Brittle asthma

Jon G Ayres, Jon F Miles, Peter J Barnes

The term "brittle asthma" was first used in 1977 to describe patients with asthma who maintained a wide variation in peak expiratory flow (PEF) despite high doses of inhaled steroids.[1] It was coined at a time when patterns of PEF variability were beginning to be described with respect to clinical patterns of disease, such as the morning dip in PEF[1 2] and the "double dip" pattern of morning and evening dips[3] seen in patients with less well controlled asthma. The brittle asthmatic PEF pattern of variability was identified as a separate group, being described as chaotic showing no such obvious repeating pattern. The significance of the brittle pattern was not completely clear at that time, although the inference was that these patients had more severe asthma that was, by definition, more difficult to control. Three papers published shortly afterwards showed that this chaotic pattern of PEF could lead to death from an acute severe attack[4–6] and the authors raised the possibility that these patients tended to be poorly compliant with treatment. Nevertheless, not all non-compliant patients showed this chaotic pattern, so clearly other factors were important. However, it is not clear how these patients would fit into a classification of severe asthma which would include all those patients at risk of death or repeated hospital admissions.

Some physicians are unhappy with brittle asthma being classified as a separate asthma phenotype, regarding these patients as simply the severe end of the spectrum. However, it is our belief that definition of differing asthma phenotypes is important, so what follows represents our view that brittle asthma should be considered as a specific asthma phenotype. We suggest how further study of patients of this type may help in unravelling the pathogenesis and treatment of at risk asthma.

Definitions

After Turner-Warwick's initial definition of brittle asthma, the term began to become used in different ways by different physicians and in the first British Thoracic Society Asthma Guidelines[7] the term was used solely to describe those patients with sudden, severe, life threatening attacks, usually out of the blue. However, studies of asthma deaths have consistently identified PEF variability as a risk factor for death.[4–6 8] More recently a definition of brittle asthma based on PEF variability, amount of treatment, and repeated attacks has been proposed.[9] Brittle asthma was defined as a diurnal PEF variability (amplitude % maximum) of >40% for more than 50% of the time (for example, 16 days a month) despite maximal medical treatment—namely, high doses of inhaled corticosteroids with repeated doses of inhaled bronchodilator, often by nebuliser, and maintenance or courses of oral corticosteroids.[9] However, it became apparent that this definition of asthma based on PEF variability required scrutiny if it was to be used as a tool for epidemiological studies into severe asthma. The definition itself lacked precision since the phrase "considerable medical therapy" did not specify precise doses of treatment such as inhaled steroid dose or use of nebulised bronchodilators. In addition, there was no clear idea of the duration of observation necessary before the label "brittle asthma" could be applied. Further doubts were cast on a predominantly PEF based definition of brittle asthma when the reliability of PEF meter readings came under question. Recent evidence indicates that several makes of hand held mechanical PEF meters show non-linear inaccuracy in their readings such that they tend to underestimate low and high PEF readings whereas the mid range readings are overestimated.[10 11] As a result, a prospective evaluation of more than 10 000 patient days of PEF data from patients with severe asthma was undertaken, correcting for PEF meter inaccuracy. A specified dose of inhaled corticosteroid therapy was used—namely, more than 1.5 mg per day beclomethasone or budesonide or more than 0.75 mg inhaled fluticasone propionate daily—and a definite period (150 consecutive days) over which such variability occurred was employed to overcome the transient PEF variability[12] seen after acute exacerbations or allergen exposures. Although it is our impression that a period of three months may be an acceptable period over which to assess variability in the clinical context, this tighter case definition is needed for epidemiological work and was used in a series of studies which explored aetiological/risk factors for brittle asthma.

However, this definition does not take into account those patients who are subject to sudden severe life threatening attacks often on a background of apparently good asthma control. Premenstrual asthma may be one such example as some women develop a marked drop in PEF in the few days before menstruation.[13] Sometimes these premenstrual exacerbations are so severe that they necessitate ventilation. To allow for this the following classification of brittle asthma is suggested:

Type 1 brittle asthma: characterised by a maintained wide 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) (fig 1, lower plot).

Type 2 brittle asthma: characterised by sudden acute attacks occurring in less than three hours without an obvious trigger on a background of

Heartlands Research Institute, Birmingham Heartlands Hospital, Birmingham B9 5SS, UK
J G Ayres
J F Miles

National Heart and Lung Institute, London SW3 6LY, UK
P J Barnes

Correspondence to:
Professor J G Ayres.

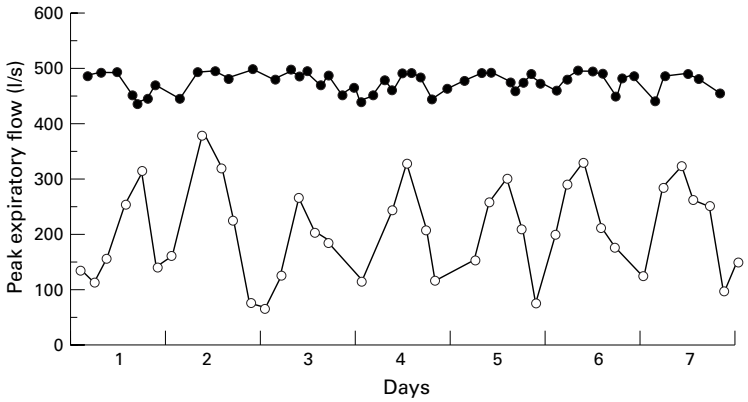

Figure 1 Peak flow chart in a patient with type 1 brittle asthma before (○) and after (●) treatment with continuous subcutaneous terbutaline.

apparent normal airway function or well controlled asthma.

These definitions may not include all patients who suffer repeated severe attacks and who might be labelled as having brittle asthma, but when beginning to try to disentangle these severe patients an initial definition has to be attempted. Future work may show that these definitions may not stand up to critical analysis and alternatives might be found. For instance, attention could be given to assessment of 100 and 50 day periods of peak flow variability as criteria for inclusion as a definition. However, as they stand they do provide a basis for research in this area.

Epidemiology

Little is known about the incidence or prevalence of brittle asthma, partly because of the problems with definition discussed above. There is no doubt that it is rare but it is not possible to estimate the prevalence from any of the studies of "near miss" asthma. The West Midlands Brittle Asthma Register has identified 76 patients with type 1 or 2 brittle asthma within an approximate asthma population of 300 000. A conservative estimate of the numbers not yet identified by the register would be around 150, giving an overall prevalence for brittle asthma of 0.05% of all asthmatic patients. The type 1 patient is more likely to be female (2.5F:1M), most being aged between 18 and 55 years,[14] whereas in patients with type 2 brittle asthma there appears to be no sex difference. There is little information available regarding peak flow variability prior to death from asthma in children.[15]

MORTALITY

Patients with wide variations in PEF have an increased risk of dying from acute asthma as discussed above,[4–6 8] but what proportion of patients with brittle asthma die from their condition is not known.

HOSPITAL ADMISSIONS

Hospital admissions are frequent in patients with type 1 brittle asthma, not only for acute severe attacks but also for assessment and stabilisation and consequent substantial prescription of medication. Patients with type 2 brittle asthma are admitted for acute severe asthma but at erratic and unpredictable intervals, although in general their use of health care resources is less than that of the type 1 patients. Both types of patient may require ventilation in acute attacks, although there is no information as to whether patients with either type 1 or type 2 brittle asthma are likely to need ventilation for shorter or longer periods than ventilated patients who do not have brittle asthma. It has, however, been shown that patients ventilated for acute severe asthma whose asthma attack came on suddenly (less than three hours) are more likely to be men and to have severe acidosis due to extreme hypercarbia, but are more likely to be ventilated for a relatively short period of time.[16] These patients would appear to be similar to the patient with type 2 brittle asthma. In the same study patients who were ventilated after a period of unstable asthma were likely to be ventilated for longer periods, less likely to be so acidotic, and much more likely to be female, perhaps similar to the patients with type 1 brittle asthma. Rapid onset attacks have also been shown to be associated with a predominance of submucosal neutrophils compared with those with slower onset attacks where eosinophils predominate,[17] although this may reflect the kinetics of granulocyte infiltration. It is of interest that the type 2 attacks, being both rapid in onset and in recovery, are similar in that way to the attacks suffered by the patients involved in the Barcelona soya bean induced asthma outbreaks[18] which could lend support to the hypothesis that allergic triggers are important in type 2 brittle asthma.

MORBIDITY

Type 1 brittle asthma is a cause of significant morbidity with frequent accident and emergency attendances and is a condition for which large amounts of medication are prescribed. Patients with type 1 disease are very likely to be using maintenance oral steroids (40% in the Birmingham series) and to suffer the effects of such therapy—for example, osteoporosis and weight gain. They also suffer almost uniformly from oesophageal reflux[19] which may be due in part to their treatment with high doses of bronchodilators and consequent oesophageal smooth muscle relaxation. Preliminary findings suggest that these patients do, however, have reduced values of both total lung capacity and functional residual capacity at around 80% predicted compared with control patients without brittle asthma,[20] which would support the idea that these patients generate more negative intrapleural pressures resulting in reflux.

Risk factors

There are very few data available on risk factors for type 1 brittle asthma, and it is not possible to extract specific risk factors from the studies of asthma deaths with respect specifically to those patients with variable PEF prior to death. In the Birmingham case control study of type 1 brittle asthma[14] atopy, psychosocial factors, and food intolerance appeared to be important

associations. We believe that patients with type 1 brittle asthma can spiral down into a brittle state by combinations of various initiating and exacerbating factors, although it is as yet unclear why a particular individual becomes "brittle". For patients with type 2 disease there are no published data on risk factors.

ATOPY

Over 90% of patients with type 1 brittle asthma are atopic as defined by at least one positive (>4 mm diameter weal) skin prick test greater than the response to a negative control.[14] The degree of positivity—that is, the cumulative size of the weals to those allergens tested—was more than twice that of a control group matched for age, sex, and dose of inhaled steroid. In particular, responses were greater for horse, cat, wheat, and chocolate. The reaction to *Dermatophagoides pteronyssinus* was not statistically different between the two groups, although RAST test responses to Der p 1 were greater in the type 1 patients. It is difficult to be sure what this finding indicates, particularly as there was no difference between the two groups in terms of total IgE[14] regarded by some as the bench mark for atopy.[21] These findings would, however, be compatible with the hypothesis that type 1 brittle asthma is associated with increased sensitisation to common allergens. However, there is also increasing evidence that viral infections[22] and asthma medication, in particular β_2 agonists,[23] may increase IgE synthesis. However, the causes of increased atopy in patients with brittle asthma remain to be explained.

Some patients with type 2 brittle asthma may be triggered by exposure to aeroallergens such as fungal spores. *Alternaria* spores have been identified as a cause of sudden and severe asthma attacks in some patients[24] although positivity to *Alternaria* was rare in the Birmingham study of type 1 brittle asthma.[14]

RELATIVE IMMUNOGLOBULIN DEFICIENCY

In a study of patients with severe asthma, most of whom had type 1 brittle asthma, mean circulating IgG and IgA levels were lower, a finding which seemed to be unrelated to the current dose of oral steroid taken by each patient.[25] This might suggest an impairment of local immunity which increases susceptibility of these patients to respiratory infections. Preliminary findings from a double blind placebo controlled study of immunoglobulin replacement in these patients showed no benefit over a three month treatment period,[26] although the dose of immunoglobulin used was lower than that normally employed in the treatment of combined humoral immunodeficiency states.

FOOD INTOLERANCE

Two thirds of patients with type 1 brittle asthma report at least one foodstuff which makes their asthma worse (Ayres, unpublished observations), with 20% reporting allergic reactions to peanuts, an allergy known to be occasionally fatal.[27] Equivalent data for patients with type 2 disease are not yet available. However, in the Saskatchewan study relating prescriptions to death and near death in asthma there was a significant association between a history of asthma symptoms after eating certain foods and the risk of death or near death.[28]

PSYCHOSOCIAL FACTORS

A case-control study of patients with severe asthma, many of whom had type 1 brittle asthma, showed an increase in psychosocial morbidity with increases in both General Health Questionnaire (GHQ60) and life events scores.[29] A subsequent study of patients with type 1 brittle asthma, also of case-control design, has confirmed the finding of increased psychosocial morbidity[30] with significantly greater GHQ60 scores and poorer quality of life scores (Living with Asthma questionnaire[31]). This study also demonstrated abnormal coping strategies for managing deteriorating asthma in these patients. They delay going for medical help, self-treating by increasing β agonist use and trying to avoid either starting or increasing oral steroids if at all possible. A study of group support in eight type 1 patients showed significant reductions in medication use, particularly oral steroid, with a tendency to improvement in quality of life scores over a six month period, although these improvements were of modest degree.[32]

It is difficult to be certain whether brittle asthma is associated with personality disorder or whether the threat of severe asthma induces psychological instability. Certainly these patients often cope badly with deteriorating asthma and show clear evidence of panic in their responses.

POOR PERCEPTION

There is evidence that patients who have had near fatal asthma attacks have a reduced perception of worsening airway function[33 34] and this might be a relevant factor in both type 1 and type 2 brittle asthma.[35] Whether impaired perception of asthma is inherited or acquired is not yet certain. Patients with previous episodes of near fatal asthma also have a reduced hypoxic drive, even when their lung function is normal, suggesting that during an acute exacerbation they may not have a normal ventilatory response.[36 37]

BETA-AGONISTS

The role of β agonists as a causal factor in death from asthma has been much discussed and remains controversial.[37–43]

Although normally prescribed doses of inhaled β_2 agonists are likely to be safe, some patients with type 1 brittle asthma take excessive doses, particularly with home nebulisers, when doses of more than 30 mg of salbutamol daily are often used. There is some evidence that high concentrations of β_2 agonists result in impaired glucocorticoid actions in vitro.[44] If extrapolated to the clinical situation, this suggests that high doses of β_2 agonists may induce steroid resistance and worsen control of asthma; this could be relevant to patients with type 1 brittle asthma and would appear to support the original epidemiological data.

However, more recent studies from New Zealand[45 46] suggest that the associations from earlier work were largely due to residual confounding by severity. This would also help to explain the apparent paradox of patients with type 1 brittle asthma being effectively treated by continuous subcutaneous terbutaline (see section on "Treatment" below).

Possible underlying mechanisms

INVESTIGATION

Any attempts to elucidate possible mechanisms in brittle asthma are hampered by the difficulties in establishing clear cut definitions, as discussed above. Furthermore, these patients are difficult to investigate because of the potential danger of invasive investigations. Even the measurement of bronchial reactivity may be contraindicated in such patients. Many patients find that more than one forced expiratory manoeuvre is enough to cause significant worsening of their condition without adding a further bronchoconstricting stimulus. Although fibreoptic bronchoscopy has proved extremely valuable in elucidating the inflammatory mechanisms of asthma,[47–49] it is not known whether these techniques may be applied safely to patients with brittle asthma. It is likely, therefore, that advances in knowledge on mechanisms are more likely to occur through other investigative means.

Non-invasive methods such as exhaled nitric oxide (NO)[50] or measures of inflammatory mediators such as urinary leukotriene E_4,[51] plasma cytokines such as interleukin 5,[52] and eosinophil cationic protein[53] may also shed light on the degree and nature of the inflammatory process in brittle asthma. Induction of sputum using hypertonic saline[54–56] might in theory be useful but is likely to cause severe bronchoconstriction in this group of patients.

It remains, however, of particular importance to determine whether the inflammatory pattern is the same in brittle asthma as in the other types of asthma, whether the expression of cytokines and inflammatory enzymes is similar, and whether there are structural abnormalities, including innervation, that differ from the findings in mild asthmatic patients.

ACUTE AIRWAY NARROWING

The mechanisms of the sudden severe airway narrowing that characterises brittle asthma are unclear. It is likely that airway smooth muscle contraction is an important component, although this is not readily reversed by doses of β_2 agonists which suggests that oedema of the airways due to plasma exudation from leaky post-capillary venules may play a part. As discussed earlier, patients who die from asthma attacks of sudden onset have airways characterised by infiltration of neutrophils rather than eosinophils[17] which suggests either that neutrophils appear earlier than eosinophils in any given asthma attack or that this is a characteristic of patients with attacks of precipitous onset.

Irritants might induce rapid airway narrowing via activation of a cholinergic reflex bronchoconstriction, but also by the activation of a local or axon reflex via the release of bronchoconstrictor and inflammatory peptides from airway sensory nerves,[57] substance P,[58] and other tachykinins.[59]

The association between food allergy and brittle asthma may suggest that an anaphylactic reaction could occur in the airways, and a major component of this response might be airway oedema. The therapeutic consequences of this might be important as adrenaline, through its α-adrenoceptor anti-oedema action, might be expected to be more effective than a β_2 agonist in relieving airway obstruction.

Another airway component that may contribute to airway narrowing in brittle asthma is the airway vasculature through acute vasodilatation or venous congestion in the bronchial circulation resulting in airway narrowing.[60]

STEROID RESPONSIVENESS

Patients with type 1 brittle asthma are usually treated with high doses of inhaled and/or oral steroids, yet their asthma often remains poorly controlled which suggests that there may be a degree of resistance to the anti-inflammatory effects of steroids. True steroid resistance in asthma is very rare[61] but relative resistance to the anti-asthma effect of steroids is more common. In severe asthma, where there is an intense inflammatory response, there may be excessive activation of AP-1 and other transcription factors that bind to, and therefore consume, glucocorticoid receptors.[62] This could then reduce the response to inhaled and oral steroids, resulting in a secondary steroid resistance. Whether this is a factor in brittle asthma is not yet clear, but recent studies in patients with steroid resistant asthma have demonstrated a marked inflammatory response in the airways despite the fact that these patients have been treated with steroids.[48 49]

Treatment

COMPLIANCE

Patients with brittle asthma are, by definition, extremely difficult to manage. Many of them have fallen out with their doctor who, perhaps understandably, has run out of therapeutic options and often patience. The standard management guidelines such as the BTS guidelines[7] are inapplicable to these patients once they have become brittle. They are taking large doses of inhaled steroids and the only way to increase the dose when the condition worsens is to resort to oral steroids which many resist because of side effects. Many patients also use very large doses of β_2 agonists, taken either as a metered dose inhaler (often more than one canister per week) or through a nebuliser, often using more than 30 mg of β_2 agonist daily. It is therefore essential that the physician realises that what the patient wishes to say and do concerning management assumes a greater importance than in "ordinary" asthma.

Non-compliance (or non-adherence) has been much studied in mild to moderate asthma, and is recognised to result from interaction of many factors, particularly

psychosocial factors.[63] The same is true of patients with brittle asthma who often try quite bizarre management tricks to avoid having to start or increase a dose of oral steroids. If the physician is prepared to barter with the brittle asthmatic patient, then advances can be made, albeit slowly. Large improvements in control are unlikely in one step and many patients have over-ambitious hopes of how much their doctor can do. When these are not achieved patients can regress psychologically, thinking themselves or the medical care a failure. If this overambition can be restrained and more achievable and realistic targets set, then success can be achieved. Small successes, if perceived as such by the patient, can prove psychologically very helpful in the short term.

ALLERGEN AVOIDANCE

Control of allergen exposure may be of help in these patients although there is only anecdotal evidence that this is effective. The logistics of allergen control are great, not only in terms of practicality but also cost. Many patients with type 1 brittle asthma have animals at home and removal of what is often their best companion will be met with resistance. Unpublished data from the Birmingham group show that patients with brittle asthma are exposed to much higher levels of pet allergens (but not house dust mite) than other asthmatics, but whether this will result in removal of pets and important reductions in allergen exposure in this severe group remains in doubt.

STEROIDS

These patients by definition are using high doses of inhaled and/or oral steroids, and the possibility of steroid resistance in at least some of these patients has been raised, as discussed above. Whether alternative immunomodulatory treatment such as methotrexate or cyclosporin A will be effective is not yet certain.

SUBCUTANEOUS β_2 AGONISTS

Patients with type 1 brittle asthma can be treated with a long term continuous subcutaneous infusion of β_2 agonist, usually terbutaline (CSIT), at doses of 3–12 mg/day.[64 65] Using a two day single blind period of subcutaneous saline before increasing through the doses of terbutaline, about 50% of patients with type 1 brittle asthma showed considerable improvements in symptoms, variation in PEF (fig 1), and use of other asthma medication including oral steroids, about 25% showed some improvement in symptoms but less improvement in PEF, while the remainder did not seem to respond.[10] Chronic steroid dependent asthmatics without a wide variability in PEF did not respond. Although mean blood levels of terbutaline achieved by this technique are around 150 nmol/l,[66] similar to those seen in patients who have taken deliberate overdoses of terbutaline,[67] changes in serum potassium or glucose levels are rare (unpublished data) which suggests tolerance to the side effects of this form of treatment.

The reason why subcutaneous β agonists rather than high dose nebulised β agonists are effective is far from certain and deserves further investigation. However, the fact that inhaled β_2 agonists cause measurable and reproducible further bronchodilation in patients on CSIT[68] suggests that there may be a separate population of β receptors which are not accessible by the infused route. There is evidence from animal studies that two such populations exist in the major airways.[69]

There are problems with CSIT which, in some patients, prove too much to continue the treatment. The main problem is the development of subcutaneous nodules or inflammatory lesions. The more indolent form show an eosinophilic infiltrate on biopsy specimens.[70] These usually settle down once that area of skin is avoided, but often leave a fibrotic nodule. More recently a more aggressive type of lesion has been demonstrated which sometimes leads on to frank abscess formation, the pus from which is usually sterile. The formulation of the drug has not changed nor have the preservatives, so the reason for these changes is not clear, but preliminary findings suggest that sensitivity to latex in the rubber tip of the syringe plunger is not involved.[71] Although the use of nebuliser solution rather than the injectable form of terbutaline may help, in some the skin changes are so severe that administration has to be changed to continuous intravenous infusion via an indwelling line. Muscle cramps are common and sometimes may be severe, with an increase in the plasma levels of creatinine phosphokinase[72] although levels of the myocardial fraction are normal. Some patients complain of an effect on memory and ability to concentrate but these have not been formally studied. Occasionally menorrhagia is seen[9] but this is not usually severe.

LONG ACTING INHALED β_2 AGONISTS

In view of the marked fluctuations in PEF and the efficacy of subcutaneous β_2 agonist infusions, it might be expected that long acting inhaled β_2 agonists would be effective in stabilising the airways. However, in our experience salmeterol has proved to be disappointing in these patients for reasons that are not yet clear. Whether formoterol, which is a full agonist, may be more useful than salmeterol, a partial agonist, remains to be determined. There is an anecdotal report of a patient showing symptomatic and lung function improvement with formoterol, but not to salmeterol.[73]

ADRENALINE

Adrenaline may have theoretical advantages over selective β_2 agonists, because of its action as an α-adrenoceptor against reducing airway oedema as discussed in the section on acute airway narrowing above. Preloaded syringes (Epi-Pen; Ana Pen) may be useful as an emergency treatment, particularly for patients with type 2 brittle asthma with their unexpected and rapidly progressive attacks. It is not yet certain whether inhaled adrenaline may be more effective than a selective β_2 agonist inhaler.

NOVEL THERAPIES

New therapeutic approaches are urgently needed in the management of brittle asthma. The logical development of such treatments will depend partly on our increased understanding of the mechanisms involved. In type 1 brittle asthma an alternative to steroids appears to be indicated. Whether novel anti-inflammatory treatments such as type IV phosphodiesterase inhibitors or cytokine inhibitors will prove to be useful is not yet certain. The sudden and reversible airway narrowing in brittle asthma may be due to non-inflammatory mechanisms and alternative treatments such as tachykinin antagonists or opioids may prove to be useful in the future.

Anti-leukotrienes (leukotriene receptor antagonists or 5-lipoxygenase inhibitors) may have a place in the management of some patients with type 1 brittle asthma. Some patients with more severe asthma appear to respond to this group of drugs[74] which would merit a trial in patients with brittle asthma.

Psychogenic mechanisms are clearly important in some patients with brittle asthma, yet little attention has been paid to the influence of psychological factors on airway responses and whether these could be modified by some forms of psychological treatment such as conditioning. Group therapy may have a role in some circumstances but attention to coping with deteriorating asthma may help to reduce the amount of treatment used and may have an impact on hospital admissions.

Summary

We believe that the asthma phenotypes we have defined as types 1 and 2 brittle asthma appear to be defined subgroups of asthma. For example, we have characterised patients with type 1 brittle asthma, as defined in this review, on the basis of peak flow variability and treatment and these patients remain a separate group when assessed by other means such as psychosocial factors, immunoglobulin levels, and atopy. The question remains as to whether they are truly separate groups with entirely different pathogenetic influences or whether they simply represent the severe end of the spectrum.

Our suggested classification into types 1 and 2 forms a useful start for studies of this condition, although prospective evaluation of patients with severe asthma is the only way of substantiating the validity of these definitions which will then enable investigation of possible mechanisms. However, these patients are rare and in order to study them as a group a national register would need to be set up along the lines of the West Midlands Brittle Asthma Register, perhaps recruiting all "at risk" patients and then using this resource as a means of exploring the different asthma phenotypes within this broad grouping, including brittle asthma.

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