Editorials

Brittle asthma: fiend or phantom?

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In the 1970s the introduction of regular monitoring of peak expiratory flow rate (PEFR) in asthma patients led to the recognition of patterns of variation that had clinical importance. Most noticeable was severe "morning dipping" or diurnal variation which was shown to be a prominent feature in small numbers of patients shortly before death or successful cardiopulmonary resuscitation from apparently suddenly worsening asthma.^{1,2} This phenomenon has subsequently been attributed to the effects of normal circadian rhythms in airway calibre on increasing bronchial hyperreactivity³ and the underlying mechanisms are at least partly understood. Turner-Warwick also described another pattern, "brittle asthma", which showed similar large changes in the magnitude of PEFR, responsiveness to frequent use of inhaled bronchodilators, but a chaotic pattern of variation.⁴ Some authors suggested that asthma patients could die within very short periods of apparently good asthma control,⁵ although others debated whether these deaths were only perceived to be sudden through poor supervision.⁶ Twenty years on these phenomena remain an enigma. Two papers in this issue of *Thorax* seek to define these conditions more precisely and determine their true nature.

Ayres *et al*⁷ have reviewed current thinking on brittle asthma. Their definition, and those of other workers, differ from that of Turner-Warwick as can be seen from fig 1 of their paper which illustrates a PEFR record that she would have described as "morning dipping" since it has a clear diurnal pattern, rather than a chaotic one. They base their criteria on magnitude of diurnal PEFR variability, rather than the pattern of variability. They also describe two subclasses; maintained variability (type 1) or sudden onset of acute airway obstruction (type 2). They believe that, although rare, brittle asthma is a separate asthma phenotype while others are not convinced that it is anything more than the extreme end of a disease spectrum.

On the basis of their hypothesis that this is a distinct form of asthma, they have attempted to define it more precisely. They have taken pains to eliminate inaccuracies in the measurement of diurnal variation in PEFR due to the non-linear characteristics of mini-peak flow meters. Moreover, for type 1 brittle asthma they require a monitoring period of at least 150 days during which variation of >40% is observed for >50% of the time in spite of high doses of inhaled steroids. They believe that this definition will facilitate more reliable epidemiological studies so that a distinct group of patients can be identified for further study. Unfortunately this definition is likely to prove too cumbersome for the practising clinician who needs to identify rapidly patients who might be at high risk.

They suggest that type 1 brittle asthma is more common in women and is associated with psychological instability, oesophageal reflux, reduced total lung capacity, atopy, food

intolerance, reduced perception of worsening airway function, reduced hypoxic drive, and a predominance of neutrophils over eosinophils in airway inflammation. This list certainly suggests a discrete entity; however, at least some of these features might simply be factors which would be expected to lead to a poorer prognosis.

Whether this is a distinct disease or not, this clinical picture is familiar and such patients are well recognised as being very difficult to manage. The authors highlight the adverse effects of psychological factors on compliance in some patients. They discuss possible mechanisms that might underlie brittle asthma and offer structured advice on drug therapy. Of particular interest are their arguments that brittle asthma may be partly due to steroid resistance through inflammatory depletion of glucocorticoid receptors. These patients often appear more responsive to intensive bronchodilator therapy. Moreover, it is not clear why they often show an additional response to inhaled bronchodilators when already on intravenous therapy. Two populations of receptors may be involved. New drugs are urgently needed to help these patients. The introduction of the new leukotriene receptor antagonists and 5-lipoxygenase inhibitors might be helpful since these drugs should reduce airway irritability.

Patients with brittle asthma are widely regarded as being at increased risk of sudden life threatening attacks. The paper by Kolbe *et al*⁸ suggests that this may not be as true as has previously been supposed. In a cross sectional study of 316 patients admitted with acute asthma they carried out detailed interviews to determine the true frequency of rapid onset asthma (defined as attacks lasting less than six hours) compared with attacks of slower onset. Their results show that patients underestimated the duration of their acute attack. Only 8.5% of their patients were classified as having rapid onset asthma. Patients in this category did not appear to have the characteristics of type 1 brittle asthma described by Ayres *et al*⁷ and were more typical of type 2 brittle asthma. Males predominated and psychological problems were no more common than in patients with slow onset asthma. These authors were not able to identify any particularly helpful features which characterised this group of patients.

How dangerous, then, is brittle asthma? Although rare, type 1 brittle asthma, in particular, has an appreciable morbidity in terms of hospital admissions, side effects of treatment, and considerable cost. Evidence that it is directly related to asthma death is, however, limited since most patients who die from asthma do not leave detailed peak flow records behind them. Many patients with type 1 brittle asthma might be in a "stable state of instability". In the absence of better knowledge close supervision is wise, but we should beware of continuing drugs, particularly high dose steroids, which are not clearly conferring benefit.

It is salutary to consider perhaps the earliest description of brittle asthma by Sir John Floyer.⁹ Three centuries ago he kept the first asthma diary for seven years, noting that his attacks “never seize me but in the night”. Nevertheless he survived 30 years of asthma, recommended opium as the best treatment, and enjoyed a 12 year remission “on moving to the clean air of Oxford”.

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