Brittle Asthma: A Separate Clinical Phenotype of Asthma?

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ABSTRACT

There is now good evidence that brittle asthma should be regarded as a separate clinical phenotype of asthma at the severe end of the spectrum. Two types of brittle asthma can be identified. Type I is characterized by wide swings in peak expiratory flow (PEF) despite maximal therapy and type II by very sudden attacks out of the blue. Type I brittle asthma is more common in females and although the exact aetio-pathogenic mechanisms are not yet known, several factors including allergen sensitization (with exposure) and psychosocial factors may be important. Peak expiratory flow monitoring is essential for recognising these patients. Treatment of type I brittle asthma is difficult and needs to be holistic, with particular attention being paid to psychosocial factors where required. Continuous subcutaneous infusion of terbutaline (or salbutamol) and dietary exclusion of relevant foods to which the patient may be allergic may be helpful in selected patients. Type II brittle asthma is less difficult to manage and includes the use of self-administered subcutaneous adrenaline to abort the rapidly developing exacerbations.

Key words: Brittle asthma, Peak expiratory flow.

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Bronchial asthma is an inflammatory disease of the airways with a very wide clinical spectrum, at one end of which is the patient with mild intermittent symptoms and at the other extreme the patient whose symptoms are difficult to control despite best all-round efforts. With the advent of daily peak expiratory flow (PEF) monitoring in the mid seventies several clinical phenotypes of asthma were described, based on the patterns of PEF variability. Asthmatics were labelled as 'morning dippers' if they had an early morning fall in their PEF, 'double dippers' if the PEF dipped twice in a day or 'chronic persistent' if their PEF showed low values with less variability. In 1977, Turner-Warwick used the term 'brittle asthma' (BA) for the first time to describe asthmatics whose PEFs were "chaotic", i.e. followed no set pattern. Poor compliance with treatment was considered as a major cause of this variation, but inappropriate use of treatment could not be the explanation for the underlying variability in airflow. This type of asthma was difficult to control and could lead to death in a sudden attack. Subsequently, the term has been used in different ways, with the first British Thoracic Society Asthma Guidelines recognizing only those patients as BA who had sudden, severe life threatening attacks, usually without any pre-morbidity. However, PEF variability has been identified as a significant risk factor for asthma deaths in several studies. Broadly, two types of brittle asthma have been described, type I and II. These

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two types of brittle asthma simply represent two recognizable phenotypes amongst those patients regarded as having severe asthma. Severity of asthma can be defined in many ways and, to a certain extent, all those at the severe end of the spectrum can be managed along similar lines. However, defining separate phenotypes, such as BA enables identification of different etiologic contributors, treatments strategies and genetic factors, which may contribute to severe asthma.

**DEFINITION**

*Type I brittle asthma.* This is characterized by more than 40% diurnal variation in PEF for more than 50% of time maintained over a period of at least 150 days despite maximal medical treatment including inhaled gluco-corticosteroids (ICS) of at least 1500 μg of beclomethasone (or equivalent). This definition was arrived at after careful study of more than 10,000 patient days of PEF data from patients with severe asthma, correcting for PEF meter inaccuracies. The minimum duration of 150 days has been incorporated to avoid misclassification due to transient increased variability after infections or allergen exposure.

*Type II brittle asthma.* This is characterized by sudden acute attacks occurring in less than three hours on a background of apparently well controlled asthma.

These are only initial definitions for epidemiological purposes and may not include all the patients with 'brittle asthma', who have repeated life threatening attacks. However, they provide a good starting point for specific research looking into this end of asthmatics.

**PREVALENCE**

Lack of consensus in defining the condition makes it impossible to know the exact incidence or prevalence of brittle asthma, but it is uncommon. Data from the West Midlands Brittle Asthma Register in the UK suggests that the prevalence is of the order of 0.05% of all asthmatics. Type I brittle asthma is more common in females (2.5 F:1M) and in the age group 18-55 years while there appear to be no sex differences in type II brittle asthma.

**MORBIDITY**

Type I brittle asthma patients need more frequent and longer hospital admissions compared to type II patients whose admissions are shorter and at unpredictable intervals. Both types may require mechanical ventilation. Acute asphyxic asthma with rapid attacks and hypercapnia has been described that may be similar to type II brittle asthma. This is more common in men and the duration of ventilation is relatively short. Type I brittle asthma in general is associated with greater morbidity than type II brittle asthma and other patients with asthma because of repeated hospital admissions and iatrogenic problems. Oral corticosteroids are prescribed in large cumulative doses over time leading to glucose intolerance and weight gain, the latter leading to obstructive sleep apnoea (OSA) in some. In the brittle asthma clinic at Birmingham (England) 12% of type I patients had obstructive sleep apnoea problems requiring nasal CPAP. The symptoms of OSA in brittle asthma are typical but nocturnal disturbance being a classic symptom of brittle asthma, the diagnosis of OSA can be missed. They also almost uniformly have oesophageal reflux, partly as a side effect of bronchodilators and partly due to increased negative intra-pleural pressures generated by these patients having airflow obstruction.

**MORTALITY**

Patients with wide variability of PEF are at increased risk of death from asthma, but exact mortality rates for brittle asthma are as yet unknown.

**RISK FACTORS FOR AND PATHOGENESIS OF TYPE I BRITTLE ASTHMA**

*Female sex.* Women are more prone to develop type I brittle asthma although the reason is not known. Hospital admission is more common in
women with asthma as a whole and as some women with asthma exhibit worsening of their asthma in relation to menstrual cycle, this raises the likelihood that progesterone/oestrogen fluctuations are important. In brittle asthma these exacerbations can be very severe and, in our experience, are more common.

Atopy. More than 90% of brittle asthma patients are atopic and, in addition, the degree of reaction to skin prick tests to allergens is greater compared to age, sex and treatment matched controls with the usual asthma. Despite this sensitized patients are more likely to be exposed to higher levels of the relevant indoor allergens, (notably Can f 1) which may act to perpetuate their condition.

Food intolerance. Over 60% patients with type I brittle asthma report at least one food or drink that makes their asthma worse. Double blind placebo controlled food challenges have confirmed food intolerance in over 50% patients with wheat and dairy products being the commonest culprits.

Psychosocial factors. Both short and long term psychosocial factors have been shown to be important in type I brittle asthma. There is a high incidence of depression and frequent evidence of broken relationships and physical or sexual abuse amongst these patients. Acutely, these patients often cope badly with worsening symptoms, part of which may be due to a panic reaction and consequent hyperventilation and/or vocal cord adduction. Vocal cord adduction is often regarded as a condition uniformly associated with psychological factors. The danger in severe asthma patients lies in attributing all symptoms to the vocal cords while losing sight of the asthma. In addition, these patients often delay taking appropriate therapeutic steps. Poor perception of worsening airway function may also be important for both type I and II brittle asthma.

Beta agonists. Use of \( \beta_2 \) agonists has often been implicated in the increase in asthma deaths over the 1980s in the UK amongst the asthmatics. As \( \textit{in vitro} \) studies have shown that high concentrations of \( \beta_2 \) agonists may induce steroid resistance, this could in theory be relevant in type I brittle asthma as these patients use high doses of inhaled or nebulised \( \beta_2 \) agonists. However, there is no direct evidence for this and, indeed, some of type I brittle asthma patients improve with use of continuous subcutaneous infusion of \( \beta_2 \) agonists (see management below).

Other factors. All severe asthma phenotypes will embrace multiple causal factors in differing proportions. In brittle asthma, in addition to the factors defined above, relative immunoglobulin deficiency, impaired hypoxic drive or ventilatory response, nutrient deficiency, autonomic imbalance or hyper-reactive upper airways leading to vocal cord dysfunction, unique inflammatory or neuronal pathways and a relative resistance to the anti-inflammatory actions of steroids, all have some support as contributing factors, yet all remain poorly defined.

DIAGNOSIS

Diagnosis of brittle asthma involves careful exclusion of all the factors that may be responsible for poorly controlled asthma. As is implied in the definition, PEF monitoring is essential for diagnosis and can help in evaluation of therapeutic interventions. In countries like India, where PEF monitoring is not routinely available or practised, identifying such patients is even more difficult. It is, therefore, important that at least for a few selected patients who are difficult to control on apparently good medication, domiciliary peak flow monitoring should be undertaken.

MANAGEMENT OF TYPE I BRITTLE ASTHMA

The British Asthma Guidelines are not of much help in patients with brittle asthma. Treatment of type I brittle asthma is a test of patience for the patient as well as the treating clinician. Many patients fall out with their doctors who, understandably, seem to have run out of options or ideas. Most patients will be taking large doses of ICS and \( \beta_2 \) agonists. Many of them are reluctant to take oral corticosteroids, even for tackling their
worse periods, because of side effects. Compliance and doctor-patient rapport under these circumstances are crucial and need to be handled with the appropriate balance of firmness and sensitivity. Over ambitious aims should be avoided and a clear understanding of what is achievable in terms of control is essential for both the patient and the clinician. Large improvements in control in a single step are unlikely though the progress can usually be made, albeit slowly. Even small successes, if perceived correctly by the patient can be psychologically beneficial.

Allergen avoidance. Control of allergen exposure is desirable but often not logistically successful and the suggestion that pets be removed from the household is often met with resistance. Identification and avoidance of allergic foods can be effective, remarkably so in some. Formal double blind placebo controlled food exclusion/challenge should ideally be done for identification of offending foods, but this is a long and tedious process requiring hospitalization. If such studies are not feasible locally then arbitrary exclusion of specific foods starting with dairy products and wheat can be tried sequentially for two months each. Good dietary support and expert advise is essential during the exclusions and the patients need to be honest and reliable with the foods they choose to eat.

Immuno-modulators. By definition these patients are on high doses of ICS and/or oral steroids and may have relative steroid resistance. The use of alternative immuno-modulators like cyclosporin and methotrexate, though seemingly logical, has been of only modest help in a minority of patients.

Long term subcutaneous $\beta_2$ agonists. Continuous subcutaneous infusion of terbutaline (CSIT) was developed fifteen years ago and is effective in selected patients$^{22,23}$. Terbutaline or salbutamol is delivered by a syringe pump in doses usually of 3-12 mg/day. About 50% patients of type I brittle asthma show marked improvement in PEF variation with CSIT (Figure 1), 25% show improved symptoms and reduction in use of other medications while the remainder show no effect$^{24}$. It is imperative to demonstrate the benefit of CSIT in a double blind placebo controlled evaluation as placebo responders are not infrequent (Figure 2) and identification of these rare patients prevents them from being treated with a long term, unnecessary and sometimes troublesome treatment. Chronic, persistent, steroid dependent asthmatics without PEF variability also do not show any response. The reason why CSIT is effective remains somewhat of an enigma. The blood levels achieved by this technique are high at around 150 nmol/L$^{25}$, but side effects are not as frequent as might be expected, indicating tolerance to the side effects. It has been shown that inhaled $\beta_2$ agonists can cause an additional measurable and reproducible bronchodilation in patients on CSIT suggesting that there may be a population of $\beta$ receptors accessible only to inhaled drugs$^{26}$.

![Figure 1](image1.png)

**Figure 1.** Peak flow chart in a patient with type I brittle asthma before (o) and after (●) treatment with continuous subcutaneous terbutaline. *(Reproduced with permission from CME Bull Respir Med 2000; 2 : 34-37).*

![Figure 2](image2.png)

**Figure 2.** Peak flow chart in a patient with type I brittle asthma during infusion of continuous subcutaneous infusion of terbutaline (■) and saline (placebo) (●). *(Reproduced with permission from CME Respir Med 2000; 2 : 34-37).*
There are some side effects\textsuperscript{25}, the main problem being the development of subcutaneous nodules at the infusion sites, although these generally resolve by fibrosis once the site is changed\textsuperscript{27}. Sterile abscess formation is not uncommon, probably due to poor aseptic technique. Sometimes local site problems necessitate permanent vascular access as a last resort for continuation of therapy, in itself not without its problems. Muscle cramps and increased levels of creatinine phosphokinase are other common side effects of CSIT, but there is no evidence of myocardial damage.

\textit{Long acting }\beta_2\textit{ agonists.} Long acting inhaled \beta_2 agonists (salmeterol and formoterol) should logically be effective in brittle asthma in view of the wide variation in PEF and the success of CSIT. However, in our experience, these drugs have been of limited use, although it has to be accepted that since the arrival of these drugs, some new patients who would previously have been labelled as type I brittle asthma have been very effectively treated.

\section*{MANAGEMENT OF TYPE-II BRITTLE ASTHMA}

Managing type II brittle asthma is less complex. In view of the rapid onset of symptoms patients should be provided with a card giving relevant information and alerting the attending physician, similar to the ones frequently carried by diabetic and epileptic patients in the West (Medic-Alert bracelets). Identification of inhaled or ingested allergens is crucial, but the mainstay of treatment is immediate administration of adrenaline, which in the Western Countries is often self-administered provided through pre-loaded syringes (Epi-pen, Ana-pen). If the intervening period shows significant PEF variability, even if not perceived, it should be tackled using standard asthma management protocols.

\textit{Novel therapies and future prospects.} New therapeutic approaches are urgently required. Leukotriene antagonists (Montelukast, Zafirlukast) are useful in some patients with type I brittle asthma and should be tried at least once for a trial period of one month. Psychological support, either individually or in a group and behavioural therapy with special attention to coping techniques may be helpful in some situations.

\section*{CONCLUSIONS}

There is now good evidence that type I and type II brittle asthma should be regarded as separate clinical phenotypes of asthma at the severe end of the spectrum. This classification forms a useful starting point for further studies on severe asthma, although prospective evaluation of asthmatic subjects is the only way to substantiate the validity of these definitions and also to delineate, if any, aetio-pathogenic mechanisms that lead to development of brittle asthma. However, these patients are rare and pose difficult and complex management problems. Several small interventions, both pharmacological and non-pharmacological, can lead at best to modest improvements in control of brittle asthma, but overall management needs to be holistic.

\section*{REFERENCES}


