom and lung function measurement, which do not correlate closely to the level of underlying airway inflammation (1,2).
Exhaled nitric oxide is considered the most easily available clinical test to assess the level of eosinophilic airway inflammation in asthma (3,4) indirectly, and to predict the efficacy of anti-inflammatory treatment with inhaled corticosteroids (ICS) (5).
Nitric oxide (NO) is synthesized by different cell types through the enzyme NO synthase. This enzyme is encoded by three different genes in the human genome: nNOS (in neurons), eNOS (in endothelial cells) and iNOS (in macrophages, neutrophils, eosinophils and in epithelial cells). The first two forms are constitutive, the last one inducible, and therefore, the expression of iNOS increases following inflammatory stimulation (6).

Among the variety of biological effects it is involved in, NO mainly relaxes airway smooth muscle, affects ciliary beat frequency and mucus secretion, increases vascular leakage and eosinophil infiltration and is also involved in neurotransmission (7).
In the normal subject, the levels of nitric oxide in the nasopharynx and paranasal sinuses are higher than in the lower airways, this being a defence mechanism that may inhibit the proliferation of bacteria, viruses and parasites in upper airways (8).
In 1991 Gustafsson et al. offered the first description of the presence of NO in exhaled air (9). Levels of exhaled NO have been shown as increased in patients suffering from inflammatory airway diseases, in particular allergic asthma, due to the up-regulation of iNOS (10,11).

Measurement of nitric oxide

In 1997, the European Respiratory Society (ERS) (12), and in 1999, the American Thoracic Society (ATS) (13), defined guidelines for the correct measurement of FeNO, which were updated in a joint document in 2005 (14).
From a practical viewpoint, it is possible to measure the level of exhaled NO using online or offline methods. The most widely used online method employs techniques that enable NO in exhaled air to be measured in a single exhalation, calculating the value at the end-expiratory plateau. This method can be used with cooperating children: the child inhales NO-free air trough a mouthpiece, then exhales for at least six seconds at a constant rate (50 ml/s) through a mouthpiece directly into the analyzer device. For children under age 12, a four second exhalation may be sufficient. It is important to maintain a pressure of between 5 and 20 cm H2O during the exhalation to exclude nasal contamination and to keep flow constant. The test should be repeated twice, with values within 10% of each other (13,15), the final value being the mean. For non-cooperating children, an alternative method has been proposed: the child breathes spontaneously trough a mouthpiece or a facial mask, and the exhalation flow is kept constant manually or adjusted using an automatic control system (16,17).
The offline method is based on collection of exhaled air into a balloon for later analysis. Bodini et al. have evaluated possible differences between samples analyzed at different times, and in different humidity and temperature (18). They concluded that the level of exhaled NO remains stable for nine hours. In the same study, they demonstrated that environmental temperature does not influence the measurement for the first nine hours after collection, but the use of silica gel can alter the results. In current clinical settings, the offline technique is considered obsolete and is no longer recommended.

Exhaled nitric oxide in diagnosis

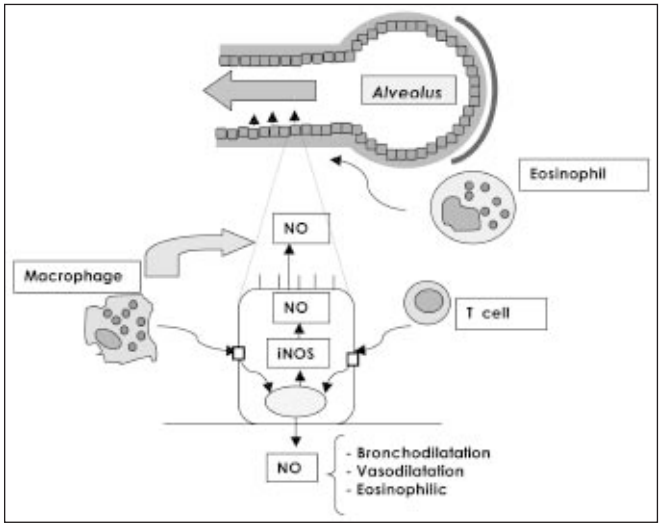
Asthma is an inflammatory disease of the airways characterized by variable clinical symptoms and recurring obstruction of the airways. Traditional diagnostic methods, including lung function, responsiveness of the airways and associated symptoms, often correlate poorly with the underlying level of airway inflammation (19).
According to international guidelines, the diagnosis of asthma should be based on symptoms, peak flow measurement and spirometry including response to bronchodilator, but several studies show that exhaled NO could be a better method for monitoring airway inflammation in clinical practice. In fact, in asthma diagnosis, peak flow measurement and spirometry present low sensibility and may be normal in mild asthmatics.
Smith et al. have shown the superiority of exhaled NO measurements and induced sputum analysis in the diagnosis of asthma compared with conventional tests (20).
In a subsequent analysis of their data, the same authors reported that the combination of FENO (cut-off point 33 ppb) and spirometry (cut-off point for FEV1 of 80% predicted) yielded a sensitivity of 94% and specificity of 93% (21).
Dupont et al. have shown that the concentration of exhaled NO in patients with asthma was significantly higher than in patients with comparable symptoms but without asthma, and in normal subjects (22).
Exhaled NO has also been reported as closely related to asthma and allergy symptoms, whereas spirometric indices, such as percent predicted FEV1, were not (23).
Exhaled NO values are increased in both allergic and non-allergic asthmatic patients, being higher in the first group, without significant correlation to FEV1 (24).
Compared to other techniques, measurement of exhaled NO is easy to implement, reproducible and feasible in young children—it can easily be performed during outpatient visits to follow up asthmatic patients.
One major disadvantage of exhaled NO as a diagnostic test for asthma lies in a number of confounding factors that might influence the level of exhaled NO, like viral infection of the upper airways, which needs to be taken into consideration at the time of each evaluation (10).

The use of exhaled NO to diagnose asthma has been demonstrated as a less expensive alternative to standard diagnostic tests (25).

Exhaled nitric oxide and asthma treatment

In allergic asthma, eosinophils are the main inflammatory cell type, representative of the level of underlying disease at the site of the airway. Accordingly, it is particularly noteworthy that FeNO is significantly correlated to the percentage of eosinophils in samples from induced sputum in patients with allergic asthma (4,26).
Lower FeNO values were observed in subjects for whom bronchial inflammation was not eosinophilic, directing physicians to different diagnoses (neutrophilic asthma, gastroesophageal reflux, chronic obstructive pulmonary disease, etc.) (27).
Additionally, the relationship between eosinophilia and FeNO could also be of interest in patients with difficult asthma, aiming at distinguishing between the eosinophilic and neutrophilic phenotypes (28).
In a clinical setting, the assessment of markers of airway inflammation could have direct implications for the therapeutic approach to asthma patients, particularly children.
During acute asthma exacerbations, exhaled NO is a more perceptive indicator than serum markers, such as eosinophilic cationic protein (ECP) or interleukin-soluble. It would also appear to be a more helpful indicator to assess response to glucocorticoid therapy in young asthma patients (29).
FeNO has been demonstrated to promptly mirror the anti-inflammatory effect of inhaled corticosteroid in asthmatic patients (30) and the rebound of airway inflammation after cessation of therapy (16).
The hypothesis that FeNO can be effective in identifying patients with a higher probability of response to inhaled steroids treatment has been tested further and demonstrated in a study by Smith et al. This study showed that asthmatics with higher levels of FeNO (>47ppb) had a better response in terms of improved symptoms, lung function and airway hyperreactivity compared to those with lower levels of FeNO. (31). Szefler et al. have shown that levels of FeNO were the only indicator capable of identifying children responsive to steroid therapy in a study designed to evaluate the response profiles of fluticasone and montelukast in mild-to-moderate persistent childhood asthma (32).
FeNO measurements have also been reported as practically useful in detecting patients at risk of relapse after withdrawal of inhaled steroid therapy in children with clinical asthma remission (33).
On the basis of the above evidence, since asthma symptoms and lung function measurement correlate poorly with the degree of airway inflammation, biomarkers indicating airway inflammation levels are regarded as potentially useful guides in managing treatment. Because of its simple application in clinical practice, the potential to let FeNO measurement drive decision strategies in the therapy adjustment of asthmatic adults and children has been widely investigated.
In a study by Smith and colleagues, the adjustment of inhaled corticosteroid treatment on the basis of either FeNO, or an algorithm based on conventional guidelines, was compared in 97 patients with asthma (34). That study showed an evident, though not statistically significant, reduction in the number of asthma exacerbations and a 40% lower maintenance dose of inhaled corticosteroid needed to control the asthma, in the group following the FeNO algorithm, concluding that this approach offers a logical alternative to the use of clinical data alone for dose adjustment of inhaled corticosteroids in the management of asthma.
Similar conclusions were reported by Pijneburg et al. in a group of 85 children with atopic asthma in whom treatment with inhaled steroids was guided on the basis of either symptoms or FeNO (35). The authors showed better

Figure 1 – Schematic representation of the source of exhaled NO in the airway. NO synthesized throughout the bronchial tree is harvested by the expiratory flow. The level of NO at the mouth is flow-dependent, with an inversely-related function



control of airway inflammation, lung function and airway hyperreactivity in the group treated according to FeNO levels, though failing to achieve a reduction in the required dose of steroid. They concluded that an algorithm using FeNO for inhaled steroid dose titration every three months for one year was advantageous in comparison to conventional treatment adjustment based on symptoms.

More recently, several studies have failed to show significant advantages when using FeNO as a tool for treatment tailoring in asthmatics compared to conventional approaches based on guidelines (36, 37) or compared to frequent home monitoring of symptoms (38).

In patients with chronic, persistent asthma, corticosteroid treatment can be successfully titrated with the use of FeNO measurements.

In the study by Szefler et al. (36), the authors concluded that addition of fractions of exhaled NO as an indicator of the control of asthma resulted in higher doses of inhaled corticosteroids, without clinically significant improvements in symptomatic asthma control. Nevertheless, the proportion of patients requiring at least one course of oral corticosteroids in the FENO group was 24% lower than the control group. Furthermore, in two important and relatively large subgroups, the primary outcome of the study (maximum number of days with symptoms) was significantly reduced. Thus, patients with a BMI of > 30, representing 28% of all patients, had 0.6 fewer maximum days with symptoms (p=0.0245), and patients with total IgE of > 460 kU/L (33% of patients) had 0.5 fewer maximum symptom days (p=0.0296).

Moreover, Taylor and Bush observed that the FENO management protocol did not allow for a reduction of inhaled corticosteroid dose when FeNO was low in symptomatic patients, which may have affected the conclusions substantially (39).

Gibson has systematically assessed the studies where exhaled nitric oxide has been used to tailor asthma therapy (34-38, 40, 41) and concluded that those studies were disadvantaged by the choice of algorithm decisions being based on healthy subjects rather than on the specific population of asthmatics, with sufficient possibilities for decision-making to enable discernible benefits.

Price et al. have evaluated asthma treatment and management guided by FENO measurement with NIOX MINO instead of symptoms and lung function from an economics perspective (25). They showed that a FENO-based strategy can result in a reduction of annual costs of £341 for patients with mild-to-severe asthma and of £554 for those with moderate-to-severe asthma with similar health benefits.

Conclusions

The body of literature available in the field of nitric oxide measurement in patients with respiratory disease highlights the potential application of this recent marker in the practice of respiratory and allergy physicians with differing targets. In fact, it has been demonstrated as highly effective in the diagnosis of allergic asthma, and capable of identifying those patients with a higher response probability to inhaled corticosteroids, and to a lesser extent, contributing to the management of the disease. The possibility of easily taking measurements of FeNO in an office setting even by relatively young children, and the availability of a portable device, opens a significant perspective for the routine use of FeNO evaluation in daily practice.

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Climate change and increase of allergic diseases

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Introduction

Several studies have demonstrated that the asthma prevalence is increased from the early sixties, with a growth concerning both children and adults in different countries with different ways of life.
Other allergic diseases has increased all over the world too. Among the supposition suggested, we can find the air pollution and the Hygiene Hypothesis (1). Climate Change is a further additional and supplementary element that it could come into play to explain the increase in allergic diseases observed during recent years. In recent years the Climate Change discussion has carried on from the field of academic studies into the political field. Certainly, this matter does not bring to an objective understanding of the problem. This is the reason why I'll not debate if the real cause of the Climate Change lies in the anthropogenetics factors or in a natural cycle of the earth.

Kyoto Protocol

On 16 February 2005, after a series of Climate Change Conferences organized by the United Nations, the Kyoto Protocol has entered into force; the agreement signed in the Japanese city in 1997, with which 160 countries committed themselves to carrying out Industrial and Environmental polices, tending to reduce the global warming. All acceding countries, including Italy, EU, Russia and Japan, but not USA, should check and reduce emissions of gaseous pollutants in the Atmosphere, especially those derived from industrial. Economic sanctions would be expected for those countries which won't observe the rules.
It is certain that in the 19 Century, an increase in global average temperature of 0,6% has already occurred. In parallel to the rise in temperatures has occurred an increase in atmospheric concentrations of some gasses, such as CO2, because of human activities. The consequences of that phenomenon are countless. On worldwide, the mean sea-level has an yearly growth from 1 to 2 mm. Actually, it is known to all the decrease of non-polar glaciers.
Moreover, consequently to the rise in temperatures, it takes place an early blooming and an early return of migratory birds. Other consequences of rising temperatures are: anticipated seasons and the appearance of insects in the northern Hemisphere. No need to neglect the eventuality of a continental precipitation increase of 5-10% in the northern Hemisphere.

Scientific evidences

Many evidences show the form with the Climate Change alter the clinical manifestations of allergic diseases too. On this topic, recently, they have been published some review (2, 3).
Firstly, it could assert that, in certain changing climatic conditions, plants produce a greater quantity of pollens. Secondly, there are some evidences in increased allergenicity in pollens produced by trees exposed to highly temperatures. Moreover, it seems that the temporal and geographical distribution of pollen has been altered by the Climate Change. For instance, some studies have shown that the trend towards early pollinic seasons spread in some species (4,5).
Some others studies have checked other characteristics from allergenic plants. The allergenic plants seem produce greater number of pollen if exposed higher carbon dioxide concentration.

Atmospheric events and asthma

The climate change seems to be associate to an increase of the frequency of intense rain and thunderstoms. It is known for long time the relation between storms and asthma crisis, in which the release of pauci-micronic particles should come into play, thanks to Gramineae pollens and a more highly fungal spore concentration (6-8). Also others pollens, like the Parietaria, can be asthma cause (9,10) . During thunderstorms should not be ignored the rising in the air of the wind and electric discharges, because they should have an asthmatic effect derived from aspecific hyper-reactivity. There is also who suppose that an increase in the number of lightning all over the world is correlated to the Climate Change, but this ipothesis is not still supported from valid studies.
Also other atmospheric event, like the Nino, in the Tropical Pacific (becoming more frequent and persistent, especially in the last 30 years), have been considered cause of allergic symptoms, but not there is unanimous agreement on this. Indeed, it is present only a paper, in literature, based on only three years of data (11).

Increasing in temperatures and asthma

The importance of increasing in temperatures has already been noted in 1998 by Hales (12), and he learnt a significant correlation between asthma prevalence and average temperatures. Other studies – that showed the importance of climate factors in the asthma prevalence – has been done by Weiland (13) and Zanolin (14). The first study conclusions were that the asthma prevalence is correlated inversely to the altitude, and directly to indoor relative humidity levels. In the second study asthma symptoms are correlated with the lowest latitude in proximity of the sea, with highest annual average temperatures and also with lower temperature ranges.

Early blooms

We hold scientific evidences that suggest the Climate Change has already caused a relevant impact on the behaviour of migratory animals and on flowering plants. For instance, Menzel's (15) studies have showed that in Europe, from 1969 up till now, spring blooms come about 6 days early and the autumn is 4,8 days late. In Great Britain, Fitter (16) showed that in the last ten years the average of flowering date of 385 plant species is 4,5 days early.
Emberlin highlight, in two different reports (17, 18), information that show how in the last 30 years in Europe there was an advanced of 5-10 days of birch flowering and he shows that in the last 10 years in Worchester (UK), the Alnus spp and Corylus spp flowering season is more prolonged and severe. A similar situation has been showed by Garcia Moro (19) in Spain : in the last 10 years in the Iberian Peninsula the Fagaceae flowering 15 days earlier than the Quercus. Stach's work (20) shows that the average temperature plays an important rule in flowering and with its rise the temperature influences also the advance in flowering. Moreover, Stach emphasizes how the temperature is correlated to the concentration of Artemisia pollen. In addition to anticipating the flowering, the temperature support the contents of pollen within the pollen granules. Ahlholm (21) has found to notice a large content of Bet v 1 within pollen granules picked in gardens with the average of the average daily temperature.

Anthropogenic Climate Change

Human activities lead to an increase in CO2 and a resulting Climate Change (IPCC). Carbon dioxide, one of the environmental pollution factors, is the more important gas to greenhouse effect and it is growing in parallel with the average temperature level. Some studies (22, 23) showed, both greenhouse and outdoor, that a large Ambrosia pollen production is joined to a growth in atmospheric CO2. At high carbon dioxide levels ragweeds plants (*Ambrosia artemisifolia L.*) showed greater biomass and reproductive effort with increase of pollen production. One of the clearest changes is earlier onset of flowering and lengthening of the growing season (24). The consequence of this is the greater exposure of the atopic patients, with increased risk of sensitizations and onset of symptoms.

Conclusion

The data that we have exposed indicate that an association exist between the increase of air temperature and an earlier flowering period. Therefore, the people with allergies are exposed to a greater pollen allergen with a consequent increase of sensitization and symptoms. In our experience, in the space of 30 years, in our outpatients' de-

partment, we have checked those information on patients. Particularly, we have noticed that in the last 30 years, in the Mediterranean area, some flowering were in remarkable advance, such as the *Parietaria spp* and the *Olea aeropea*. Also other species have showed a significative advance, such as the Cupressacee and the Graminaceae. Closed to those advance, there is an increase in days with presence of pollens and also in total pollen count, in most pollens produced, in the space of a year.

In parallel, as a likely consequence of growing exposure, there is an increase in preponderance of sensitization to inhaled allergens over atopic subjects living in the area where the aerobiological study took place. We can conclude that the allergic respiratory diseases, especially the asthma, are complex diseases with a large number of causal factors that interact with each other. The Climate Change get worse those diseases. The Climate Change hypothesis is not clashed with the Hygiene Hypothesis one, but it is a further hypothetical explanation.

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Thoracic high resolution computed tomography (HRCT) in asthma

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Key words

Asthma, HRCT, Remodelling, Bronchiectasis

Summary

Introduction: *High-resolution computed tomography (HRCT) is a widespread medical imaging method for the study of thoracic diseases. In asthma it is very useful particularly when it is difficult to achieve an effective control of disease, and in severe deterioration.* ***Aim:*** *It was intended to evaluate the imaging changes by HRCT in asthmatic patients and to assess the expression according to the symptoms and duration of disease.* ***Material and methods:*** *Thirty three patients from the Outpatient Department, with asthma classified in the different clinical severity stages according to GINA, were randomly included. They were submitted to HRCT (Somaton Plus-4, Siemens®). The lesions were classified in reversible (mucoid impaction, acinar pattern centrilobular nodules and lobar collapse) and irreversible (bronchiectasis, bronchial wall-thickening, sequellar line shadows and emphysema).* ***Results:*** *The 33 asthmatic patients (20 female) had an average age of 44.76±16.98 years and a mean disease evolution time of 23.39±14.83 years. 30% had mild persistent asthma, 43% moderate persistent asthma and 27% severe persistent asthma. All the patients were under inhaled corticotherapy. Only 6 patients had normal HRCT: 4 with mild persistent asthma (4 to 25 years of duration of disease) and 2 with moderate persistent (10 to 48 years of duration of disease). 81.81% of the patients had changes in HRCT, being the irreversible lesions the most frequent. The most important irreversible lesions were observed in severe asthma patients with longer duration of disease. All the patients with reversible lesions had also irreversible changes. Most of the bronchiectasis were centrally located and were found in severe asthma patients. Irreversible changes were identified in 3 patients with mild asthma and a maximum of 6 years of duration of disease.* ***Discussion:*** *HRCT findings were related with asthma severity and long lasting disease but there are some asthmatics that also present early abnormalities, even in milder forms. All the groups of asthmatic patients presented all types of imaging changes, including the irreversible ones. In asthma these changes can be the result of individual patterns of response to frequent exacerbations, leading to a persistent chronic inflammatory process that will determine airway remodelling, even in early stages of disease and/or mild asthma.*

Introduction

Bronchial asthma is characterised by reversible airflow obstruction and bronchial hyperresponsiveness (1, 2). It is a chronic inflammatory disease, where most patients can achieve complete reversibility with bronchodilators and/or anti-inflammatory medications (2, 3). However, in many asthmatics this inflammatory condition can be followed by healing that may result in an altered structure, due to the remodelling of the airways (3, 4). Structural changes can occur in central and peripheral small airways and are thought to result in an irreversible component of the airway obstruction seen in asthma and perhaps also in the development of airway hyperresponsiveness (1, 2, 5). Patients with an irreversible airflow obstruction can experience considerable morbidity and account for a high percentage of the health costs related to asthma (6).

The detection and quantification of airway remodelling have been based on histological examination (7). However, the development of high resolution computed tomography (HRCT) has provided a potential non-invasive technique for its measurement in vivo, even though the information that can be obtained from HRCT is essentially less detailed than that obtained on histological examination (6, 7).

With conventional chest radiography one can only evidence a limited number of abnormalities in asthmatic patients (8.

The dimensions of the central airway in patients with asthma can be assessed quantitatively by computed tomography (CT), but these measures are considered indirect measures of airway remodeling and analysis of the wall area or luminal area of small airways are beyond the spatial resolution of conventional CT9,10. Measures derived from full-expiratory scans by HRCT can indicate the presence of air trapping in asthma (2, 9, 11) and hyperlucency should identify hyperinflation (12). Subsequently, HRCT has been tried as an alternative procedure and some authors describe its potentiality in evaluating the airways in patients with asthma (2, 13). The HRCT scans of asthmatics patients have shown both decreased and increased bronchial lumen area, excessive airway narrowing in response to a variety of stimuli and airway wall thickening, in addition to mosaic perfusion and gas trapping on expiration (7).

The aim of this study was to evaluate the imaging changes by HRCT in asthmatic patients and to assess their relationship with the clinic and the duration of disease.

Methods

Subjects: The patients were selected from our outpatient department. During 33 consecutive weeks we selected the first adult asthmatic patient that had a scheduled appointment each Monday. All the patients were non-smokers, with previous clinical and functional diagnosis of asthma, according to the GINA criteria (14). They should be under appropriate optimized therapy, according to clinical severity. Demographic and clinical data such as age, duration of disease, medication used and severity of disease were taken into account. Allergic sensitizatisation was defined by positive skin-prick tests to common aeroallergens (Leti, Spain) and/or serum specific IgE levels higher than 0.35 kU/L for at least one allergen.

Only the patients without respiratory infections or exacerbations of asthma in the last month were selected for this study. Written informed consent was obtained from all the subjects.

HRCT image acquisition: CT scans were performed using a single detector device (Somaton Plus 4; Siemens, Erlangen, Germany). Two sets of 15 to 20 images (according to the size of the patient's thorax) were acquired at full inspiration. The scans were performed on the whole lung using a sequential mode (1 mm section thickness at 20 mm increment intervals), in order to get images from the apices to the diaphragm. CT scans were performed using the following parameters: 120 kV, 200 mAs, pitch 1,0 and 0.5 to 1 second rotation time.

The images were reconstructed using a high spatial resolution algorithm and visualized with a window setting of 1500 Hounsfield units (HU) width and -700 HU level.

The scans were sequentially interpreted by two radiologists that did not have any previous knowledge about the chest X-ray and the clinical severity of the disease. Both internal and external diameters of the apical bronchus of the right upper lobe were measured in order to evaluate the agreement between the 2 observers. Consensus reading was regarded as the average of the two observer's measurements.

The following lesions were taken into consideration for the proposal of analysis: reversible and irreversible, and classified from mild to severe (+ to +++). Several HRCT scan abnormalities were annotated: reversible lesions as mucoid impaction, acinar pattern and lobar collapse, and irreversible forms of damage as bronchiectasis, bronchial wall thickening, sequellar line shadows and emphysema (4).

All the data was collected and analyzed, in order to iden-

tify possible relationships between the changes in HRCT and clinical characteristics of the patients.

Statistical analysis: Statistical analysis was performed with SPSS 15.0 (2006 SPSS Inc, Chicago, Ill, USA). Distribution of frequencies was obtained for the different groups of patients. Additionally, average and standard deviation were calculated for quantitative variables. Association between allergic sensitization and abnormal HRCT scans was evaluated by chi-square tests (Pearson or Fisher's exact test). Differences between patients with more than one irreversible lesion and those with only one as well as patients with more than one reversible lesion and those with only one were analysed by Mann-Whitney U test. Significance was considered for a p value less than 0.05.

Results

Thirty-three patients were included, 20 female and 13 male. The mean age of the sample was 44.76±16.98 years old and the mean duration of disease was 23.39±14.83 years old. According to the clinical classification 30% of the sample had mild persistent, 43% moderate persistent and 27% severe persistent (Table 1). Allergic sensitization was present in 24:33 patients (house dust mites=16; grass pollen=7; mites and grass pollen=2).

All the subjects were under optimized therapy, according to clinical and functional severity, namely inhaled corticosteroids. No patient was under immunotherapy or were previously submitted to this treatment. No one had systemic corticosteroids therapy in the last 6 months either.

Table 2 shows the clinical and radiological characterization of the patients. A full concordance of imaging results interpretation was obtained from the two imagiologists.

Only 6 out of 33 patients had HRCT without changes (Table 1). These patients had a mean age of 35.83±17.99 years and 16.50±17.22 years of duration of disease. From these patients, 4 had mild persistent (duration of disease 10.25±9.88 years; 4 to 25 years) and 2 moderate persistent asthma (duration of disease 29.00±26.87 years; 10 and 48 years). The other 29 patients (81.81%) showed abnormalities, as outlined in Tables 1 and 2; the mean age of these patients was 46.74±16.44 years, with a duration of disease of 24.93±14.15 years. Despite a higher frequency of abnormal HRCT scans in atopic patients compared to non atopic (20 versus 7 patients), these differences had no statistical significance (p=0.533).

The most common irreversible lesion was bronchial wall thickening (69.7%), followed by bronchiectasis (45.5%), sequellar line shadows (30.3%) and emphysema (24.2%) (Figures 1 and 2).

Bronchial wall thickening was found in 88.9% of the patients with severe persistent, in 78.6% with moderate persistent and in 40% of the mild persistent asthma patients.

In the majority of patients, the bronchiectasis were centrally located (86.7%). These patients had mostly severe forms of ashtma. Nonetheless, 2 patients with mild persistent asthma had also bronchiectasis. These lesions were present in 77.7% of the patients with severe persistent, 42.9% of the moderate persistent patients and in 20% of those with mild persistent asthma.

Ten patients had sequellar line shadows shown by HRCT. This lesion was found in 66.7% of patients with severe

Table 1 - Summary of the radiological lesions, according to the asthma severity classification.

		Mild persistent	Moderate persistent	Severe persistent	Total
Total of patients		10	14	9	33
Irreversible lesions	Bronchial wall thickening	4	11	8	23
	Bronchiectasis	2	6	7	15
	Sequellar line shadows	0	4	6	10
	Emphysema	0	4	4	8
	Total of patients				26
Reversible lesions	Acinar pattern	1	3	2	6
	Lobar collapse	1	3	2	6
	Mucoid impaction	0	1	0	1
	Total of patients				7
Normal		4	2	0	6

Table 2 - Clinical and imaging characterization of the patients. Asthma classification: MiP=mild persistent; MoP=moderate persistent; SP=severe persistent. Sensitization: HDM=house dust mites. P=pollens. N=study without changes. Reversible lesions: MI=mucoid impaction ; AP=acinar pattern; LC=lobar collapse. Irreversible lesions: Br=Bronchiectasis (C=Cylindrical, V=Varicose, Q=Cystic); BWT=bronchial wall thickening; SLS=sequelar line shadows; Em=Emphysema (C=Centrolobular, P=Paraseptal, B=Bullous. UL-R: right upper lobule. Ling.=Lingula)

Patient	Gender	Age	Disease	Classification	Atopy	Sensitization		Reversible lesions			Irreversible lesions			
	(Years)	(Years)	(Years)			HDM	P	MI	AP	LC	Br	BWT.	SLS	Em
1	F	50	30	MiP	Yes	Yes	No					+		
2	F	40	25	MiP	Yes	No	Yes	N	N	N	N	N	N	N
3	M	28	21	MiP	Yes	No	Yes				C, V			
4	F	24	12	MiP	Yes	No	Yes					+		
5	F	23	6	MiP	Yes	No	Yes	N	N	N	N	N	N	N
6	M	21	6	MiP	Yes	Yes	No	N	N	N	N	N	N	N
7	M	22	5	MiP	Yes	Yes	No					+		
8	F	19	5	MiP	No	No	No		+	UL-R	C, V			
9	F	23	4	MiP	Yes	Yes	No	N	N	N	N	N	N	N
10	F	54	2	MiP	Yes	Yes	No					+		
11	F	68	48	MoP	No	No	No	N	N	N	N	N	N	N
12	F	61	46	MoP	No	No	No				C, V		+	+
13	F	55	45	MoP	Yes	No	Yes			+		++	++	
14	F	46	40	MoP	Yes	Yes	No		+	+	C, T, V	+++	++	+
15	F	43	30	MoP	No	No	No					+		
16	M	51	30	MoP	No	No	No					+		
17	M	70	26	MoP	No	No	No			Ling.		+	++	
18	F	38	23	MoP	Yes	Yes	No	+	+	+	C, V	++		
19	M	18	17	MoP	Yes	Yes	No				C, V	++		
20	F	17	16	MoP	Yes	Yes	Yes					++		
21	F	65	17	MoP	No	No	No				V	+		
22	F	57	11	MoP	Yes	No	Yes					+		
23	M	40	10	MoP	No	No	No	N	N	N	N	N	N	N
24	F	36	8	MoP	Yes	No	Yes		+		V	++		
25	M	75	60	SP	Yes	Yes	No				C, V	+	+	C
26	M	51	45	SP	Yes	Yes	No				C	+		C, B
27	F	44	33	SP	Yes	Yes	No						+	
28	M	48	30	SP	Yes	Yes	No				Q, V, C	++	+	
29	M	51	29	SP	No	No	No				C	+		
30	M	61	29	SP	Yes	Yes	No		+		C	+	+	
31	M	58	25	SP	Yes	No	Yes				C	+	+	
32	F	60	23	SP	Yes	Yes	No		+	UL-R	T, C, V	+	+++	P
33	F	60	15	SP	Yes	Yes	No					+		+

persistent and in 28.6% of the moderate persistent asthma patients. None of the asthmatics with mild persistent form showed this lesion.

Concerning emphysema, no mild persistent asthmatic presented this lesion, however it was found in 28.6% of the moderate persistent patients and in 44.4% of those with severe persistent asthma.

The most important irreversible lesions were more common in patients with severe and long-lasting asthma. Three patients with mild asthma and duration of disease lesser than 6 months had irreversible lesions: 2 with bronchial wall thickening, one with central bronchiectasis and another one with varicose bronchiectasis. The patients with more than one irreversible lesion were older and had a longer duration of disease, than those with only one: 53.31±14.12 versus 37.18±15.29 years (p=0.009) and 29.88±13.89 versus 17.73±11.61 years (p=0.064), respectively. At least two irreversible lesions were more frequently found in atopic patients than in non atopic (12 patients versus 4 patients), (p=0.081).

Reversible lesions were less common than the irreversible ones. Moreover, all patients with reversible lesions had also irreversible abnormalities. Patients with more than one reversible lesion had a mean age of 40.75±17.11 years and duration of disease of 22.75±14.29 years. Those with only one reversible lesion had a mean age of 55.50±14.39 years, with a mean duration of disease of 27.00±15.17 years. These differences were not statistically significant.

Figure 1 - HRCT scan image of a patient with varicose and cystic bronchiectasis, sequellar line shadows and emphysema

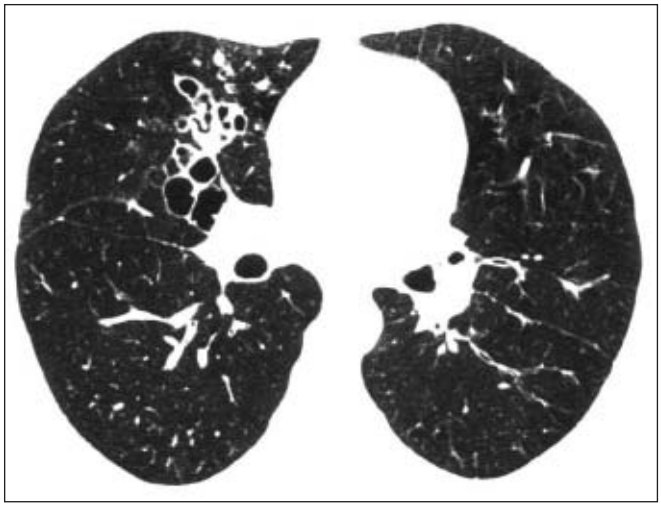
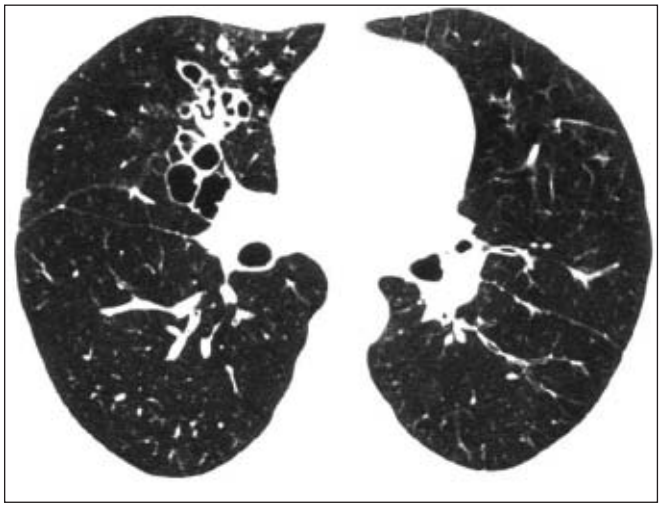


Figure 2 - HRCT scan image of a patient with mucoid impaction and bronchial wall-thickening



Discussion

We studied non smoker asthmatic patients, in order to establish a relationship between the clinical severity, duration of disease and lesions detected by HRCT. The previous chest X-ray results obtained for all the patients did not allowed to suspect the morphological abnormalities showed by HRTC. The majority of the mild and moderate asthmatic patients had normal images on chest X-ray, and only the patients with severe forms or long lasting asthma showed bronchial wall thickness features.

The prevalence of abnormal HRCT scans in our study was higher, comparing to similar reports from other groups; perhaps the degree of differentiation of our outpatient clinic can explain this disparity. In a sample of 31 asthmatic adult patients with clinical and functional worsening of disease submitted to chest radiographies and thorax HRCT scans, Rimondi et al. found abnormal HRCT scans in 61% of the patients (15). Vignola and coworkers in a study of 30 asthmatic patients and 12 patients with chronic obstructive pulmonary disease described 70% of abnormal HRCT scans among asthmatic patients (16). Paganin and colleagues found 71.9% of abnormal HRCT scans, in a study with 57 asthmatic patients8. A study with 48 asthmatic patients, undertaken by Lynch et al., described a higher abnormality rate than our results, with 92% of the sample with abnormal HRCT scans (17).

We found all types of imaging changes in all groups of patients, including the irreversible ones, although the

most severe lesions were more frequently found in asthmatic patients with the worst clinical impairment and longer duration of disease. There are some previous studies that corroborate our findings. Awadh and co-workers described that all groups of patients with near fatal attack of asthma, even those with moderate and mild asthma had greater airway wall thickening than the normal subjects (13). In the same study they found a greater airway wall thickening in the patients with the most severe symptoms comparing with those with milder forms (13). In a study comparing patients with near fatal, mild-to-severe asthma, and healthy controls Lee YM et al did not found significant differences in the bronchial wall thickening between the different groups of patients (18).

We found a high frequency of irreversible lesions among different groups of asthmatic patients even in those with milder forms. All patients with abnormal HRCT scans presented irreversible lesions. These severe injuries were present in 81.81% of our sample, being the most frequent bronchial wall thickening, followed by bronchiectasis, sequellar line shadows and emphysema.

Regardless of the majority of our patients being atopic, the presence of HRCT scan abnormalities were not related with allergic sensitization. Other groups found similar results (9, 19).

Bronchial wall thickening is the result of airway remodelling. It is considered an irreversible structural abnormality in asthmatic patients (8, 18, 20), and can be responsible for irreversible airflow obstruction and an increase in airway responsiveness (2). The airway wall thickness results from mucosal infiltration with inflammatory cells, smooth muscle hypertrophy, deposition of connective tissue, and mucous gland hyperplasia (13). It has been demonstrated that these structural changes can occur not only in the central, but also in the peripheral small airways (2, 21). Other studies have been suggesting an association between asthma severity and bronchial wall thickness (6, 13). Bronchial wall thickening was the most frequent irreversible lesion detected by HRCT in our study (69.7% of the patients). This finding is corroborated by the results of other studies, where this lesion was the most common, but with different prevalence rates: 44% (Park et al.) (22) and 92% (Lynch et al.) (17).

Bronchiectasis is recognized as an important cause of respiratory morbidity, particularly in developing countries (23). We found bronchiectasis in 45.5% of our sample, mainly centrally located and mostly in patients with severe asthma. This percentage was lower than the data obtained by other groups. Rimondi et al. reported this abnormality in 53.8% of the patients (15). In 1992, Paganin and co-workers observed bronchiectasis, mostly cylindrical, in 37 of 57 asthmatic patients (8). Another classic study, undergone by the Lynch group, found a prevalence of 77% of bronchiectasis among a group of 48 asthmatic patients (17).

Another irreversible lesions found in our study were the sequellar line shadows, present in 30.3% of our sample; we did not found this lesions in patients with mild asthma. Patients with this radiological pattern had a longer duration of disease. Harmanci et al. correlated this radiological pattern with the duration of asthma, in a group of 160 asthmatic patients (24).

The less frequent irreversible lesion was emphysema; nevertheless it was observed in almost a quarter of the sample. This injury had been associated with severe asthma in the past, but only recently its role in asthma was well established; the use of HRCT scans, providing a high degree of anatomical detail, was helpful in determining this association (25).

In our sample, the irreversible lesions were dominant in early-onset than in late-onset asthma. We also found this type of severe abnormalities in younger patients and in those with short duration of disease, suggesting an early appearance of lesions.

In addition, patients with more than one lesion had a longer duration of disease; however one patient from the group of moderate persistent asthma and the longest disease evolution time had a normal HRCT scan.

We stress that some patients (ex. 7, 8 and 10) with mild forms of asthma and with reduced duration of disease have already irreversible lesions. Probably this could represent an expression of distinct phenotypes of asthma not discriminated by a classical clinical classification.

Eight patients were studied 5 years later with another HRCT scan (data not published). All of them were regularly observed in the outpatient department. Two patients changed their clinical severity pattern from moderate to mild and from severe to moderate, respectively. We found an increase of imaging abnormalities, with one patient presenting cylindrical bronchiectasis, despite the excellent clinical evolution and another one with a previous normal CT scan, showing brochiectasis, in spite of the maintenance of the same clinical severity.

The abnormalities described in our patients are probably related to the remodelling process. The parenchymal and airway changes that become irreversible throughout the long course of the disease, as structural changes can occur early during the course of disease (16, 26). In the past, Pa-

ganin et al. demonstrated the reversibility of the remodelled airways, after antiasthmatic therapy, with mucoid impaction, acinar patterns, and lobar collapse considered reversible lesions; however, lesions as bronchial wall thickness, bronchiectasis, and emphysema were described irreversible (8, 20). A more recent study illustrated bronchial wall thickening as partially reversible, after intensive anti-inflammatory therapy; however air trapping was not improved18. It seems that bronchial wall thickening is reversible when submucosal inflammation or oedema predominates, and irreversible when the airways are remodelled extensively (18).

As outlined before, we believe that morphological abnormalities occur earlier at the beginning of the disease, probably delayed by anti-inflammatory therapy. Perhaps, there are individual genetic factors, not yet clarified, that enhances or limits the remodelling and the severity of asthma. It seems that the HRCT findings are related with asthma severity and long lasting disease but there are some asthmatics that also present early abnormalities, even in milder forms. So this technique has a role in the management of the asthmatic patients, namely for the early identification of bronchiectasis that need a convenient therapeutic approach.

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Ready-to-use house dust mites atopy patch test (HDM-Diallertest®), a new screening tool for detection of house dust mites allergy in children

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Key words

Ready-to-use atopy patch test, house dust mites, atopic dermatitis, children

Summary

Aim: *to assess the accuracy and safety of a ready-to-use atopy patch test (HDM-Diallertest®, DBV Technologies, Paris) in the diagnosis of sensitization to house-dust mite (HDM) allergens in children with or without atopic dermatitis.* ***Patients and methods:*** *prospective analysis of a systematic allergic work-up was carried out in 47 children, age 57.4+42 months (mean + SD, range 7 to 176 mo), presenting with isolated or combined atopic dermatitis (AD, n=28) or other symptoms without AD (control group, n=19). Children were routinely tested for specific HDM-IgE [against D. pteronyssinus (DPT) and D. farinae (DF)], and skin testing based on HDM (DPT & DF) skin prick test (SPT) and ready-to-use HDM-ATP (HDM-Diallertest®), with a reading at 72 hours.* ***Results:*** *15 children (31.9%) exhibited specific IgE against both DPT and DF, 16 children (34.04%) exhibited positive SPT against DPT and 17 (36.1%) against DF. HDM-Diallertest® was positive in 15 cases (31.9%). Among these, 9 exhibited with an eczematous reaction showed an excellent correlation with both SPT and specific IgE for DPT and DF, respectively 93.3%, 97.77%, 90.47%, and 90.47%. The different diagnostic techniques of HDM sensitization neither differ between groups, nor correlated specifically with the different clinical manifestations. No side effect was observed during and after patch testing, except for a local reaction without diffusion outside the local test area.* ***Conclusion:*** *The 3 diagnostic techniques exhibited a comparable level of accuracy for the diagnosis of HDM allergens sensitization. The excellent concordance of the highest class reactions of HDM-Diallertest® with the other diagnostic techniques indicates a potential role as a screening tool for the detection of HDM sensitization in infancy.*

Introduction

The atopy patch test (APT) with aeroallergens was introduced by Platts-Mills et al (1) as an experimental model and as a diagnostic tool. These authors showed that the application of house dust mite (HDM) antigen to the epidermis leads to a considerable percentage of positive local reactions in sensitized individuals with atopic dermatitis (AD). However, differences in methodology and lack of gold standard for methodology and interpretation are two major obstacles for development of the APT. The aim of our study was to assess the accuracy and safety of a ready-to-use HDM-APT (HDM-Diallertest®) and the correlation with specific HDM IgE [D. pteronyssinus (DPT) and D. farinae (DF)], and skin prick test (SPT) for DPT and DF, in the assessment of a pediatric allergic population, together with its usefulness in the diagnosis of sensitization to allergens of HDM in children with or without atopic dermatitis (AD).

Methods

Patients

A prospective study of a systematic allergic work-up was carried out between January 2005 and June 2005 in a population of 47 children, age 57.4+42 months (mean + SD, range 7 to 176 months), 18 girls and 29 boys, enrolled following referral to the outpatient clinic of respiratory, cutaneous and food allergy. Patients exhibited AD (n=28, 59.57%), isolated (n=23, 48;9 %), or combined (2 children with digestive manifestations and 3 with pulmonary manifestations), or no AD symptoms, i.e. non AD group, n=19 (40.43%), consisting of patients with digestive manifestations such as colic, vomiting, gastro-esophageal reflux and failure to thrive (n=10, 21.27%), or pulmonary manifestations (n=2, 4.25%), ear nose throat (ENT) manifestations (n=2, 4.25%), angio-edema (n=2, 4.25%), and combined digestive, pulmonary and ENT manifestations (n=3, 6.38%). All abnormal cutaneous, digestive, pulmonary, ENT and angio-edema reactions were analyzed by the parent's child and then validated by the physician. Children were not enrolled if under any food elimination diet, presenting with important skin lesions thus preventing from the possibility of patch testing, and having been treated with antihistamine and oral or cutaneous steroid medications for the last week.

Study design

Children were routinely tested via a blood sample for measurement of HDM specific IgE (DPT and DF), SPT with DPT and DF and ATP, using the ready-to-use technique HDM-ATP (HDM-Diallertest®). All children were randomized for the application of APT on the right or the left side of the back. AD was assessed at enrollment using a routine local score based on the severity and extension of eczematous skin lesions as follows: no, mild, moderate, severe and very severe atopic dermatitis. The physician responsible for the study also did the SPT reading but was blinded to the results of specific IgE. All side effects related to HDM-Diallertest® technique were recorded throughout the study duration, according to a questionnaire explained by the research nurse. A written parental consent was obtained in all cases from both parents.

Methods

DPT & DF specific IgE were analyzed using the RAST Cap System (Phadia, Uppsala, Sweden) calibrated with reference to the World Health Organization standards for IgE. Its specificity was already assessed and its use in children already reported (2). References data for HDM specific IgE were those of the manufacturer with the lowest detection level at 0.35 KU/L, class 1, 0.35-0.70 KU/L, class 2, 0.70-3.5 KU/L, class 3, 3.5-17.50 KU/L, class 4, 17.50-50 KU/L, class 5, 50-100 KU/L, and class 6, > 100 KU/L. (3, 4). A specific HDM-IgE class > was considered as positive.

SPTs were performed with a drop of commercially available extracts of DPT and DF from (ALK®, Copenhagen, Denmark) with a potency of 10 HEP, which, according to the company, is equal to 20 000 BU/ml. The procedures were performed on the children back if aged less than 12 months and on the volar part of the forearm in those above 12 months. Histamine di-hydrochloride (ALK, Copenhagen, Denmark), 10 mg/ml, and glycerosaline were used as positive and negative controls. The wheal size reaction scoring system was class 1 from 3 to 5 mm, class 2 (6-10 mm), class 3 (11-15 mm), and class 4 (>15 mm). A positive reaction implied a wheal diameter 3 mm larger than the negative control after 15 minutes (5).

The ready-to-use HDM ATP (HDM-Diallertest®, DBV-Technologies, Paris, France), 11 mm diameter, consisted of 3 parts, already described (6). A same mixture of pure HDM, 50% DPT and 50% DF was deposited on

the central plastic support in the form of micro granules (5-40 Ìm) mixed with dry powder of glucose forming a homogeneous mono-layer, retained by electrostatics forces. Each HDM-Diallertest® thus contained 300 µg ± 30 µg of DPT & DF. The ready-to-use APT serving as control had the same structure but was deprived of any HDM powder in the central part.

A phone call was given 24h after application of the APTs in order to assess the safety of the HDM-Diallertest®, a specific surveillance of the reaction through the transparent patch membrane being requested from parents The occlusion time was 48 hours, and the results were read by the same investigator 24 hours following removal of the devices, i.e. at 72 hours. Digital pictures were taken at 72 hours and kept into a computer. HDM-Diallertest® reactions were graded according to the criteria used in conventional contact allergy patch testing [International Contact Dermatitis Research Group (ICDRG) rules] with the modifications of the European Task Force on AD (ETFAD) consensus meeting (7, 8); i.e. - as negative; ?, only erythema (class 1); +, erythema and infiltration (class 2); ++, erythema, few papules (up to 3) (class 3); +++ erythema, papules 4 to < many (class 4); ++++, erythema, many or spreading papules (class 5); +++++, erythema, vesicules (class 6). The reaction was considered positive if at 72h the HDM-Diallertest® exhibited a skin reaction graded above that of the negative control, i.e. presence of clear redness and palpable infiltration > class 2, as described by Holm et al et al (9). The same physician evaluated all tests.

Statistical analysis

All statistical tests were performed with the Statview program (Abacus®, Ca, USA). Calculation of mean, median and extremes were done for all quantitative parameters. Differences between qualitative and quantitative parameters were analyzed by the chi-square test and Anova multiple analysis test. A p value of < 0.05 was considered as statistically significant. The concordance test kappa of Cohen was used to assess the degree of concordance between the different diagnostic allergic tests used in this study. The concordance between the different parameters was considered function the value of kappa as; excellent between 0.81 and 1, good 0.61 and 0.8, moderate 0.41 and 0.6, weak 0.21 and 0.4, and finally bad 0 and 0.2.

Results

Among the 47 children, 15 children (31.9 %) exhibited positive specific IgE titers against both DPT and DF, whereas 16 children (34.04%) exhibited positive SPT against DPT and 17 (36.1 %) against DF. The HDM-Diallertest® was positive in 15 cases (31.9%), Table 1. Among these 15 positive HDM-Diallertest®, 9 exhibited an eczematous reaction and showed an excellent concordance with DPT & DF-SPT and specific IgE against DPT & DF, respectively 93.3%, 97.77%, 90.47%, and 90.47%. The different HDM sensitization diagnostic techniques used neither revealed any differences between groups, nor correlated specifically with the different clinical manifestations, Table 1.

Table 1 - Characteristics of AD and non AD patients, n=47

	AD patients	Non AD patients	P	Total
	n=28	n=19		n=47
Female/Male	10/18	8/11	ns*	18/29
Age, months, median (range)	42.3 (7-128)	79.6 (8-176)*	0.002**	49 (7-176)
Positive HDM-Diallertest®, n(%)	11 (39.28)	4 (21.05)	ns*	15 (31.9)
Positive specific DPT-IgE, n(%)	10 (35.7)	5 (26.31)	ns*	15 (31.9)
Positve specific DF-IgE, n(%)	10 (35.7)	5 (26.31)	ns*	15 (31.9)
Positve DPT-SPT, n(%)	11 (39.28)	5 (26.31)	ns*	16 (34.04)
Positive DF-SPT, n(%)	8 (28.5)	9 (47.36)	ns*	17 (36.1)

*According to Chi square test
** According to Anova test
ns : not significant

HDM-Diallertest® exhibited a tendency towards a correlation with the highest RAST and SPT classes, whereas only 7 children exhibited negative HDM-Diallertest® concomitant with RAST-DPT & DF classes above 1. Similarly, only 7 and 8 children exhibited negative HDM-Diallertest® concomitant with SPT-DPT & DF classes above 1, Tables 2 & 3 Children exhibited positive HDM-Diallertest® results concomitant with either positive specific IgE or SPT in 76.4% of cases, whereas those exhibited positive HDM-Diallertest® > grade 3 concomitant with either positive specific IgE or SPT in all cases. The HDM-Diallertest® exhibited also excellent concordant results with both HMD-IgE and SPT against both DPT & DF, kappa between 0.81 and 0.95, Table 4.

Finally, among the 47 children, no side effect was observed during and after patch testing, the reaction being always confined to the local testing area, without diffusion outside.

Discussion

We show in this first pilot and preliminary study carried out in 47 children that the 3 diagnostic techniques exhibited a comparable level of accuracy for the diagnosis of

Table 2 - Correlation between serum specific IgE (RAST classes) to Dermatophagoides pteronyssinus (DPT), Dermatophagoides farinae (DF) and HDM-Diallertest® reactions to HDM extract

RAST classes (DPT), n HDM-Diallertest®	0	1-3	4-6	Not done
Negative	18	4	3	5
Class 1	0	1	1	0
Class 2	6	0	1	0
Class 3	2	0	0	0
Class 4	1	1	1	0
Class 5	0	1	1	0
Class 6	0	0	1	0
RAST classes (DF), n HDM-Diallertest®	0	1-3	4-6	Not done
Negative	18	3	4	5
Class 1	0	1	1	0
Class 2	6	0	1	0
Class 3	1	0	0	1
Class 4	1	1	1	0
Class 5	0	1	1	0
Class 6	0	0	1	0
				0

RAST class of > 1 and APT of > 2 were recognized as positive

Table 3 - Table III : Correlation between skin prick test (SPT) to Dermatophagoides pteronyssinus (DPT), Dermatophagoides farinae (DF) and HDM- Diallertest® reactions to HDM extract

SPT classes (DPT), n HDM-Diallertest®	Negative	Class 1	Class 2	Class 3	Class 4	Not done
Negative	21	2	3	1	1	2
Class 1	0	1	1	0	0	0
Class 2	6	0	0	1	0	0
Class 3	0	2	0	0	0	0
Class 4	1	0	2	0	0	0
Class 5	1	1	0	0	0	0
Class 6	0	1	0	0	0	0
SPT classes (DF), n HDM-Diallertest®	Negative	Class 1	Class 2	Class 3	Class 4	Not done
Negative	20	4	3	1	0	2
Class 1	0	0	1	1	0	0
Class 2	5	1	1	0	0	0
Class 3	2	0	0	0	0	0
Class 4	0	0	3	0	0	0
Class 5	1	0	1	0	0	0
Class 6	0	1	0	0	0	0

SPT of > 1 and APT of > 2 were recognized as positive

HDM allergens sensitization. The excellent concordance of HDM- Diallertest® with other diagnostic techniques during eczematous reactions strongly suggests its use as a reliable non invasive diagnostic tool of HDM sensitization.

The APT was introduced to assess sensitization to inhalant allergens in patients with AD (10, 11), and according to the first observations results, it was assumed that, during patch testing, allergens could induce locally eczematous lesions in AD patients, restricted to those who also gave a positive immediate skin reaction to the same allergen (12). From now on, APT is considered the only provocation test currently available with clinical relevance for contact IgE-mediated sensitization in AD patients. (11). Consequently, APT is regarded as specific for AD patients as it was confirmed in numerous studies (5, 7, 8-13). In a recent paper by Fuiano et al. results of HDM-APT were compared with those of SPT in 297 individuals AD and/or respiratory symptoms. The rate of APT positive was significantly higher in AD children and SPT positive in children with respiratory diseases. Interestingly, in the present study, the rate of eczematous reactions after HDM-Diallertest® was not statistically different in AD and non AD patients probably due to the small number of APT positive patients.

The significant correlation both between SPT, specific IgE and HDM-Diallertest® confirms results reported in the literature (8), the highest grades of skin reaction generating the highest degree of correlation. Fuiano and Incorvaia compared HDM SPT and APTs in children and adults with AD and/or respiratory diseases (13). APTs were more frequently positive than SPT not only in AD patients (86.2% vs 21.6%) but also in those with respiratory symptoms only (78.7% vs 34%). The average positivity rate was significantly lower in our study with the ready to use device (36%), in accordance with data other obtained in AD, 26,9% (14) and 47,2% (11). Contrary to Fuaino's results (13), we found a good correlation between HDM-Diallertest® and SPT in both AD and non AD patients, as well as for DPT SPT and DF SPT, with a correlation rate of 73,3 and 66,6% respectively for the lower grades HDM-Diallertest® reactions and 93,3 and 97,7% respectively for the higher grades.

This good correlation between specific IgE, SPT and APT during HDM testing, is not a common rule for other allergens. In AD patients compared to non-atopic controls, Goon et al. tested HDM, cat dander, Bermuda grass and German cockroach: only the HDM APT showed a correlation with specific IgE, APT for cat dander being well correlated with SPT (15). In addition, during food allergy, APT is badly correlated with SPT and specific IgE (6, 16), immediate reaction tending to be correlated with specific IgE and SPT and delayed ones with APT (6, 16),

In terms of potential routine utilisation of a ready to use APT, the more striking result of this is the very good correlation of specific IgE and SPT with the higher classes of HDM Diallertest®. This point could become crucial in a daily clinical use. When considering only the strongest reactions to HDM, i.e. with infiltration, erythema and few papules, the high degree of predictive value of APT may lead to propose this technique as a non invasive first step when HDM sensitization is suspected.

In a recent study in children under 3 years old with AD, Devilliers et al, have a relatively high number of immedi-

Table 4 - Concordance results of the HDM-Diallertest® compared to the other diagnostic techniques, (n=47)

	Discordant results n	Concordant results n(%)
HDM-Diallertest® vs SPT-DPT		
Overall		30 (66.66)d
Class 1 to 2	13	32 (71.11)d
Class 3 to 6	2	43 (95.55)a
HDM-Diallertest® vs SPT-DF		
Overall		29 (64.44)d
Class 1 to 2	13	32 (71.11)d
Class 3 to 6	3	42 (93.33)a
HDM-Diallertest® vs IgE-DPT		
Overall		29 (69.04)d
Class 1 to 2	13	29 (69.04)d
Class 3 to 6	3	39 (92.85)a
HDM-Diallertest® vs IgE-DF		
Overall		26 (63.41)d
Class 1 to 2	13	28 (68.29)c
Class 3 to 6	2	39 (95.12)a

According to the concordance test Kappa of Cohen;
a kappa is considered excellent between 0.81 and 1
b kappa is considered good between 0.61 and 0.8
c kappa is considered moderate between 0.41 and 0.6
d kappa is considered weak between 0.21 and 0.4
e kappa is considered bad between 0 and 0.2

ate types, urticarial APT reaction. These reactions had only been observed in patient with elevated serum levels of HDM- IgE titers (17). In our study population, we did not noticed such side effects even when HDM-IgE level was very high.

Conclusion

In a population of children with AD, isolated or combined to other symptoms or other symptoms without AD, a high correlation was found between SPTs and specific IgE measurements and the HDM- Diallertest®, when considering the highest grades of reactivity. The excellent concordance with higher class reactions of is highly suggestive for its use in the detection of the IgE and non-IgE mediated HDM sensitization mechanisms in children. These first results should be confirmed by further study in adult and children with a high number of patients in order to verify the good level of accuracy and safety of HDM-Diallertest® before its use in practical as a screening tool for detection of HDM sensitization.

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A case of anaphylaxis: Horse-fly or Hymenoptera sting?

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Key words

Anaphylactic reaction, Diptera, Hymenopteras, Venom immunotherapy

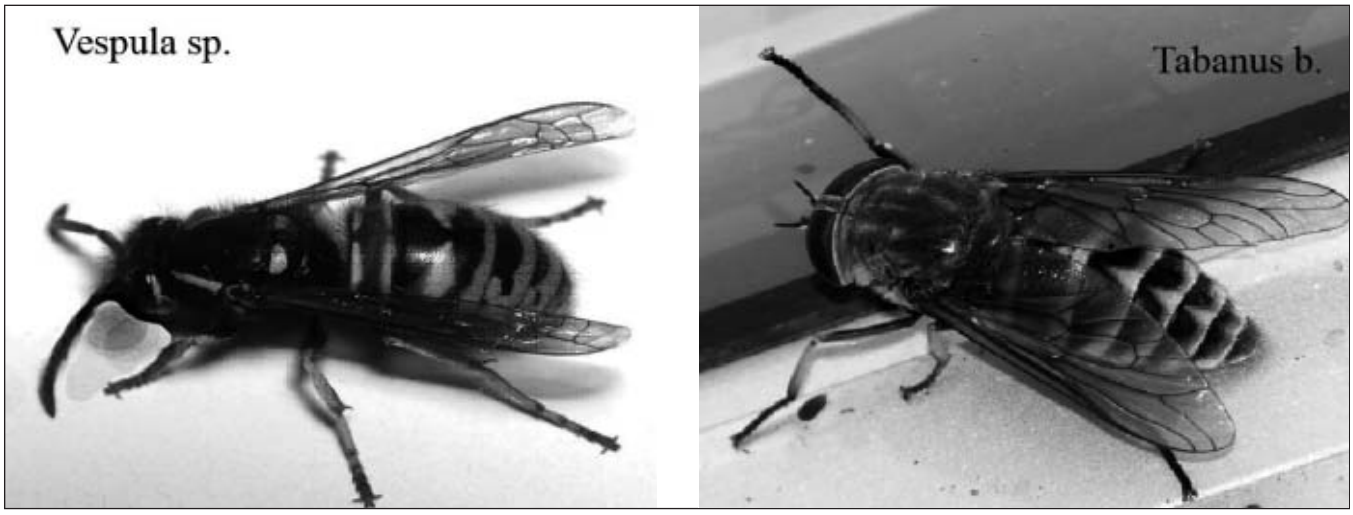
Summary

In literature it has been described a high risk of systemic reaction after blood-sucking Dyptera bites, like mosquitoes and horsefly, in people sensitive to hymenoptera.
A 51 year old man, allergic to hymenoptera venom and with a history of IV reaction after Mueller , who has been treated with Vespula sp. ITS for the last 3 years, was stung by a yellow, black and green insect on the neck.
Five minutes after the bite, he suffered generalized hitching and urticaria, oral cavity and lower limbs paresthesia, followed by lost of consciousness. At the Emergency Room he was successfully treated with adrenaline, intravenous antihistamines and corticosteroid.
The description of the insect as well as the lack of the sting on the site suggested a wasp as the culprit. By studing one of these insect that has been captured by the patient, it turned out it wasn't a Vespula, but a horse fly, the Tabanus bovinus, wich resembles Hymenoptera. Skin prick test and RAST for Tabanus *confirmed the allergology diagnosis.*
In conclusion, also Tabanus bovines *can cause systemic reaction up to anaphylactic shock.*

Introduction

Subjects sensitive to hymenoptera are reportedly at high risk of systemic reactions following blood-sucking Dyptera bites, especially by mosquitoes and horse-flies (1). This clinical event has been called Wasp-mosquito syndrome (2).
We have recently shown that this may also occur with other families of Dyptera, such as Tabanidae and Hippoboscidae (3). The bite of such insects can also cause severe reactions (up to anaphylaxis) with a clinical presentation described as wasp-horsefly syndrome (4).
Specific immunotherapy (SIT) with stinging hymenoptera lyophilized venom is generally regarded as safe and tolerable, though adverse reactions, sometimes even severe, may occur during the treatment (5, 6). In case of further bites followed by severe reactions during SIT course, an increase the vaccine dosage is needed, which exposes the patient to a higher risk of adverse reactions from the treatment. In these cases it therefore essential to identify the stinging insect triggering the new reaction.
We report a patient being treated with SIT for Vespula spp. for three years who experienced an anaphylactic reaction after the bite of an insect, which was subsequently identified as Tabanus bovines, a horse-fly, which can be easily confused with a wasp-like insect.

Figure 1 - Vespula sp and Tabanus b.: the light differences



Case report

A 51-year-old man, allergic to hymenoptera venom and with a history of type IV reaction after Mueller (7), who was being treated with Vespula spp. SIT for the last three years was stung on the neck while outdoor on a hilly side near the woods, by a yellow, black and green insect. He reported an acute pain at the site of the bite with a slight blood drip. Five minutes after the bite the man experienced generalized itching, paresthesia at the oral cavity and lower limbs, and generalized urticaria followed by loss of consciousness. The man was successfully treated at the Emergency Room with adrenaline, and intravenous antihistamines and corticosteroids.

The description of the insect as well as the lack of a sting on the site suggested a wasp (Vespula) as the culprit. However, we were puzzled by the fact that in this patient another previous Vespula bite during the SIT course had not caused any systemic reactions. By thorough interview we found that in that rural area, characterized by many pastures, the culprit insect was rather common. Moreover, the patient reported that the insects flew around him for some time before biting him. Also the blood dripping on the site of the bite resembled more a tabanus bite (8) than the typical sting of hy-

Table 1 - Diptera classification

ORDER	SUBODER	DIVISION	SUPERFAMILY	FAMILY	SPECIES
Diptera	Nematocera	Culicomorpha	Culicoidea	Culicidae	Culex p
					Aedes a
					Anopheles m.
				Simulidae	Simuliom d
		Tipulomorpha	Tipuidea	Tipulidae	Stipula sp
Diptera	Brachycera	Orthorrapha	Tabanoidea	Tabanidae	Crysops sp
					Tabanus sp (bovinus)
					Haematopota p
		Cyclorrapha	Drosophiloidea	Drosophilidae	Dorsophila sp
			Hippoboscoidea	Glossinidae	Glossina sp
				Hippoboscidae	Ornihomia a
					Liptotena c
					Hippobosca e

menoptera. In effect, by studying one of these insects that had been captured by the patient it turned out it wasn't a Vespula but a horse fly, the Tabanus bovines, which resembles hymenoptera (see photo 1). This insect is very common in rural areas, near streams and animals, since it feeds itself with their blood. A positive skin prick test with a mixture of Tabanus whole body and a positive RAST for Tabanus (2.75 kU/l, Class 2) confirmed the diagnosis.

The type of reaction as well as the confusion between these two insects, can easily have consequences on the SIT course. In fact, the correct identification of the insect causing the anaphylactic reaction leads to avoid doubling the maintenance dose of the Vespula SIT, as recommended by the position paper (9), in patients who show systemic reactions following further stings, thus reducing the risk of causing adverse reactions and a decrease in quality of life.

In conclusion, this case suggests that Tabanus bovines may cause a systemic reaction (up to anaphylactic shock). Further, an accurate diagnosis, based on the correct identification of the insect, is warranted before any measure potentially causing a higher risk is started, is always needed.

Finally, since specific SIT for Tabanus sp. and/or Hippobosca is currently not available and the hymenoptera vaccine doesn't protect against allergic reactions to Tabanus bites, both prevention and emergency symptomatic therapy are essential.

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Omalizumab: when the non-responder is a late-responder

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Key words
Omalizumab, steroid-resistant asthma, spirometry, quality of life

Summary
Omalizumab is an anti-IgE monoclonal antibody available since 2006 for the treatment of GINA step 4 asthma. We studied a 41-year old male who has been suffering from severe steroid-resistant asthma with severe co-morbidity and treated with Omalizumab. He was found to be non-responder to the treatment until the 48th week, starting from which we began to see a distinct improvement in the symptoms and all the correlated parameters, in addition to remission of the co-existent allergy to milk.
Conclusions: we wish to point out the late response to Omalizumab, which occurred way beyond the times envisaged in literature. It seems possible that some patients are late responders to the drug.

Introduction

Omalizumab is a chimeric monoclonal antibody binding the free IgE before they bind to the FcεRI-II receptors on the mast cells and basophils. The drug has made it possible to significantly improve the quality of life and asthma control in patients with GINA step 4 asthma (1). The patients selected must have certain features to be considered as suitable for the treatment (2), but about 20% of these do not respond to the drug (3).
In this study we describe the case of a man suffering from steroid-resistant asthma associated with important co-morbidity treated with Omalizumab and non-responder after the 16 weeks envisaged for assessing the efficacy. Administration of the drug was prolonged over time, with a dramatic improvement of the clinical condition and the spirometric parameters.

Case Report

In December 2007, a 41-year old patient was brought to our notice, with a history of severe persistent asthma and oculorhinitis since 1983. The case history revealed past secondary thoracic trauma following a serious road accident with consequent breakage of the aortic arch treated surgically by means of endovascular prosthesis, MTHFR genotype mutation with repeated thrombotic episodes, steroid-induced bilateral cataract and allergy to cow's milk proteins (casein and lacto albumin). The patient did not present history of tobacco smoking. He was a trader.
The treatment under way at the time of the first visit was the combination preparation Salmeterol-Fluticasone 50/500 μg/day inhalation powder, Salbutamol spray metered dose inhaler (MDI) daily 3-4 times/day, prednisone 25 mg/day tablets, Momethasone 200 mcg/day intranasal

spray, Tiotropium bromide 18 mcg/day inhalation powder, Montelukast 10 mg/day tablets. (Tab.1). Sodium Warfarin tablets to prevent clotting.
The patient had frequent flare-ups, mainly on an infective basis, treated by increasing systemic steroids and antibiotics; he was also admitted to the Pneumology ward in 2004 and 2006 for the same reasons. In 2007, he entered 4 times in Emergency Room and he was subjected to 3 outpatient examinations.
Positive to skin prick test for dust mites, gramineae, alternaria and cladosporium while the total IgE dosage was 256 IU/ml with body weight of 95 kg.
The haematochemical examinations were regular, as well as immuno-rheumatological tests (ANA test, rheumatoid factor, ANCA, aspergillus specific Ige and IgG antibodies). Spirometry showed an important obstructive ventilatory syndrome (FEV1 57% FVC 67% FEV1/FVC 70%) (Tab.2). A physical examination of the chest revealed rale and hissing sounds during expiration. Thorax High Resolution Computed Tomography (HRCT) did not revealed relevant anomalies.
We used the Asthma Quality of Life Questionnaire score (AQLQ) to assess the patient's quality of life (4), with an initial score of 2,69 points.
The Asthma Control Test (ACT) used for assessment of asthma control gave a score of 6 points during the first visit (5).
The patient was selected as suitable for additional treatment with Omalizumab, administered subcutaneously in a dosage of 300 mg (2,4 ml) every two weeks (calculated on the basis of the total IgE baseline value and body weight), starting from February 2008.
The response to the drug was assessed every 16 weeks (as envisaged by the directives of the Italian Drug Agency, Agenzia Italiana del Farmaco - AIFA) (6), by monitoring the respiratory functions and asthma control (2). During the first control, as the protocol rules, we did not find any clinical improvement and the patient had two serious infective flare-ups which were treated in both cases by increasing oral steroid (prednisone 50 mg/day, then tapered) and antibiotics. Lack of response was confirmed by the spirometric test and the ACT questionnaire score (9 points). We decided to continue administering the drug, then carried out a second control at the 32nd week (substantially overlapping the previous one) and a third control at the 48th week (January 2009). Starting from this moment, the patient began to report physical wellbeing, which was confirmed by significant improvement of the spirometry (FEV1 88%, FVC 83%, FEV1/FVC 87%). The result of the thoracic examination was distinctly better and so were the symptoms related to oculorhinitis.
The clinical response was confirmed by the marked increase of the AQLQ and ACT scores (respectively 6,51 and 23 points). Symptoms control was found to be stable during the subsequent visits, and this made it possible for us to gradually reduce and then stop systemic steroid, Montelukast and Tiotropium, maintaining only inhalatory treatment with Salmeterol/Fluticasone 50/500 twice/day. The patient was also once again able to take milk and its derivatives.
In March 2009 spirometry was repeated, and showed further improvement of the parameters (FEV1 95% FVC 89% FEV1/FVC 87%) (Tab. 2).
The patient is currently taking only the combination Salmeterol/Fluticasone 50/500 and has no longer had flare-ups, not even after inflammatory episodes of the upper and lower airways, unlike the situation before starting treatment with Omalizumab.

Discussion

The patient examined had poorly controlled severe asthma (GINA step 4), with considerable impairment of the

Table 1 - Treatment at first and last visit

First visit- 01/2008	Last visit- 3/2009
Salmeterol/fluticasone 50/500 μg twice daily (inhalation powder)	Salmeterol/fluticasone 50/500 μg twice daily
Salbutamol 300-400 μg/day (MDI)	Salbutamol (MDI) unfrequently
Prednisone 25 mg/day (tablets)	
Mometasone 200 μg/day (intranasal spray)	
Tiotropium bromide 18 μg/day (inhalation powder)	
Montelukast 10 mg/day (tablets)	

Table 2 - Spirometry at first and last visit

First visit- 01/2008	Last visit- 3/2009
FEV1 57%	FEV1 95% (+38%)
FVC 67%	FVC 89% (+22%)
FEV1/FVC 70%	FEV1/FVC 87% (+17%)

spirometric values and serious co-morbidity. From the various studies reported in literature, it is seen that positive response to treatment with anti-IgE antibody is mainly assessed on the basis of the response and symptoms control even in the absence of significant improvements of the respiratory function (2).

Health-related quality of life (HRQoL) was assessed by means of the AQLQ score (4). The AQLQ is composed of 32 questions which cover four domains: activity limitation, symptoms, environmental stimuli and emotional function. Subjects recall their experiences during the previous 2 weeks and score a number of asthma-related problems on a 7-point scale from 1 (maximum impairment) to 7 (no impairment). We used an overall summary index, which is the mean of the responses to the 32 items (total AQLQ score). The AQLQ was found to be valid, reproducible and responsive to change over time and a change in questionnaire score of 0.5 or more points has been determined to be the minimal clinically important difference (7). AQLQ score at first visit revealed a quality of life compromised in any evalued aspects (2,69 points).

The symptoms control was monitored by means of the ACT, which is a brief validated questionnaire consisting of 5 questions for adults and 7 for children, and has shown good correlation with the changes in pulmonary function and the HRQoL (5, 8). The score of the abovementioned questionnaire is expressed in a range between 5 and 25 points, with the lowest score indicating the lack of asthma control and consequently a poorer quality of life.

In the case in question, the ACT carried out during the first visit showed very poor control of the disease which was already impaired by the severe thoracic trauma suffered during the car accident and the repeated thrombotic events.

From the data present in literature and the Omalizumab data sheet it is clear how assessment of the treatment efficacy must be done after 16 weeks starting from the first administration of the drug; this is because it takes 70 to 90 days to obtain the down-regulation of the FcεRI receptors on the mast cells and basophils (9, 10). Moreover, the time schedule is regulated by the AIFA by monitoring the treatment efficacy on a site specially instituted for the purpose starting from the end of 2008 (6).

The element of novelty in this clinical case is the extremely delayed symptomatological and instrumental response to the drug (48 weeks).

After a long period of apparent resistance to treatment, we obtained a good functional and clinical response registered by the net increase of the ACT score calculated during the last controls and associated with evident improvement of the spirometric obstruction indices. Mention must be made of the remission of the allergy to milk proteins, probably because of the blocking of the free IgE. The improvement of the clinical condition made it possible for us to stop not only systemic steroid but also the inhalatory drugs, except for the salmeterol/ fluticasone association.

Symptoms control in terms of reduction of the flare-ups was also evident, since exacerbations no longer occurred after stabilization of the respiratory condition, and these results are way beyond the data from earlier studies, which show a 50% reduction of the asthma exacerbations and 44% reduction in emergency care (9). These intercurrent infectious events were not qualified as adverse reactions to omalizumab, considering their frequency and characteristics during the previous clinical history. Besides, literature shows that, among adverse events, upper respiratory tract is mainly involved (11).

Consequently, the quality of life is improved and the AQLQ score in January is marked increased (6,51 points).

The decision to continue treatment with Omalizumab is usually made on the basis of the assessment of the response to the drug, characterized by better disease control, increased HRQoL and reduction of exacerbations. On the basis of these indications, our patient ought to have stopped the anti-IgE monoclonal antibody, and resumed conventional treatments at the maximum dosage, already shown to have poor efficacy. Moreover, the poor quality of life and frequent recourse to hospitals would have resulted in further costs in terms of reduction of working performance and medical expenses.

The decision to continue with treatment beyond the time schedules envisaged was mostly supported by one of our earlier reports (12) submitted during the international clinical trial on Omalizumab (CIGE025A2425), for which ours was the Coordinating Centre for Italy and for which the data are currently being published; the main end-point of the protocol was assessment of the persistence of the efficacy of the drug after 32 weeks of treatment. One of the patients enrolled was suffering from a serious and inveterate

form of asthma with a very large number of flare-ups and hospitalization and had responded to pharmacological treatment with Omalizumab at the 32nd week, well beyond the expected time schedules. This past experience led us to proceed with the treatment on this occasion as well.
The delayed response may be explained by the presence, on both occasions, of a severe form of asthma which probably led to significant remodelling of the bronchial walls (13).
It is a known fact that patients suffering from steroid-resistant asthma may be identified as a sub-phenotype characterized by marked inflammation of neutrophils, with less importance of the eosinophil component. There is greater evidence of tissue damage and bronchial remodelling in this group (14). The marked effect of Omalizumab on immuno-phlogosis (mainly on eosinophils and high affinity IgE receptors) (15) could have influenced these alterations, while, however, requiring longer times than those expected before clinically evident results could be observed.
In order to assess the economic impact of the new treatment strategy, a cost analysis was carried out. The cost related to the resources consumption (hospitalization, emergency room access, visit and pharmaceutical treatment) was estimated considering the public tariffs and the net price of the drugs (16, 17). In the period 2004-2007 the average annual healthcare cost was 5,446 euro. The total costs were 21,783 euro. This amount is underestimated because it does not consider some other further healthcare costs (e.g. the surgical intervention for the steroid-induced bilateral cataract), the indirect costs (cost supported by patient such us drug not reimbursed by National Healthcare Service and reduction of the working activity) and intangible costs (economic value associated to the poor quality of life) (18).
It is not feasible to carry out a complete cost analysis of the next 4 years (2008-2011) and to assess the cost effectiveness of Omalizumab as in previous analysis(19). It is possible to assume that due to the improvement of the morbidity level, there will be just the costs of the pharmaceutical treatment and not the costs of hospitalizations or Emergency room access. In addiction, considering the age of the patient, it could be interesting to give a monetary value to the difference with respect to the previous period in the working capability and in the quality of life. An analysis published in 2006 found that the indirect costs represent the 60% of the cost of illness (20).
In conclusion, Omalizumab is a therapeutic option which, in selected cases, is capable of substantially modifying the clinical history of serious asthma with relevant consequences on patient morbidity and quality of life. However, it is possible (and this fact must be given maximum consideration) that some patients are found to be apparently "non-responders" even after prolonged periods of treatment with the drug. It is to be hoped that studies on a larger scale will make it possible to identify with greater precision sub-phenotypes of asthma apparently resistant to Omalizumab and the predictive factors, if any, which can help prevent therapeutic failures or premature discontinuation of treatment.

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News

Changes in Weather May Trigger Child's Asthma

ARLINGTON HEIGHTS, Ill., September 15, 2009 – Changes in humidity and temperature result in an increase in Emergency Department (ED) visits for pediatric asthma exacerbations according to a report published this month in*Annals of Allergy, Asthma & Immunology*, the scientific journal of the American College of Allergy, Asthma and Immunology (ACAAI).

"We found a strong relationship between temperature and humidity fluctuations with pediatric asthma exacerbations, but not barometric pressure," said Dr. Nana A. Mireku, an allergist at Dallas Allergy Immunology private practice in Dallas, formerly at Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit. "To our knowledge, this is the first study that demonstrated these correlations after controlling for levels of airborne pollutants and common aeroallergens.

"Our study is also one of the few to examine the possibility that the weather one or two days before the asthma exacerbation may be as important as that on the day of admission, as the additional ED visits occur one to two days after the fluctuation," she said.

According to the report, patients experiencing an asthma attack often complain that weather fluctuations are a major trigger. Dr. Mireku said, "the latest National Institutes of Health guidelines list 'change in weather' as a possible precipitating factor for asthma, but no previous studies have really examined this potential trigger in a rigorous fashion."

The retrospective 2-year study was performed at a large urban hospital of 25,401 children visiting the ED for an asthma exacerbation. Data on climactic factors, pollutants and aeroallergens were collected daily. The relationship of daily or between-day changes in climactic factors and asthma ED visits was evaluated using time series analysis, controlling for seasonality, air pollution and aeroallergen exposure. The effects of climactic factors were evaluated on the day of admission and up to five days before admission.

A 10 percent daily increase in humidity on a day or two before admission was associated with approximately one additional ED visit for asthma. Between-day changes in humidity from two to three days prior to admission were also associated with more ED visits. Daily changes in temperature on the day of or the day before admission increased ED visits, with a 10°F increase being association with 1.8 additional visits.

Asthma is a chronic inflammation of the lung airways that causes coughing, chest tightness, wheezing or shortness of breath. More than 22 million Americans have asthma, including 6.5 million under age 18.

"Asthma is the most common chronic illness in childhood," said allergist Richard G. Gower, M.D., president of ACAAI. "Allergists have long known that weather conditions such as extremely dry, wet or windy weather can affect asthma symptoms. This study further defines the role of temperature and humidity on children's asthma and confirms the importance of working with patients to identify the source of their symptoms and develop treatment plans that help prevent them."

Citation: Mireku N, et al. Changes in weather and the effects on pediatric asthma exacerbations. Ann Allergy Asthma Immunol 2009;103:220-224.

Patient information on asthma and other allergic diseases is available by calling the ACAAI toll free number at (800) 842-7777 or visiting its Web site at www.allergyandasthmarelief.org.

The American College of Allergy, Asthma and Immunology (ACAAI) is a professional medical organizationheadquartered in Arlington Heights, Ill., that promotes excellence in the practice of the subspecialty of allergy and immunology. The College, comprising more than 5,000 allergists-immunologists and related health care professionals,fosters a culture of collaboration and congeniality in which its members work together and with others toward the common goals of patient care, education, advocacy and research.