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Brittle asthma

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Abstract. – **Brittle asthma is a rare form of severe asthma characterized by a wide variation of Peak Expiratory Flow (PEF), in spite of heavy doses of steroides.**

Brittle asthmatic patients had very serious and often, life threatening, attacks.

Type 1 brittle asthma is characterized by a mantained 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 stabilitation their asthmatic condition.

Type 2 brittle asthma is characterized by acute attacks that are very severe and could led 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 β_2-agonists, used with an inhaler or with subcutaneous infusion.

The patients affected with type 1 had to be nearly monitered and treated.

Patients affected with type 2 brittle asthma, are mostly free by simptoms, 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, β_2-agonist.

Introduction

Asthma is a chronic inflammatory disease of the airways that is an important cause of mortality and morbidity.

Asthma causes recurrent episodes of coughing, wheezing, chest tightness and breathlessness.

In the year 2000 in USA than 11 milion 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[1].

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 celles, T lymphocites, neutrophils that infiltrated airways.

Moreover in bronchial walls of asthmatic people there is a deposition of collagen in the subbasament 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 beetween Th1-Th2 lymphocytes.

According to the recent guidelines[1] 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 a wide variation in peak expiratory flow (PEF), despite high doses of inhaled steroids, which could lead to death from an acute severe attack.

The term Brittle Asthma was first used in 1977 by Turner-Warwick to describe another pattern of airflow obstruction in chronic asthma[2].

The brittle asthmatic PEF pattern is a very chaotic, so different from the morning dip

and the double dip pattern of morning and evening, described for asthma[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[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[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 inadeguate 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[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)[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 occuring within minutes, that coul lead to death, with a background of well controlled asthma[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 stabilitation 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 oseophageal 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[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[10]. The reaction to *Dermatophagoides pteronyssinus* is greater in type 1, but no statistically significative[6]. Many patients in this group report a food intolerance, for example peanuts, fish, wheat.

Table I. Patients' characteristics with brittle asthma.

	Type 1	*Type 2*
Sex F/M	2.5 F: 1 M	1F:1M
Age yr	15-55	*–
Atopy	Yes	No
Food intolerance	Yes	No
Psychological factors	Yes	No
Morbidity	High	–
Mortality	–	High

*No prevalence.

Type 2 brittle asthma may worse after exposure to fungal spores such as *Alternaria*[10].

Type 1 is correlated with a personality disorder, as depression or psychological instability[11].

All 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[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[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[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 demonstred the thickening of the subbasement membrane, the irreversible changes in smooth muscle, and the changes of glandular components, that conduced to stable and irreversible obstruction of airways[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[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[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 steroides 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[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 β_2-agonist use.

There is a possibility to treat the patients with continuous subcutaneous infusion of β_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[21].

The use of long-acting inhaled β_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[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 af 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[6-22].

A good attention physicians may have for psychologicol 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[6].

Patients with brittle asthma expecially type 1 are in severe clinical conditions, and in a "stable state of instability"[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

1) *National Asthma Education and Prevention Program Expert Panel Report.* Guidelines for the Diagnosis and Management of Asthma. NIH-NHLBI Pubblication N° 02-5074 June 2003.

2) *Turner Warwick M.* On observing patterns of airflow obstruction in chronic asthma. Br J Dis Chest 1977; 71: 73-86.

3) *Clark TJH, Hetzel MR.* Diurnal variation of asthma. Br J Dis Chest 1977; 71: 87-92.

4) *Connolly CK.* Diurnal rhythms in airway obstruction. Br J Dis Chest 1979; 73: 357-366.

5) *British Thoracic Society, British Paediatric Association, Royal college of Physicians of London et al.* Guidelines on the management of asthma. Thorax 1993; 48 (Suppl): S1-24.

6) *Ayres JG, Miles JF, Barnes PJ.* Brittle asthma. Thorax 1998; 53: 315-321.

7) *Gupta D, Ayres JC.* Brittle asthma: a separate clinical phenotype of asthma? Indian J Chest Dis Allied Sci 2001; 43: 33-38.

8) *Balfour-Lynn Jan.* Difficult asthma: beyond the guidelines. Arch Dis Child 1999; 80: 201-206.

9) *Hetzel MR.* Brittle asthma: fiend or phantom? Thorax 1998; 53: 235-236.

10) *Miles JF, Cayton RM, Tunnicliffe WS, et al.* Increased atopic sensitization in brittle asthma. Clin Exp Allergy 1995; 25: 1074-1082.

11) *Miles JF, Garden GM, Tunnicliffe WS, et al.* Psychological morbidity and copyng skills in patients with brittle and non-brittle asthma: a case-control study. Clin Exp Allergy 1997; 27: 1151-1159.

12) *Kikuchi Y, Okabe S, Tamura G, et al.* Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 1994; 330: 1319-1324.

13) *Barnes PJ.* Blunted perception and death from asthma. N Engl J Med 1994; 330: 1383-1384.

14) *Kuwano K, Boskev CH, Par PD, et al.* Small airways dimensions in asthma and chronic obstructive pulmonary disease. Am Rev Respir Dis 1993; 148: 1220-1225.

15) *American Thoracic Society.* Proceeding of the ATS Workshop on refractory asthma. Am J Respir Crit Care Med 2000; 162: 2341-2351.

16) *Jatakanon A, Uasuf C, Maziak W, Lim S, Chung KF, Barnes PJ.* Neutrophilic inflammation in severe persistent asthma. Am J Respir Crit Care Med 1999; 160: 1532-1539.

17) *Sur S, Crotty TB, Kephart GM, et al.* Sudden-onset fatal asthma: a distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa. Am Rev Respir Dis 1993; 148: 713-719.

18) *Adcock IM, Lane SJ, Brown CA, et al.* Abnormal glucocorticoid receptor/AP1 interaction steroid resistant asthma. J Exp Med 1995; 182: 1951-1958.

19) *Baker JC, Tunnicliffe WS, Duncanson RC, Ayres JG.* Reduced dietary intakes of magnesium, selenium and vitamins A, C and E in patients with brittle asthma. Thorax 1995; 50 (Suppl 2): P97.

20) *Baker JC, Tunnicliffe WS, Duncanson RC, Ayres JG.* Dietary antioxidants and magnesium in type 1 brittle asthma: a case control study. Thorax 1999; 54: 115-118.

21) *Ayres JG.* Subcutaneous terbutaline in the management of brittle asthma. Br J Hosp Med 1992; 47: 569-571.

22) *Ulrik CS, Kok-Jensen A.* Different bronchodilating effect of salmeterol and formoterol in an adult asthmatic. Eur Respir J 1994; 7: 1003-1005.