Asthma causes recurrent episodes of coughing, wheezing, chest tightness and breathlessness. In the year 2000 in USA than 11 million peoples had an asthma attack. In the year 1999, 478,000 people had been admitted in hospital for acute asthma and 4426 people died for asthma.

Asthma is characterized by variable airflow obstruction, reversible either spontaneously or with treatment. The chronic inflammation of airways causes an increase of bronchial hyperresponsiveness, that is inherited, to a variety of stimuli. Many cells are implicated in pathogenesis of asthma: eosinophils, mast cells, T lymphocytes, neutrophils that infiltrated airways. Moreover in bronchial walls of asthmatic people there is a deposition of collagen in the subbasement membrane, hyperplasia and hypertrophy of the bronchial smooth muscle, with remodelling bronchus. The major risk factor that causes asthma is atopy, that is the ability of syntethesize IGE antibodies to allergens. In the development of asthma recent studies established that airway inflammation is due also to the loss of normal balance between Th1-Th2 lymphocytes.

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According to the recent guidelines there is a gradually approach to asthma. Asthma is classified in four steps: intermittent, mild, moderate, severe and will be treated according to the steps. Brittle asthma is a rare form of severe asthma characterized by wide variation of Peak Expiratory Flow (PEF), in spite of heavy doses of steroids. Brittle asthmatic patients had very serious and often, life threatening, attacks.

Type 1 brittle asthma is characterized by a maintained PEF variability despite therapy, and it affected mostly female, aged between 15 and 55 years. Type 1 is associated to skin prick tests positivity and food intolerance. Several studies have referred a correlation with personality disorders. The patients affected with type 1 have high morbidity, and frequently they have hospital admission for assessment and stabilisation their asthmatic condition.

Type 2 brittle asthma is characterized by acute attacks that are very severe and could lead to death or mechanical ventilation for respiratory insufficiency. Brittle asthma is very difficult to recognize and to treat. In type 1 brittle asthma, the therapy is based on inhaled and/or oral steroids, and β2-agonists, used with an inhaler or with subcutaneous infusion.

The patients affected with type 1 had to be nearly monitored and treated. Patients affected with type 2 brittle asthma, are mostly free by symptoms, but they have severe attacks that led them to emergency treatment.

Brittle asthma is a rare form of severe asthma, that the clinicians may recognize and treat very strictly, because of high morbidity and mortality.

Key Words:
Asthma, Airflow obstruction, Inhaled corticosteroids, β2-agonist.

Introduction

Asthma is a chronic inflammatory disease of the airways that is an important cause of mortality and morbidity.
and the double dip pattern of morning and evening, described for asthma\textsuperscript{3,4}.

Different physicians and British Thoracic Society used the term brittle asthma only to describe a severe attack of asthma, without regard to PEF patterns\textsuperscript{5}.

The importance to recognize the typical PEF patterns of brittle asthma is related to be a risk factor for death.

In 1998, Ayres et al. defined brittle asthma as a specific asthma phenotype, suggested a classification based on magnitude of diurnal PEF variability, describing two subclasses: type 1 and type 2, with different characteristics\textsuperscript{6,7}.

Many authors considered the possibility that the patients with a chaotic pattern of PEF, were only non-compliant with the treatment, and so they could lead to death for inadequate treatment.

Another important question was to define the disease asthma with precision, to avoid to include in Brittle asthma the patients with severe symptoms despite the treatment, that suffer with other diseases such as vocal cord dysfunction, gastro-oesophageal reflux, immunodeficiencies, bronchiectasis, cystic fibrosis, and so on, that have the same symptoms or coexist with asthma\textsuperscript{8}. So it was necessary a correct definition of Brittle asthma that could based on a specific pattern of PEF variability, as well as a correct diagnosis of asthma.

### Definition

Brittle asthma is a distinct form of asthma, characterized by a diurnal PEF variability, despite maximal medical treatment (high doses of inhaled or oral corticosteroids, high doses of inhaled bronchodilator)\textsuperscript{6}.

Brittle asthma is classified in two types: type 1 characterized by a maintained wide PEF variability (> 40% diurnal variation for > 50% of the time over a period of at least 150 days) despite maximal medical therapy including at least 1500 µg/day of inhaled beclomethasone or equivalent.

Type 2 is characterized by acute attacks occurring within minutes, that could lead to death, with a background of well controlled asthma\textsuperscript{6}.

### Epidemiology

Brittle asthma is a rare disease, with a prevalence of 0.05% of all asthmatic patients. The type 1 affected mostly female (2.5 F:1 M), aged between 15 and 55 years, while type 2 brittle asthma seems to be no prevalence in sex and age (Table I).

### Morbidity and Mortality

Type 1 brittle asthma has high morbidity in terms of frequent hospital admissions, for assessment and stabilization of asthma. The patients with type 1 brittle asthma are taking a considerable amounts of medications, as inhaled steroid and bronchodilator, or oral steroids, with many adverse effects. Consequently, they suffer from oesophageal reflux, osteoporosis, weight gain, that conduct them frequently to hospital admissions.

Type 2 brittle asthma is correlated with an high hospital admission for acute severe attack, and is associated with a most higher mortality. The patients are well controlled for a long period, but when they have an attack, it is very severe, and may require ventilation\textsuperscript{6,9}.

### Risk Factors

Type 1 brittle asthma is associated with atopy, demonstrated by a skin prick test positivity for cat, horse, wheat and chocolate\textsuperscript{10}. The reaction to *Dermatophagoides pteronyssinus* is greater in type 1, but no statistically significative\textsuperscript{6}. Many patients in this group report a food intolerance, for example peanuts, fish, wheat.

### Table I. Patients’ characteristics with brittle asthma.

<table>
<thead>
<tr>
<th>Type</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex F/M</td>
<td>2.5 F:1 M</td>
<td>1F:1M</td>
</tr>
<tr>
<td>Age yr</td>
<td>15-55</td>
<td>*</td>
</tr>
<tr>
<td>Atopy</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Food intolerance</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Psychological factors</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Morbidity</td>
<td>High</td>
<td>–</td>
</tr>
<tr>
<td>Mortality</td>
<td>–</td>
<td>High</td>
</tr>
</tbody>
</table>

*No prevalence.
Type 2 brittle asthma may worse after exposure to fungal spores such as *Alternaria*\(^\text{10}\). Type 1 is correlated with a personality disorder, as depression or psychological instability\(^\text{11}\).

A II severe asthmatic patients have psychological problems correlated with the state of the disease, so that is difficult to define if brittle asthma is associated with personality disorder (Table I).

Both patients with type 1 and 2 brittle asthma have a reduced perception of worsening airways obstruction, and a reduced hypoxic drive\(^\text{12,13}\).

**Possible Hypothesis Regarding the Pathology of Brittle Asthma**

An important mechanism in brittle asthma is airway smooth muscle contraction, that is activated rapidly by a cholinergic reflex, and by local release of tachykinins, substance P, broncoconstrictor and inflammatory peptides. Many allergens might induce fastly this mechanism\(^\text{6}\).

Another important factor is the edema of the airways due to acute vasodilatation, plasma exudation that produce the acute airway narrowing in brittle asthma\(^\text{14}\).

The smooth muscle is also remodeled in severe asthma and so much increased in bronchial walls of patients who dying for asthma attack. Bronchial biopsy demonstrated the thickening of the subbase ment membrane, the irreversible changes in smooth muscle, and the changes of glandular components, that conduced to stable and irreversible obstruction of airways\(^\text{15}\).

Moreover in patients dying of acute asthma, an infiltration of neutrophils rather than eosinophils have been seen, which suggest that neutrophils are the predominant cells which appear earlier\(^\text{16-17}\).

In type 1 brittle asthma the treatment with high doses of inhaled or oral steroids may often not controlled asthma, probably due to a steroid resistance. Several studies try to explain the steroid resistance in asthma, and in brittle asthma it has been better defined as an “altered” steroid responsiveness\(^\text{18}\).

**Treatment**

Brittle asthma is very difficult to treat. The patients with brittle asthma have poor adherence to the treatment and have to be monitored firmly.

The standard guidelines for asthma are not applyble, because the brittle asthmatic patients are taking high doses of inhaled steroids and bronchodilators, so when their conditions are worsening, they have to take oral steroids.

The treatment of type 1 brittle asthma begins with reduced allergen exposure, and with avoid foods for which the patients are intolerance.

Some authors have demonstrated that in type 1 brittle asthma is very important a good diet supported with minerals such as selenium, magnesium and anti-oxidant vitamins A, C, B, that are deficiency\(^\text{19,20}\).

The therapy is essentially based on high doses of inhaled corticosteroid, and when the patients have an acute attack it is necessary to prescribe oral steroids and increase the use of \(\beta_2\)-agonist use.

There is a possibility to treat the patients with continuous subcutaneous infusion of \(\beta_2\)-agonist, such as terbutaline, needed doses ranges between 6 and 15 mg a day, that may be given trough a battery-powered syringe driver (CSIT). It is important to maintaine the therapeutical range for terbutaline, to avoid adverse effects as changes in serum potassium or glucose concentrations in blood\(^\text{21}\).

The use of long-acting inhaled \(\beta_2\)-agonists may have advantages to stabilizing the airways; in several studies salmeterol has disappointed by the patients, whether formoterol has improved lung function and has reduced symptoms\(^\text{22}\).

The treatment of patients with type 2 brittle asthma, that are relatively symptom free, consists to avoid allergen exposure, to identify the triggers, self management, and to treat the acute attacks with injection of adrenaline with preloaded syringes.

These patients have unexpected attacks, that request emergency hospital admission, for acute respiratory insufficiency and they may underwent to mechanical ventilation.

New therapy such as leukotriene receptor antagonists and 5-lipoxygenase inhibitors,
oral cyclosporin or methotrexate, or intravenous immunoglobulin, may help the treatment in brittle asthma.\textsuperscript{6,22}

A good attention physicians may have for psychological aspects that in asthma, and especially in brittle asthma, could influence the disease.

In conclusions, brittle asthma is a rare form of asthma, which has a particularly phenotypes, and a specific pattern regarding the PEF variability, that may have to identify and treat.\textsuperscript{6}

Patients with brittle asthma especially type 1 are in severe clinical conditions, and in a "stable state of instability".\textsuperscript{9}

These patients have several hospital admissions to establish their therapy, to treat the worsening symptoms, and side effects of treatment, with high costs.

Patients with type 2 brittle asthma may have a severe attack that bring to respiratory insufficiency, and needs ventilatory support.

Brittle asthma may have been considered with a great attention, since it poses many difficult problems to management.

References


