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Diagnosis and treatment of refractory asthma

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Abstract. – Asthma is an inflammatory disorder of the airway associated with airflow obstruction and bronchial hyperresponsiveness that varies in severity across the spectrum of the disease. Asthma affects 5-7% of the population of North America and Europe, and the prevalence is increasing. Most patients with asthma are easily diagnosed, responding to standard treatment with a short-acting inhaled β_2-agonists for symptom control, and to long-term therapy to including inhaled glucocorticosteroids to control airway inflammation. However a subgroup of patients with asthma (likely ~10%) have more troublesome disease reflected by high medication requirements to maintain good disease control or persistent symptoms, asthma exacerbations, or airflow obstruction despite high medication use. A term to describe this subgroup of asthmatic patients is "Refractory Asthma". Patients with difficult to control asthma require a rigorous and systematic approach to their diagnosis and treatment. It is critical to make a diagnosis of asthma and to exclude other airways diseases and to identify whether there are any correctable factors that may contribute to their poor control. Another poor adherence to therapy is common reason for a poor response. Treatment involves optimizing corticosteroid inhaled therapy, assesing additional controllers, such as inhaled β_2-agonist, leukotriene inhibitors, anti-immunoglobulins (Ig), oral corticosteroids and sustained-release theophylline.

Key Words:

Refractory asthma, Airflow obstruction, Corticosteroids, β_2-agonists.

Introduction

Asthma is an inflammatory disorder of the airway associated with airflow obstruction and bronchial hyperresponsiveness that varies in severity across the spectrum of the disease. Asthma affects 5-7% of the population of North America and Europe, and the prevalence is increasing[1]. The rate of asthma increases as communities adopt Western lifestyles and become urbanised. Most patients with asthma are easily diagnosed, responding to standard treatment with a short-acting inhaled β_2-agonists for symptom control, and to long-term therapy to including inhaled glucocorticosteroids to control airway inflammation. Inadequately controlled asthma, although afflicting a small percentage (likely ~10%) of the asthma population, remains a frustrating disease for both patients and the clinicians treating them. These patients have a disproportionate impact on the healthcare utilitation, accounting for up at least half of the direct and indirect cost for asthma[2]. Asthmatics whose disease is inadequately controlled have more extensive use of asthma medication. It has been identified that these individuals are 15 times as likely to use emergency medical care as mild-to-moderate asthmatics and are 20 times as likely to require hospital admission[2]. These severe asthmatic also have greater absenteeism from work on account of their disease. Because these patients remain difficult to treat and prone to severe exacerbations, they contribute disproportionately to the overall costs of asthma[3].

Definition

Before in-depth studies of any disease can be undertaken a recognised definition must be developed. This is especially important in a complex disease such as asthma, which is likely a collection of different phenotypes, rather than a single, specific disease with a unifying pathogenetic mechanism.

The most comprehensive attempt at a definition was undertaken by an American Thorachic Society-sponsored workshop, the proceeding of which were published in 2000[4]. "Refractory Asthma" should be defined on the basis of med-

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ication requirements, asthma symptoms, frequency of asthma exacerbations, and degree of airflow limitation. In the Proceedings of the ATS Workshop on Refractory Asthma the partecipants agreed on two major and seven minor criteria (Table I) with refractory asthma being defined as one or both major criteria and at least two minor criteria[4].

In considering a term to describe this subgroup of asthmatic patients with troublesome disease is "Refractory Asthma"[4]. "Refractory asthma" is not meant to describe only patients with "fatal" or "near fatal" asthma[5], but is meant to encompass the asthma subgroups previously described as "severe asthma"[6], "steroid-dependent and/or resistant asthma"[7], "difficult to control asthma"[8] "poorly controlled asthma"[8], "brittle asthma"[7] or "irreversible asthma"[7] (Table II).

Diagnosis

Before treating patients with difficult asthma, some other factors should be considered. Misdiagnosis may be as high as 10% (Table III), exposure to factors that may contribute to a poor response to conventional therapy, nonadherence with oral steroid therapy has been reported at 30%, and in some cases there is a significant psycological factors to patients' symptoms and percetion of their asthma[9-12].

Table I. Refractory asthma: workshop consensus for typical clinical features[4].

Major characteristics
- Treatment with continuous or near continuous (>50% of year) oral corticosteroids
- Requirement for treatment with high-dose inhaled corticosteroids

Minor characteristics
- Requirement for daily treatment with a controller medication in addition to inhaled corticosteroids, e.g., long acting β-agonist, theophylline or leukotriene antagonist
- Asthma symptoms requiring short-acting β-agonist use on daily or near daily basis
- Persistent airway obstruction (FEV_1 <80% predicted; diurnal PEF variability >20%)
- One or more urgent care visits for asthma per year
- Three or more oral steroids "bursts" per year
- Prompt deterioration with <25% reduction in oral or inhaled corticosteroid dose
- Near fatal asthma even in the past

Table II. Refractory asthma.

Fatal or near fatal asthma
Severe asthma
Steroid-dependent and/or resistant asthma
Difficult to control asthma
Poorly controlled asthma
Brittle asthma
Irreversible asthma

Patients with refractory asthma require a rigorous and systematic approach to their diagnosis and treatment. It is critical to make a diagnosis of asthma and to exclude other airway diseases (Table II), particularly, Chronic Obstructive Pulmonary Disease (COPD) and Vocal Cord Dysfunction (Pseudo-Asthma).

Asthma is suggested by characteristic history of recurrent episodes of wheezing, breathlessness, chest tightness, and/or cough especially at night or in early morning. The certainty that asthma is correct diagnosis is increased when either clinic spirometry or pulmonary function tests demostrate airflow obstruction that improves significantly, defined as both a 12% and 200 ml improvement in either forced exipiratory volume in one second (FEV_1) in response to inhaled bronchodilator[13].

COPD is usually easy to distinguish from asthma but sometimes the distinction from late asthma, particularly in cigarette smokers, may be difficult. In these patients, a trial of oral corticosteroids is indicated; this involves administration of oral prednisone/prednisolone (30-40 mg in the morning) for 14 days. An increase in forced expiratory volume in one second (FEV_1) or peak expiratory flow (PEF) >15% indicates asthma. A negative response may indicate COPD, or rarely refractory asthma (corticos-

Table III. Diseases that mimic asthma.

- Chronic Obstructive Pulmonary Disease (COPD)
- Bronchiectasis and cystic fibrosis
- Primary bronchiolar disorders
- Congestive heart failure
- Upper airway obstruction
- Aspiration or inhaled foreign body
- Neuromuscular weakness
- Vocal cord dysfunction
- Hyperventilaton/panic disorder
- Churg-Strauss syndrome and other vasculitides

teroid-resistant asthma with shows the characteristic bronchodilator response of asthma)[8]. A minority of patients with difficult asthma have normal lung function, yet have typical asthma symptoms that fail to respond to escalating asthma therapy, or have apparent life-threatening asthma attacks prompting maximal medical therapy. In these patients, a methacoline challenge test is especially useful[14]. The PC20 (Provocative Concentration causing a 20% fall in FEV_1) value is determined in the American Thoracic Society guidelines. Normal bronchial responsiveness is indicated by a PC20 of greater than 16 mg/ml; borderline bronchial hyperresponsiveness is present when the PC20 is between 4.0 and 16 mg/ml, with a positive test as defined as a PC20 of less 4.0 mg/ml[15]. A negative study excludes asthma with a high degree of certainty. A positive study confirms that abnormal airway reactivity is present but does not definitively diagnose asthma because atopy, upper respiratory infection, COPD, bronchiectasis, sarcoid and congestive heart failure have all been reported to cause bronchial hyperresponsiveness[14,16].

Another the risk factors that may contribute to a poor response to conventional therapy must be excluding (Table IV). After excluding these factors, only a half of the cases are truly therapy-resistant asthma or severe asthma[11].

Biologic response to corticosteroids should also be considered as a lack of biologic response may give the physician a false perception of poor compliance/adherence. A recent small study suggested that corticosteroid therapy is clinically effective in only approximately 70% of the general population with asthma, under rigorously controlled study conditions[17]. A much larger clinical trial in moderate asthma (the Gaining Optimal Asthma Control, or GOAL, study) seems to confirm a similar pattern of response to response to inhaled and oral corticosteroids[18].

Table IV. Risk factors.

Unidentified exacerbating factors
Unidentified allergens
exposure
Gastro-oesophageal reflux
Systemic diseases
Thyreotoxicosis
Carcinoid syndrome
Churg-Strauss syndrome and others vasculitides
Drugs
β-blockers
Nonsteroidal anti-inflammatory drugs
Chronic infections
Mycoplasma
Chlamydia
Psycological factors

Hypotesis Regarding the Pathology of Refractory Asthma

Surprisingly little is know about the development of severe asthma. Furthermore, it is not certain wheter any patient with asthma is at risk for developping severe asthma, or only a poorly definited subset. The ENFUMOSA group (European Network For Understanding Mechanisms of Severe Asthma) developped a common methodology and applied this to recruit a cohort of patient with severe disease from 12 centres in nine European countries. Patients aged between 17-65 yrs old and who had been receiving daily therapy with inhaled corticosteroids (ICS) for a minimum of 1 yr. All patients had to have previous evidence of variable airways obstruction within the last 5 yrs, as documented by at least one of the following: (1) reversibility in FEV_1 of >9% predicted after 4 puffs of a 100 μg salbutamol dose-aerosol, administered via a spacer; (2) a mean diurnal variation in PEF >15% (highest PEF-lowest PEF) per mean PEF on >4 days per week for a minimum of 2 weeks; (3) an increase in FEV_1 of >400 ml after a course of prednisolone 0,5 mg/kg day for 14 days; (4) a provocative concentration causing a 20% fall in FEV_1 with histamine or methacoline <8 mg/ml. Patients were excluded if they were cigarette smokers, with a smoking history of >5 pack years. Patients were also excluded if they had other active acute or chronic pulmonary disorders, or had clinically significant psychiatric diseases, or received immunosuppressant therapy other than corticosteroids. The ENFUMOSA project has provided the first comprehensive assessment of severe asthma in a variety of centres across Europe. A total of 321 patients were recruited comprising of 163 with severe and 158 with mild-to-moderate asthma. Females were 2.8 times more common in severe asthma group than male. The females with severe disease weighed more and had a greater BMI than the females with non severe asthma. Analyses of different markers of athopy consistently showed that this was inversely relat-

ed to asthma severity. The median dose of ICS was 666 μg for the subjects with controlled asthma and 1,773 μg for the severe asthmatics. The subjects with severe asthma also used other regular treatments to a much greater extent than the subjects with controlled asthma, 95.5% vs 24.7% for inhaled long acting β_2-agonist and 45.5% vs 2,5% for oral theophylline. Among the patients with severe asthma there was, in addition, a large sobgroup (n = 53) that also required regular treatment with oral corticosteroids (OCS) (median dose of prednisone 19 mg: range 4-50 mg). Patients with severe asthma had lower baseline FEV_1, lower FEV_1/FVC, a significantly reduced VC, increased RV and a trend towards increased RV/TLC ratio. Anhoter finding in the severe asthma was the presence of increased neutrophils in the circulation and in the sputum. Another a potential risk factor for severe asthma that emerged from the ENFUMOSA study was exposure to aspirin. It has long been recognised that aspirin-intolerant asthma (AIA) appears more prevalent among subjects with severe varieties of asthma[19].

Table V. Risk factors.

Intermittent
Symptoms less than once a week
Brief exacerbations
Nocturnal symptoms not more than twice a month
FEV_1 or PEF >80% predicted
PEF or FEV_1 variability <20%
Mild persistent
Symptoms more than once a week but less than once a day
Exacerbations may affect activity and sleep
Nocturnal symptoms more than twice a month
FEV_1 or PEF >80% predicted
PEF or FEV1 variability <20-30%
Moderate persistent
Symptoms daily
Exacerbations may affect activity and sleep
Nocturnal symptoms more tha once a week
FEV_1 or PEF 60-80% predicted
PEF or FEV1 variability >30%
Severe persistent
Symptoms daily
Frequent exacerbations
Frequent nocturnal asthma symptoms
FEV_1 or PEF <60% predicted
PEF or FEV_1 variability >30%

Treatment

When confronted with a patient in whom asthma appears to be to control with inhaled β-agonists and high-dose inhaled corticosteroids, it is important to adopt a logical approach (Table V). The Global Initiative for Asthma (GINA) 2005 guideline classified asthma into four steps, according to clinical features before treatment, as well as by daily medication regimen and the response to treatment[6]. Asthma is classified as follows. Step 1: intermittent, with symptoms occuring less than once a week and patients remaining asymptomatic with normal peak expiratory flow (PEF) between attacks. Step 2: mild persistent, with symptoms occuring more than once a week, but with less that 1 attack-day. Step 3: moderate persistent with daily attaks effecting activity. Step 4: severe persistent, with continous limited physical activity (Table V). Althoug estimates vary, it likely that 20% of patients have severe persistent asthma and 5-10% have uncontrolled asthma despite receiving optimized therapy (severe/difficult asthma). For patients with severe persistent asthma, the GINA guidelines reccomend the use of high-dose inhaled corticosteroids in combination with a β_2-agonist long-acting with one or more additional controller medications if required. Additional controller are anti-immunoglobulins (Ig), leukotriene modifiers, oral β_2-agonists, oral corticosteroids and sustained-release theophylline[6]. In patients with difficult asthma (the GINA guidelines step 4 criteria) who require maintenance oral corticosteroids, the lowest possible dose should be used. Oral corticosteroids have numerous beneficial effects in asthma on both in inflammatory and structural cells[20]. However, less than 25% of patient with severe asthma show clinically significant increased clearance of eitheir prednisolone or methylprednisolone. Markers of inflammationn, for example, plasma or sputum eosinophils/eosinophil cationic protein and exhalated nitric oxide, may be helpful in examining medication response in those patients in whom they are detectable[21].

The leukotriene inhibitors decrease airway eosinophilic inflammation and improves asthma control in adult patient with persistent asthma[22]. Benefit may be seen in some cases with leukotriene inhibitors, especially in the large percentage (20-25%) of patients with severe asthma who may be aspirin sensitive[19] In patient with allergic asthma and an elevated IgE level, administration of the monoclonal

antibody against IgE, omalizumab, can result in decreased airway inflammation and improved asthma control and may allow tapering of corticosteroid medications[23]. Various steroid-sparing treatment have been investigated in an attempt to reduce the dose of oral steroid and these include methotrexate, gold, cyclosporin A, intravenous gamma-globulin and colchicine but none treatment is very effective, and they all have a high prevalence of side-effects[24].

Conclusions

The pathologic processes of refractory asthma are poorly understood and it is very difficult to treat. Clinically, there is considerable heterogeneity among patients with refractory asthma, and it is not known wheter refractory asthma is one disease or multiple different diseases. Future studies should determine if multiple subtypes of disease exist under the umbrella of "refractory asthma". At present there is evidence that a rigourous and systematic approach to the evaluation and treatment of patient with refractory asthma is of benefit. In approaching a patient with refractory asthma, it is important to: (1) confirming the diagnosis of asthma, (2) evaluate and treat confounding or exacerbating factors, and (3) optimized the "standard" asthma pharmacotherapy[4,14].

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