Obstructive sleep apnoea: a progressive disorder?

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Understanding the natural history of a disease is one of the oldest and most valued functions of the physician. This is not a problem in most respiratory disorders where decades of systematic observation are available to allow confident predictions to be made. An exception is the syndrome of obstructive sleep apnoea (or obstructive sleep apnoea-hypopnoea as it is more properly described[1]). This is a relatively recently identified condition where the diagnostic criteria are still contentious and disease progression, if any, is likely to be slow. Having established to the satisfaction of doctors and patients (but not necessarily public health physicians[2]) that repetitive upper airway obstruction is a cause of sleep disruption that can be reversed with treatment such as nasal continuous positive airway pressure (CPAP) or dental appliances,[3 4] all parties concerned now want to answer the question "what will happen if nothing is done"?

These concerns have gained an added importance with the realisation that obstructive sleep apnoea (OSA) is a common problem. The exact prevalence is contentious as most epidemiological studies have defined the disease in terms of what they are able to measure – for example, number of oxygen desaturations during sleep and overnight polysomnography.[5] The most ambitious and generously funded study is the Wisconsin sleep cohort study in which polysomnographic data were reported in 602 patients drawn from a random sample of 4000 middle aged subjects.[6] Sleep disordered breathing during sleep was identified in a large number, and an estimated 4% of men and 2% of women had associated symptoms of sleepiness, snoring, and sleep disordered breathing. However, most clinicians would prefer to identify symptomatic sleep apnoea only in those with at least 15 respiratory disturbances per hour, and if this criterion is adopted the prevalence is halved. Even allowing for the high incidence of snoring in Wisconsin,[7] this represents a considerable burden. Moreover, detailed reviews of other cohort studies suggest that this frequency of symptomatic sleep apnoea is likely to be replicated elsewhere.[8] The situation is further compounded by the identification of patients with minimal or absent breathing abnormalities whose snoring is sufficiently loud to produce clinically important sleep disruption,[9] further widening the spectrum of natural histories to be considered.

Patients frequently report that their loud snoring precedes the development of daytime sleepiness by many years, which is compatible with progression of their sleep disordered breathing. To date, almost all objective studies of the natural history of snoring/OSA have been retrospective, and until further results are obtained from the Wisconsin sleep study and the even larger Sleep Heart Health study this is likely to remain the case. Limited retrospective data suggest that correction of sleep disordered breathing can reduce mortality and, by inference, that its persistence will influence prognosis. Thus, an early study from the Detroit Sleep Centre followed 385 patients for eight years.[10] Mortality was significantly higher in those patients (mean apnoea-hypopnoea index (AHI) of 35 events/hour) who refused treatment than in those whose upper airway obstruction was corrected either by CPAP or tracheostomy. Cardiovascular mortality was found to be higher in another centre among those refusing treatment.[11] A further study has suggested a difference in mortality between patients treated with CPAP and uvulopalatopharyngoplasty compared with those who rejected these treatments.[12] Whether such a benefit is related to improvement in the snoring or the upper airway obstruction is unclear, especially since this type of surgery often appears to have little impact on either.[13] Moreover, these studies may reflect bias due to patient selection at referral, responder bias during follow up series, and differences between those patients choosing to accept or refuse treatment.

There are fewer data about the progression or otherwise of the breathing disorder itself. The Bologna group, who were the first to describe systematically the association between loud snoring and apnoeas during sleep, have proposed that there is a progression from uncomplicated loud snoring to overt sleep apnoea over time,[14] an observation supported by data from Stockholm where a significant deterioration in AHI was found in 26 of 42 patients restudied a mean of 16 months after initial polysomnography.[15] Rather surprisingly, Sforza *et al*, also working in Bologna, found that six of 32 patients showed a significant fall in AHI from 45 to 15 events per hour, whilst in seven the AHI rose from 14 to 51 events per hour. The follow up period of these untreated patients was significantly longer at five years.[16] The patients in the Italian study were very similar in their baseline physical characteristics to the 19 patients with relatively severe sleep apnoea (AH1 59 events per hour) in whom no respiratory changes were seen. Those patients in whom AHI changed over time had a lower body mass index than those who remained stable, but the changes in body mass index seen in those who deteriorated appeared to be too small to explain the dramatic change in their breathing pattern.

In this issue of *Thorax* Pendlebury *et al*[17] report a further systematic attempt to address this problem. They performed polysomnography in 55 patients referred to their clinic for the assessment of snoring and excessive daytime sleepiness, and advised no specific treatment beyond general health measures in these cases. Cephalometry was performed routinely to assess upper airway and maxillofacial anatomy. Patients were restudied at variable time points thereafter (mean 77 weeks) and, using a 25% change in baseline AHI, they found that over half had deteriorated. Moreover, when the incidence of new cardiovascular problems was examined, there was a significant excess of these in patients who had deteriorated compared with the other groups. It was not possible to predict progression from either cephalometric measurements or the baseline body mass index. The conclusion that sleep disordered breathing can be a relatively rapid progressive disorder associated with a significant health impact is a challenging one.

Inevitably there are concerns about the methodology of any retrospective study, and this one is no exception. As noted already, study population selection is crucial. In this case the authors assure us that subjects chosen are representative of their previously reported population in terms of disease severity and presenting symptoms.[18] As in the other study suggesting deterioration,[15] the

follow up period here was 18 months but there was a wide variation in the time to second study. The influence of baseline AHI and the likelihood of future deterioration is not really clarified as the data are expressed as a percentage change from baseline (see fig 2). It is difficult to know whether a 500% increase represents a change from five to 25 events per hour or 20 to 100. It would have been helpful to see the absolute changes as has been shown in the two previous papers in this area.[15,16] Good data about short term reproducibility within an individual population are both expensive to collect and in short supply, and – reasonably enough – the authors have used values obtained from the literature.[19,20] Whether this is appropriate for studies of this type is open to debate, and the stability of the measurements in the short term is relevant to ensure that an appropriate sample size is studied. It would have been interesting to know more about the association of these changes to the changes in patient symptoms which are the usual trigger for introducing treatment. The fact that those who were subsequently treated had both a higher initial AHI and worse deterioration during follow up suggests that their symptoms were probably worse. Finally, the dramatic increase in cardiovascular morbidity needs confirmation in a population of similarly affected patients with OSA, simple snorers, and contemporary control subjects followed for similar periods of time. If confirmed, it will provide one of the most powerful arguments for early intervention – or at least increased surveillance – in this condition.

Several mechanisms for producing disease progression are possible. Recurrent loud snoring traumatises the upper airway for many hours per night and is thought to lead to structural remodelling, although the evidence for this occurring is better in childhood where adenoidal patients are known to show undergrowth of the mandible.[21] Repeated snoring is associated with myxoematous degeneration of the uvula,[22] changes in the muscle fibres,[23] and may produce a reduction in upper airway sensation and reflex responses relevant to maintaining upper airway calibre during sleep.[24] Oedema of the upper airway has been shown to resolve with regular CPAP treatment,[25] which may explain why some patients are able to stop CPAP for one or more nights after regular use without recurrence of the symptoms. The substantial changes in AHI reported in all three longitudinal studies of sleep disordered breathing seem to be most obvious in those patients with a more normal body mass index. It is tempting to postulate that the major reason for sleep disruption here was an anatomically narrowed airway occurring in someone without fixed fat deposition as its major determinant. In such circumstances minor variation in airway oedema or airflow resistance due to nasal problems could produce a rapid deterioration or improvement in upper airway function during sleep. This is a situation analogous to that seen in lower airways disease where small variations in airway calibre can produce dramatic increases in airway resistance when an appropriate stimulus is applied.[26]

Undertaking research into the natural history of OSA is particularly difficult and Pendlebury and colleagues deserve our thanks for their contribution to this. The continuing uncertainties about the best way of diagnosing OSA and its relation to symptoms makes a hard task even more difficult. The present study, like all good research, raises many new questions for those who will conduct future prospective investigations, in particular the physical characteristics of patients entering a study and the reproducibility of minor degrees of sleep disordered breathing. Follow up for a similar period of time in patients and control subjects is vital. At present cephalometry is a poor predictor of those in whom AHI will change substantially over time, which raises the question as to whether it is needed in routine clinical assessment or should be reserved for patients who undergo surgery. There is clearly a need for more prospective data on prognosis in a range of sleep disordered breathing so that we can answer our patients' questions about the future course of their illness – with and without treatment – with confidence.

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