

# Brittle Asthma

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**Abstract:** About 5% of asthmatics do not behave like 'classical' asthmatics and may not respond adequately to conventional therapy. The terms used to describe such non-responders include severe, refractory, near fatal, difficult and difficult to control asthma. Within the umbrella term of severe or refractory asthma, there are distinct sub-phenotypes including brittle asthma. Brittle asthma is rare and may occur in 0.05% of all asthmatics. Currently the diagnosis of brittle asthma is made on clinical grounds based on the variability of peak flow and uncertainty and unpredictability of sudden onset of disabling and severe symptoms despite maximal medical therapy with high dose inhaled corticosteroids, inhaled and nebulised bronchodilators and either maintenance or repeated courses of systemic corticosteroids.

The role of genetics, environmental exposure and infection is the focus of ongoing research in the development of severe asthma. Atopy, female sex and psychosocial factors are recognised to be associated with brittle asthma. Other factors, investigated as possible initiating or contributing factors in brittle asthma include nutrient deficiency, reduced antioxidants activity and immunodeficiency with low IgG subclass levels.

This review will highlight the related phenotypes, risk factors, mortality and morbidity, pathogenesis and management of patients with brittle asthma.

**Keywords:** Brittle asthma, refractory asthma, related phenotypes, severe asthma, pathogenesis, risk factors, management.

## INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways with airflow obstruction and bronchial hyperresponsiveness as its characteristic features. The airflow obstruction is variable and usually responds to standard management with bronchodilators and anti-inflammatory agents such as corticosteroids. However, it is also recognised that some patients with severe disease are not controlled on the standard therapy and hence suffer from higher morbidity, requiring more extensive use of medications and health care resources. Over a period of time, various names and labels have been used to describe this severe variety of bronchial asthma which may occur in approximately 5% of asthmatics. These terms include chronic severe asthma, difficult asthma, life threatening asthma, irreversible asthma, difficult or difficult to control asthma, rapid onset asthma, and fatal and near fatal asthma. In 2000, ATS Workshop Report [1] gave the term, 'Refractory Asthma' to include all patients who have been regarded as having severe asthma. This includes sub-phenotypes with specific characteristics, such as brittle asthma.

In order to have defined criteria for recognition of these variable presentations associated with the diagnosis of refractory asthma, the working party agreed on a definition based on one of two major and two of seven minor criteria. The major criteria were defined as a need to treat with continuous or near continuous (more than 50% of the year) high dose inhaled corticosteroids or oral corticosteroids to achieve

control to a level of mild-moderate persistent asthma. The seven minor criteria were related to aspects of lung function, exacerbation, disease stability, and the amount of additional medications. This definition would be applicable to patients in whom other conditions have been excluded, exacerbating factors have been optimally treated and patients have been found to be compliant with their asthma treatment [1]. Clinically, these patients may suffer from one or more of the following features; a) severe and chronic airflow limitation, b) progressive loss of lung function, c) inadequate response to corticosteroids and, d) rapid onset of a life threatening asthma episode.

In 1977, Turner Warick used the term 'brittle asthma' for the first time when describing a sub-group of patients with severe asthma who manifested wide variation in their peak expiratory flow rates despite high doses of inhaled steroids [2]. After 21 years, in 1998, Jon Ayres [3] further classified brittle asthma into two types. Type I was characterised by a chaotic, unpredictable and wide peak expiratory flow (PEF) variability (> 40% diurnal variation for >50% of the time over a period of at least 150 days despite considerable medical therapy including a dose of inhaled steroids of at least 1500 µg of beclomethasone or equivalent). The condition is more commonly seen in females (male: female ratio of 1: 3) between the ages of 15 and 55 years. Over 90% of patients are atopic. Type II brittle asthma was characterised by sudden acute attacks occurring in less than three hours without an obvious trigger on a background of apparent normal airway function or well controlled asthma. No sex difference has been identified in this group [3].

The existence of brittle asthma as a separate entity has been questioned in the literature. However, the more precise definition and description of Type I brittle asthma by Ayres

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[3] has lent support to it being a separate variety of asthma with increased morbidity and mortality. Since then, brittle asthma has been recognised as a sub-group of 1-10% of severe asthmatics (depending on the criteria used to define severe asthma), who are considered to be phenotypically different from the typical variety of severe asthmatics. Ayers *et al.*, from the West Midlands Brittle Asthma Database, estimated the prevalence of brittle asthma to be 0.05% of the asthmatic population [3]. Both varieties of brittle asthma have increased risk of death from asthma attacks and increased morbidity due to repeated hospital admissions, psychosocial problems and adverse effects of therapy particularly with systemic steroids and subcutaneous terbutaline infusion.

### Related Phenotypes

Other varieties of severe asthma have been described in the literature with overlapping features to brittle asthma. These include rapid onset asthma (ROA), severe life threatening asthma (SLTA) and near fatal asthma (NFA). Rapid deterioration of asthma with respiratory failure and need for mechanical ventilation is the common feature amongst these groups. However, other features may differ.

**Rapid onset asthma:** Gustavo *et al.* [4] defined rapid onset asthma (ROA) as life threatening asthma episode developing over a period of <6 hours. Plaza *et al.* [5] used a stricter definition of ROA as those with an asthma exacerbation, on a background of stability, leading to seeking of medical help within two hours of onset of symptoms. In the study by Plaza *et al.*, 20% (of 220) patients met the criteria for ROA, whereas, 11.3% (of 403) were classified as ROA in the study by Gustavo *et al.* Both studies showed a male preponderance, lower rates of respiratory infections causing exacerbation, higher severity indices for the asthma episode but a more rapid response to treatment compared to those patients who had a slower onset of their asthma episode. The criteria used to define ROA are very similar to that of type II brittle asthma [3], and it is possible that a new term was being used for the condition previously described as type II brittle asthma.

**Severe life threatening asthma:** A case control study of severe life threatening asthma (SLTA) by Kolbe *et al.* [6] showed that the risk of SLTA in comparison with other patients admitted with acute asthma increased with age and was more common in men. Patients with SLTA were more likely to have had a previous episode of SLTA and to be admitted to the hospital in the last year. These patients were more likely to have been on oral theophylline and less likely to have been using inhaled corticosteroids in the two weeks before their attack. They are likely to have made a self management error in terms of delayed or non use of oral corticosteroids during the attack. They also had lower rate of use of peak flow meters to monitor their disease than the controls. These patients are less likely to contact their primary physician during period of deterioration and were more likely to have called the ambulance service or present to emergency department [6]. There was no difference between the cases and control in terms of indicators of quality of ongoing care or any barriers to health care. These features indicate that SLTA is perhaps not a separate phenotype but describes a sub-group of severe asthma patients, often mid-

dle aged men, who are at increased risk of life-threatening episodes due to poor compliance with treatment and asthma care plan. The authors carefully considered and ruled out the possibility that this lack of care was due to poor education or inadequate health care provision.

**Near fatal asthma:** Near fatal asthma [7] has been attributed to poor quality of medical care in New Zealand [8-11] and some other studies [12-16]. In some cases, errors in self management plans may lead to serious asthma attacks requiring hospitalisation [17, 18].

### Mortality and Morbidity

Patients with Type I brittle asthma shows a chaotic pattern of PEF with wide diurnal variations. Studies have shown that these patients have an increased risk of dying from acute asthma [19-22]. Morbidity associated with brittle asthma is also significant. There are frequent visits to accident and emergency units following a sudden severe life threatening attack. This occurs on a background of apparent stability in type II brittle asthma and extreme lability in PEF in type I brittle asthma. The severity of acute attacks in both type of brittle asthma may necessitate invasive or non invasive ventilation for a variable duration. Both types of brittle asthmatics often use large amount of medications in high doses. This can lead to distressing adverse effects of weight gain and osteoporosis from high dose inhaled or systemic steroids, oesophageal reflux from smooth muscle relaxation with high dose beta 2 agonists and subcutaneous nodular lesions and abscess formation from continuous subcutaneous terbutaline infusions [23,24].

**Psychosocial factors:** Patients with severe asthma, including brittle asthma, have an increased psychosocial morbidity. These patients tend to have increased General Health Questionnaire (GHQ60) and life event scores [25]. The studies have also highlighted the inappropriate coping response to worsening symptoms of asthma by delay in seeking medical help, self medication by increasing the doses of beta agonist and avoiding to either start or increase the dose of oral steroids [25-27].

**Poor perception and abnormal ventilatory response:** The patients with near fatal asthma attacks may have a blunted perception for worsening of symptoms [28-30]. They may also have a reduced hypoxic drive suggesting an abnormal ventilatory response during acute exacerbations [31,32]. Alexithymia is a psychological trait which is characterised by a difficulty in recognising body sensations and describing emotions [33]. Recently, alexithymia has been linked as a possible contributory factor to poor perception in near fatal asthma (NFA) as compared to non-NFA (36% vs 13%) [34], and has been associated with recurrent severe exacerbations of asthma.

### Risk Factors

The European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) [35], was the first, large, multicentre European study designed to understand the mechanism involved, specifically in chronic severe asthma. However, it did not study brittle asthma as a separate entity. This study showed that severe asthma was more common in females by 2.8 times and these females had a higher BMI

than their counterparts with non-severe asthma. Ayers *et al.* [3] also found female preponderance in type 1, but not type II brittle asthma. A further analysis of the ENFUMOSA group of patients [36] was based on an assessment through the use of the European Community Respiratory Health Survey (ECRHS) Questionnaire. It assessed the risk factors and symptoms associated with a phenotype of severe/difficult to treat asthma. The results of this analyses confirmed that personal and maternal history of allergy is associated with mild but not severe asthma. Sharing of bedroom before the age of five was significantly associated with severe asthma but no association was seen with serious respiratory tract infections or play school attendance. There was no difference between the two groups for contact with animals, exposure to dust, seasonal exacerbation, exposure to cigarette smoke and other working and living conditions. The ENFUMOSA study suggested that atopy does not play a major role in most patients with chronic severe asthma [35]. Patients with severe asthma had fewer positive skin prick tests and radioallergosorbent tests (RAST) to common allergens and an inverse relationship to a family history of atopy.

This is in contrast to type 1 brittle asthma who show multiple positive skin tests to inhaled allergens in 90% of the cases and are often exposed to pet allergens at home. In order to determine the atopic status of patients with brittle asthma, Miles and co-workers designed a case control study. The patients and their control group were assessed by skin prick tests to 19 common allergens. In addition they measured total and specific IgE. This study showed that patients with brittle asthma had higher mean wheal diameters for grass pollen, horse hair, feathers, wheat and chocolate as compared to non brittle asthmatics. Mean RAST scores to house dust mite were also higher in brittle asthmatics. Patients with brittle asthma also exhibited a significantly greater degree of atopy by higher atopy scores as compared to the controls [37, 38].

The role of food allergy or intolerance in brittle asthma has been a controversial issue. A variety of food products including, dairy, wheat, eggs, peanuts, soya and citrus fruits have been implicated as a trigger [39, 40]. Patients with type II brittle asthma may have a high incidence of food allergy [41]. A double blind challenge identified the food intolerance in patients with brittle asthma, who then improved with an exclusion diet [42]. A suggested mechanism for sudden acute attacks in type II brittle asthma may be an anaphylactic response triggered by food, causing mucosal oedema and acute vasodilatation or venous congestion in the bronchial circulation leading to bronchial narrowing. The deficiency of vitamins and minerals and reduced anti-oxidant activity in the diets of patients with type I brittle asthma has been postulated to contribute to the disease activity [43]. Ayers *et al.* proposed impairment of immunoglobulin production, with lower IgG and IgA levels, as contributing to the pathogenesis of type I brittle asthma [44].

In woman of reproductive age, perimenstrual deterioration in asthma symptoms is well recognised. There is a four fold increase in the incidence of asthma exacerbation during the perimenstrual days and about 25% of women with near fatal asthma can have their exacerbation on the first day of menstruation [45]. Several mechanisms have been postulated to explain the worsening of asthma symptoms in these pa-

tients. These include changes in estradiol and progesterone levels, psychologic features and intake of non steroidal anti-inflammatory agents. Other studies have shown an altered  $\beta$  receptor function during the luteal phase [46] and a down-regulation of the lymphocyte  $\beta$ -receptor density and cyclic AMP response on exposure to progesterone in female patients with asthma [47].

Aspirin-intolerant asthma is recognised to be more prevalent in severe asthma [48, 49] and aspirin emerged as a potential risk factor in severe cases in this study with high urinary leukotriene E4 (LTE4) levels. However, the prevalence of aspirin intolerance in brittle asthma is not known.

Genetic susceptibility underlies asthma of all degrees of severity. The influence of genetic factors in the aetiology of brittle asthma has been highlighted by reports of increased deaths from acute asthma in the relatives of patients with brittle asthma. The identification of precise genotype awaits further research.

### Pathogenesis

The pathogenesis of brittle asthma has not been studied in detail due to rarity and unstable nature of this phenotype. However, it is likely that many features are overlapping with severe asthma. Three distinct features of pathology in chronic severe asthma include persistent inflammation despite treatment with high dose inhaled and/or oral corticosteroids, presence of neutrophilic inflammation in the airways and structural changes including airway remodelling [50].

Pathological studies of severe asthma have shown that up to two thirds of patients with severe disease have continuous, ongoing bronchial inflammation despite appropriate therapy to suppress it with high dose systemic steroids. This is manifested by the presence of persistent airway tissue eosinophils and associated increases in T-lymphocytes and markers for activation of T helper 2 type of immune responses [51]. In the ENFUMOSA study [35], presence of persistent inflammation in patients with severe asthma was reflected in the persistence of eosinophils in induced sputum and the presence of increased urinary LTE4 and eosinophilic protein X despite treatment with corticosteroids. Further evidence of persistent inflammation was the presence of high nitric oxide in exhaled air in asthmatics while on regular steroid use, suggesting relative resistance to steroid treatment in severe asthmatics. Thus severe and brittle asthma might be characterised by a diminished or suboptimal sensitivity to glucocorticoids.

**Glucocorticoid resistance:** (GCR) in asthmatic patients can be true resistance to the action of steroids or it can be a pseudo resistance or steroid dependence. The diagnosis is established by giving a formal trial of oral steroids in the form of oral prednisolone 0.25-0.5 mg/kg/day for 14-28 days. GCR is diagnosed if there is <15% improvement in FEV<sub>1</sub> from the baseline value [52,53]. Patients with steroid dependent asthma can only be controlled with oral corticosteroids and lowering the dose can lead to flare up or worsening of their symptoms [54]. Studies have shown persistence of inflammation in the airways of these patients despite high steroid dose suggesting a relative resistance to the anti-inflammatory effects of the corticosteroids [55,56]. Although true steroid resistance is rare in asthma [57,58], rela-

tive resistance to the anti-inflammatory effect of steroids is more frequent [59-61]. However, confounding factors may be present in significant number of these patients, which may disguise as steroid resistance [62]. A study from Brompton Hospital [63] showed that alternative or additional diagnosis (32%), non compliance with treatment (50% patients on >15 mg/day of prednisolone) and psychosocial factors (11%) partly explain apparent failure to respond to steroids in many severe asthmatics (pseudo steroid resistance).

There are several mechanisms postulated to account for the lack of steroid sensitivity including defective ligand binding to the steroid receptor, abnormal receptor nuclear translocation and abnormal association with pro-inflammatory nuclear proteins [64]. Bronchoalveolar lavage in patients with corticosteroid resistance has shown an increased number of cells expressing interleukin (IL)-2, IL-4 and IL-13 mRNA compared with corticosteroid sensitive patients and a lack of suppression of these cytokines by steroid therapy [65]. In addition, corticosteroids are also less effective in inhibiting the expression of inflammatory cytokines from circulating monocytes and T lymphocytes in corticosteroid resistance patients as compared to corticosteroid sensitive patients [65, 66].

A second pathological phenotype of asthma consists of patients with increased levels of neutrophils either in isolation or with persistent eosinophils [51, 67]. Studies have shown the airways to be infiltrated by neutrophils rather than eosinophils in patients dying from sudden attack of asthma. Rapid onset fatal asthma, mimicking type 2 brittle asthma, has been shown to have predominantly neutrophilic inflammation in the airway submucosa [68]. This is in contrast to patients with mild or moderate asthma who show preponderance of eosinophils. Sputum studies have also shown higher levels of neutrophils in patients with severe asthma on high doses of corticosteroids [69, 70]. This pattern of inflammation is associated with a poorer response to corticosteroids as compared to eosinophilic persistence [71]. ENFUMOSA [35] study also found the presence of increased neutrophils in the circulation and in the sputum which might contribute to tissue destruction as occurs in chronic obstructive pulmonary disease.

In addition to continuous inflammation of the airways, structural changes have been identified in patients with severe asthma. Patients with persistent eosinophilia have thicker sub-epithelial basement membrane (SBM) as compared to normal controls, milder disease and without eosinophilia [51]. The inappropriate repair process may lead to increased in the goblet cell metaplasia and mucous production in severe asthma leading to airflow limitation and air trapping [72-74]. In addition, patients dying with status asthmaticus have been shown to have increased smooth muscle mass in their airways [75]. In the ENFUMOSA study [35], there was a suggestion for structural changes, despite use of high dose steroids, from pulmonary physiological assessments. The abnormalities included increased residual volume/total lung capacity ratio, hypoxemia and reduced diffusion capacity suggesting the presence of possibly fixed airway disease with air trapping and destruction of the alveoli. Whether this is a reflection of severity alone or severity and duration of the disease remains unclear.

Ayres *et al.* [3] suggested that airway smooth muscle contraction is likely to be an important component to produce sudden severe narrowing in brittle asthma. However, lack of reversibility to high doses of beta-2 agonists might reflect that oedema of airways due to plasma exudation from leaky-post capillary venules may also play a part. Allergens or irritants may produce rapid bronchoconstriction by activating the cholinergic pathways as well as by the release of bronchoconstrictor and inflammatory mediators from airway sensory nerves by activating the local or axon reflex [3].

## Management

The management of brittle asthma is difficult because of the labile nature of the disease with continuously varying airways obstruction and unpredictable acute episodes. The unpredictable nature of brittle asthma poses lot of stress and anxiety on patients, their families and carers. These patients are best managed in a tertiary centre where appropriate expertise is available.

It is of utmost importance in brittle asthma that patient are given an understanding of the nature of their disease and have the knowledge and confidence to deal with unpredictable, rapid and severe worsening of their symptoms. A written action plan should be provided with an emphasis on early call for help. Compliance with environment control and pharmacotherapy is a major problem in severe asthma as adverse effects of drugs are likely. An understanding of the disease and feeling of self control should improve compliance [76].

A number of factors may contribute to lack of adequate control in these subjects, including allergenic and hormonal factors, psychosocial problems, vocal cord dysfunction, and undiscovered coincident disease such as bronchiectasis. Identification of these factors/diseases will result in improvement in asthma control and quality of life in the majority of these patients. A structured review is recommended where these factors are systematically investigated [63].

The treatment of acute episode is on the standard lines with high dose of parental or oral steroids and nebulised short acting  $\beta$ -2 agonist. The addition of intravenous aminophylline and magnesium may be of help. Care should be taken to avoid intravenous bolus dose of aminophylline in those taking oral theophylline. Adrenaline can be used as preloaded syringes as an emergency treatment of an unpredictable attack in type II brittle asthma associated with acute allergic reaction, resulting in oedema and narrowing of the airways. Close monitoring is required with repeated measurement of arterial blood gases and if necessary, admission to intensive care unit should be considered. These patients are at high risk of rapid deterioration with respiratory failure needing mechanical ventilation.

Steroid therapy remains the mainstay of long term treatment, although it may be difficult to strike the right balance between treatment success vs adverse effects of both oral and high dose inhaled steroids. Patients with brittle asthma often require large doses of inhaled and/or variable dose of oral steroids in addition to long acting  $\beta$ -2 agonist. A trial of leukotriene receptor antagonist, theophylline and inhaled anticholinergics may be of value in improving control and reducing the dose of steroid. Short acting  $\beta$ -2 agonist are

needed in inhaled and/or nebulised form for as required or regular use, in addition to regular use of long acting  $\beta$ -2 agonist. In case of failure of the above treatment to control the symptoms effectively, infusion of continuous subcutaneous terbutaline (CSIT) has been shown to be of some benefit in controlling variability in PEF and symptoms at doses of 3-12mg/day [23,77-79]. In a study by O'Driscoll *et al.* [23], 12 of 17 patients with brittle asthma improved (mean lowest daily PEF rising from 142 litres/min to 297 litres/min), with reduction in oral steroid dose, nebulized beta-agonist dose and number of hospital admissions. Sykes *et al.* have demonstrated that SCIT produces high plasma level of terbutaline (mean levels around 150nmol/l) and yet it is relatively well tolerated by most patients [79]. However, there are problems with prolonged use of CSIT with the production of subcutaneous inflammatory nodules which may form abscesses in severe cases [23,24]. Some patients may develop severe muscle cramps and increased plasma levels of creatinine phosphokinase may be seen [80], while others may develop menorrhagia [23].

Cytotoxic therapy e.g. cyclosporine or methotrexate have only marginal additive effect. However, where control is difficult despite high dose systemic steroids or when adverse effects of systemic steroids become intolerable, these drugs may prove to have some steroid sparing effect [81]. Adverse effect monitoring is crucial. Methotrexate is given once weekly and close monitoring of blood count is essential [81, 82]. With cyclosporine, it important to closely monitor blood pressure and renal function.

Omalizumab is a recombinant, humanised monoclonal antibody against IgE designed to inhibit the immune systems response to allergens. It prevents IgE from binding to mast cells and basophils and thus prevents IgE mediated airway inflammation. In patients with severe allergic asthma, omalizumab has been shown to be effective in reducing exacerbation, improving quality of life and a significant number of patients are able to reduce the dose of inhaled steroids [83-87]. It is likely to be useful in brittle asthma where atopy seems to play a critical role, although no studies have yet been done.

Tumour necrosis factor alpha (TNF- $\alpha$ ) is a pro-inflammatory cytokine, important in many chronic inflammatory disorders characterised by a Th1 type immune response such as rheumatoid arthritis and inflammatory bowel disease. Although, asthma is typically regarded as a Th2 type disorder, in severe and chronic asthma, additional characteristics, particularly presence of neutrophils in sputum and bronchial biopsies, suggests a role for Th1 immune responses. A recent study, confirmed a significant role of TNF- $\alpha$  in severe asthma [88]. The authors went on to do an open label study to evaluate the effectiveness of anti-TNF- $\alpha$  (Etanercept) in severe, steroid dependent asthma. The treatment was associated with significant improvement in asthma symptoms, lung function, and bronchial hyper-responsiveness [88]. These results were confirmed in a more recent cross-over trial [89]. Further double-blind, placebo controlled trials are in progress.

A combination of detailed assessment and identification of modifiable factors, patient education and environmental control supported by rational use of pharmacotherapy results in satisfactory control in most patients. The availability of

newer, biological therapies provides further hope of an improved quality of life for these patients.

## SUMMARY

In conclusion, it seems that brittle asthma might be an overlapping diagnosis with other phenotypes, such as rapid-onset and near-fatal asthma described under the overarching term of severe or refractory asthma. Brittle asthma has many distinct features but also shares some risk factors, pathogenetic mechanisms and management options with other varieties of refractory asthma.

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