Sleep disordered breathing and stroke

Sleep disordered breathing and the outcome of stroke

G J Gibson

Patients with OSA not only have an increased risk of stroke, but also a higher mortality and greater disability after stroke

Interest in abnormal breathing after stroke has a long history dating back at least to the observations of John Cheyne in 1818.[1] In recent years this interest has been reawakened by a number of publications on the relations between sleep disordered breathing (SDB) and stroke. These studies have been of two main types—those investigating the possible increased risk of stroke in individuals with obstructive sleep apnoea (OSA) and those reporting a high prevalence of SDB after stroke and its possible effects on residual disability and mortality. Unravelling the direction of causality—that is, whether OSA causes stroke or stroke causes OSA—has proved challenging.[2–5]

OSA AND RISK OF STROKE

Most of the evidence on the risk of stroke associated with OSA is circumstantial and is based on case-control studies in which a history of snoring, with or without other features suggestive of OSA, is compared in patients with stroke and matched controls.[6–11] Such studies lack objective confirmation of pre-stroke OSA, are critically dependent on the validity of the control population, and are subject to recall bias. Moreover, most studies have included subjects who had previously had a stroke where, inevitably, the direction of causality is uncertain. In studies where account has been taken of potential confounding factors such as obesity, smoking and hypertension, the estimated risk of stroke is reduced. Of the possible ''confounders'', hypertension is of particular relevance as the contribution of OSA to systemic hypertension has been demonstrated beyond reasonable doubt and clearly it offers a potential causal link with stroke. Even after statistical adjustment for hypertension, however, several studies still support an association between OSA and stroke. Various alternative mechanisms related to demonstrated abnormalities in patients with OSA have been suggested. These include abnormal cerebral haemodynamics,[12] increased platelet aggregability,[13] increased fibrinogen concentration,[14] increased blood viscosity,[15] and abnormal vascular endothelial function.[16] On the other hand, snoring alone, without other features of OSA, appears to carry little if any excess risk.[17]

Although the weight of evidence favouring OSA as an independent risk factor for stroke is suggestive, cross sectional studies can never give a definitive result. Confirmation awaits the full publication of large prospective studies which are currently in progress. Preliminary data from one such study, published so far only as an abstract,[18] support the conclusion that OSA is a risk factor for the development of stroke or transient ischaemic attack (TIA), independently of sex, body mass index, diabetes, and hypertension.

SDB AFTER STROKE

Complementing these studies of the risk of stroke associated with OSA, several others have shown a high prevalence of SDB after stroke.[19–26] Most have been observational with no control group, an important omission in light of the high frequency of apnoeas and hypopnoeas in apparently healthy elderly subjects.[27] However, three studies which included small age matched control groups[20 21 28] each showed a significantly higher apnoea-hypopnoea index (AHI) in the stroke patients. On the other hand, a recent study[29] comparing patients with TIA and individually matched controls showed no difference in AHI, although the frequency of nocturnal desaturation >4% was greater in the patient group. Two reports of sequential sleep studies after stroke showed a significant reduction in AHI 2–3 months later,[23 24] although in a third study,[30] based on oximetry only, there was no change in the desaturation index in stroke survivors restudied 3 months after the event.

Are these observations merely of curiosity value or might SDB adversely affect the outcome of stroke? In the current issue of *Thorax* Turkington *et al*[31] add further evidence that this may indeed be the case. In an earlier study of a small number of patients Good *et al*[19] showed that a higher nocturnal desaturation index was associated with greater mortality and more severe disability in survivors 12 months after the event. More recently, Iranzo *et al*[32] studied patients during the first night after a stroke and found that a high AHI was associated with early neurological deterioration, although this did not correlate with disability 6 months later. The study by Turkington *et al* has the advantage of including a larger and less selected population, which is broadly typical of patients with stroke admitted to hospital in the UK; they were generally older and more disabled than those included in many of the previous studies performed in neurological or rehabilitation units. Turkington *et al* showed clear relations between SDB in the first 24 hours after stroke and length of hospital stay, mortality, and greater dependency of survivors 6 months later. Another recent study[26] of younger patients in a rehabilitation unit also reported that SDB 6 weeks after a stroke was independently associated with longer hospital stay and greater long term functional impairment.

POSSIBLE MECHANISMS

Why then might subjects with OSA fare particularly badly after stroke? Several of the pathophysiological features accompanying OSA have also been associated with an adverse outcome in stroke populations. These include:

- Large fluctuations of blood pressure and the consequent effects on cerebral blood flow: in OSA repeated elevation of blood pressure, sometimes to an alarming degree, is seen at the termination of each apnoea.[33] In stroke patients a greater variation in blood pressure correlates with both increased mortality and greater dependency.[34]
- Baroceptor dysfunction has been reported in OSA[35] and impaired cardiac baroceptor sensitivity is associated with higher mortality after stroke.[36]
- Recurrent hypoxaemia associated with frequent apnoeas is another obvious candidate. This might have a critical effect on the ''ischaemic penumbra'' surrounding the infarcted brain and might result in extension of the neurological damage.
- Alternating hypoxaemia and reoxygenation accompanying OSA is associated with increased release of superoxides from neutrophils[37] which might have an adverse effect after

Abbreviations: AHI, apnoea-hypopnoea index; OSA, obstructive sleep apnoea; SDB, sleep disordered breathing; TIA, transient ischaemic attack

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stroke in light of evidence from animal stroke models.[38]

- Inflammatory and proinflammatory markers and mediators such as C reactive protein[39] and adhesion molecules[40] are increased in OSA while, in stroke, inflammatory changes are increasingly recognised as possibly contributing to injury of vulnerable brain tissue.[41]

Clearly, therefore, there are many similarities between the pathophysiological changes which accompany OSA and factors which influence the outcome of stroke. Further work will be required to tease out which of the above are likely to be most relevant to the associations shown by Turkington *et al*.[31]

Most of the features associated with more severe SDB after stroke are consistent with pre-existing OSA. These include a history of snoring[22 42] or sleepiness[28 30] and greater body mass index[21 22 25] and neck circumference.[22 25] Also relevant is an earlier case-control study[43] which showed a clear dose-response relationship between the reported severity of pre-stroke snoring and mortality 6 months after a stroke. On the other hand, there is little apparent relation between SDB and the characteristics of a recent stroke such as its clinical severity[24–26 30] or location,[23 26 32] or the extent of acute changes visible on CT scanning.[44] SDB is, however, more severe in patients with the lacunar syndrome[24 30] which is closely related to hypertension, and in those with CT evidence of chronic cerebrovascular disease.[44]

Taken together, a unifying hypothesis arising from these various studies would be that patients with pre-existing OSA have an increased risk, not only of developing stroke but also of an adverse outcome in terms of both mortality and disability. Such individuals may be more likely to show exaggerated SDB after a stroke and a consequent poor outcome.

CLINICAL IMPLICATIONS

Are these findings merely of theoretical interest or might they have practical relevance? The most obvious therapeutic implication relates to the potential value of treating OSA after a stroke with continuous positive airway pressure (CPAP). Although one study reported that some younger patients during rehabilitation after stroke will tolerate CPAP,[45] our experience, like that of others studying a more representative older population,[46 47] has been more pessimistic. If CPAP is to influence the outcome of stroke by limiting ischaemic damage to the vulnerable areas of brain in the ''penumbra'', it seems likely that its optimal timing would be very soon after the event. However, the practicalities of introducing such unfamiliar treatment to elderly, disabled, and sometimes confused patients in an acute hospital ward or stroke unit are such that the widespread applicability of CPAP after a stroke is unlikely. It may, nonetheless, have a role in selected individuals. Hui *et al*[47] found that the small minority of patients who tolerated CPAP shortly after a stroke had symptoms suggesting pre-existing OSA. This conclusion concurs with studies of patients with OSA in whom compliance with CPAP is better in those with more severe symptoms, particularly daytime sleepiness.[48] In practice, of course, stroke patients with features of pre-existing OSA may be the very ones to target for CPAP therapy if, as suggested above, the adverse prognosis associated with SDB following stroke is due mainly to pre-stroke OSA.

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Correspondence to: Professor G J Gibson, Department of Respiratory Medicine, Freeman Hospital, Newcastle upon Tyne NE7 7DN, UK; g.j.gibson@ncl.ac.uk

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α_1-Antitrypsin deficiency

α_1-Antitrypsin: more than just deficiency

R A Stockley

Abnormal levels of α_1-antitrypsin represent a syndrome of clinical disease entities, some relating to a deficiency while others reflect an overload

Carl-Bertil Laurell (1919–2001) was head of the Clinical Chemistry Department at Malmö General Hospital, University of Lund, Sweden (1954–84) and continued working in the department until his death in 2001. He had an interest in the initial studies of protein biochemistry, and his early paper on electrophoresis studies of serum proteins led to the discovery of subjects with deficient bands in the α_1-globulin region.[1] This region showed the greatest inhibition of trypsin, and the major protein within the band became known as α_1-antitrypsin. Having identified several subjects with a weak α_1 band seen on paper electrophoresis, Laurell and his research fellow Eriksson investigated the patients further. Three of the original five patients had severe early onset pulmonary emphysema suggesting a cause and effect.[1] For many years research focused on understanding the role of this protein in the pathogenesis of emphysema. Enzymes inhibited by α_1-antitrypsin were shown to be capable of producing many of the pathological features of COPD including emphysema, mucous gland hyperplasia, and mucus secretion. Because most of the α_1-antitrypsin in the lung is derived from the circulation by diffusion, low serum levels were associated with low lung concentrations. This resulted in insufficient amounts of α_1-antitrypsin in the lung to protect the tissues from damage by the enzymes—predominantly neutrophil elastase—normally controlled by this inhibitor (the proteinase antiproteinase theory of emphysema).[2]

The role of serum deficiency in the emphysematous process led to the introduction of augmentation therapy with purified α_1-antitrypsin in 1988. This was a logical approach leading to an increase in the serum and hence the lung concentrations of α_1-antitrypsin to ''protective'' levels. These studies resulted in ''deficiency'' being a pathological problem associated with lung disease and the outcome was that α_1-antitrypsin deficiency became largely the domain of respiratory medicine.

However, in 1969 Sharp and colleagues recognised that subjects with the

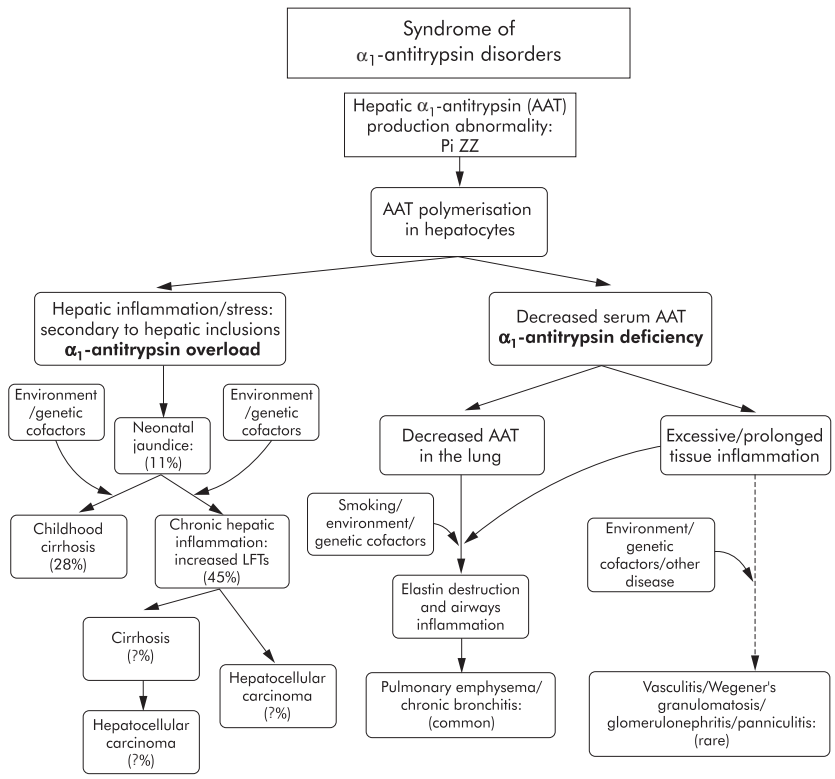


Figure 1 Hepatic polymerisation of the α_1-antitrypsin (Pi ZZ) protein results in both hepatocyte inclusions and decreased serum concentration. The low serum level is reflected in a low lung level of α_1-antitrypsin which is insufficient to protect the tissue from inflammation generated, for example, by cigarette smoking. Prolonged inflammation, together with as yet unknown environmental or genetic factors, leads to airway and parenchymal damage resulting in lung disease. The inflammatory process of vasculitides and panniculitis may also represent a failure to modulate inflammation as a result of low serum and tissue levels of α_1-antitrypsin, in combination with other cofactors yet to be determined. Within the hepatocytes the α_1-antitrypsin polymers cause inflammation that probably plays a role in the transient neonatal jaundice seen in 11% of individuals with Pi ZZ. In most this resolves, but in others childhood cirrhosis develops or the hepatic inflammation persists. Again, as yet undefined genetic or environmental factors may play a role in this persistent inflammation. With time, adult cirrhosis and hepatocellular carcinoma may occur, although the true incidence has yet to be determined.

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commonest (Pi ZZ) serum deficiency had a relatively high frequency of liver disorders, including neonatal jaundice and cirrhosis.[3] Subjects were shown to have hepatocyte accumulation of α_1-antitrypsin which is thought to be the reason for hepatocyte damage. Thus, unlike the lung disease, the liver disease became recognised as an ''overload'' problem. Accumulation of α_1-antitrypsin is the result of protein polymerisation, and the understanding of this process led to strategies to facilitate secretion and thereby protect the liver.[4]

With growing interest in the genetic nature of diseases and the clinical disorders associated with α_1-antitrypsin abnormalities, many countries developed national registries. This has resulted in the discovery of other clinical conditions that are more frequent in individuals with Pi ZZ antitrypsin, including vasculitis,[5] Wegener's granulomatosis,[6] glomerulonephritis,[7] and panniculitis.[8] Thus, the condition is associated with many clinical disease entities and is more representative of a syndrome. These aspects are outlined in fig 1.

Although Pi ZZ has classically been referred to as a ''deficiency'', this does not explain all the facets of the diseases. Some relate to ''deficiency'' while others clearly reflect an ''overload''. Much has been learned since α_1-antitrypsin ''deficiency'' was recognised by Laurell 40 years ago. This syndrome of α_1-antrypsin disorders, and particularly the disparity between ''deficiency'' and ''overload'', has brought researchers together from many fields—including pulmonary, genetics, hepatology, nephrology, dermatology and rheumatology—to extend the understanding of α_1-antitrypsin. Collaborative efforts are leading to strategies that both reduce the ''overload'' and overcome the ''deficiency'' which may resolve the many faceted nature of this genetic defect.

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Correspondence to: Professor R A Stockley, Department of Medicine, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK; r.a.stockley@bham.ac.uk

The author is a member of AIR (The Alpha$_1$ International Registry). This is based on an original concept suggested and refined by John Humphries.

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BTS guidelines for pneumonia

2004 update of BTS pneumonia guidelines: what's new?

J T Macfarlane, D Boldy

An update of the BTS guidelines for the management of community acquired pneumonia in adults

The BTS guidelines for the management of adult community acquired pneumonia (CAP), published in December 2001, assessed relevant evidence published up to 2000.[1] An update summarising more recent available evidence up to 2003 has just been published on the BTS website (www.brit-thoracic.org.uk/guidelines) using an identical search assessment and appraisal system. Minor additions or changes have been made in the sections on aetiology (related to nursing home acquired pneumonia), general investigations (use of C reactive protein and oximetry), general management, and vaccination strategies. The more important changes have been in the recommendations for the microbiological investigation of CAP, severity assessment, discharge planning, and antibiotics. At present these guidelines do not include information on severe acute respiratory syndrome (SARS), for which an updated specific guideline is available on the BTS website to help clinicians with case definition and management and will shortly be published in the *Journal of Infection*.

IMPORTANT CHANGES TO 2001 BTS GUIDELINES ON CAP MANAGEMENT

Microbiological investigation

Several studies have provided further evidence that the overall sensitivity of blood and sputum cultures in CAP is low, particularly for patients with non-severe CAP and no co-morbid disease and for those who have received antibiotic treatment before admission.[2–5] This has led to a changed recommendation that blood cultures may be omitted in a patient with no severity indicators or co-morbid disease providing the diagnosis of CAP has been definitely confirmed. The latter condition is important, particularly when dealing with a febrile patient where the site of infection is not clear and blood cultures can be very useful. The value of rapid legionella urine antigen testing was clearly demonstrated in a large outbreak of Legionnaires' disease in Holland, which found that early antibiotic management of patients could be guided by the results of rapid testing, resulting in improved outcome both in mortality and need for intensive care.[6] Outside the epidemic situation there is also evidence that early detection of urine legionella antigen can positively influence management of sporadic cases of legionella pneumonia.[7] This is an important message as there is growing evidence that delays in appropriate antibiotics adversely affect the outcome of pneumonia, particularly with legionella infection. Similarly, pneumococcal urine antigen tests have reported significantly greater sensitivity rates than routine blood or sputum cultures.[8 9] Both legionella and pneumococcal urine antigen testing are recommended for severe pneumonia, together with a rapid reporting service for legionella urine antigen for all hospitals admitting patients with CAP.

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Severity assessment

Severity assessment remains the key to deciding the site of care (whether at home, in a medical ward, or critical care ward) and guiding both general management and antibiotic treatment. The severity assessment tool recommended in the 2001 BTS CAP guidelines[1] was an amalgamation of aspects of the Fine pneumonia severity index (PSI),[10] the modified BTS severity criteria described in the 1993 BTS CAP guidelines,[11] and other adverse prognostic features published in the literature, and resulted in a rather cumbersome and non-memorable two step assessment process based on core, additional, and pre-existing adverse prognostic features. A recently published international study[12] derived and tested a simpler severity assessment tool, the CURB-65 score, with a six point scale (0–5)—one point for each of **C**onfusion, **U**rea >7 mmol/l, **R**espiratory rate ⩾30/min, low systolic (<90 mm Hg) or diastolic (⩽60 mm Hg) **B**lood pressure, and age ⩾**65** years—based on information available at the initial hospital assessment. Patients could be stratified into three groups according to increasing risk of mortality, hence adding support to clinical judgement regarding the need for hospital admission or intensive care management. Patients with a CURB-65 score of 3 or more are at high risk of death and should be managed as having severe pneumonia, those with a score of 2 are at some increased of risk of death and should be considered for short stay inpatient treatment or hospital supervised outpatient treatment, and those with a score of 0 or 1 are at low risk of death and may be suitable for home treatment. Both the BTS Pneumonia Guidelines Committee and the BTS Standards of Care Committee recommended adopting this revised severity assessment tool for the 2004 CAP update because of the more robust evidence, a single step assessment (compared with the current two step model), and a simpler algorithm to remember. Further prospective studies are needed to assess the true value of this newly adopted assessment tool, both in hospital and also in the community where a similarly predictive tool omitting the blood urea result (the CRB-65 score) can also be simply calculated.

Use of non-invasive ventilation

Non-invasive ventilation (NIV) plays a key role in the management of ventilatory failure in patients with chronic obstructive pulmonary disease, and several studies have reported that provision of NIV in patients with severe CAP can lead to initial improvement.[13–15] However, as over half of these patients later deteriorate and require intubation, this has led to the recommendation that, for CAP, trials of NIV should only occur in an appropriate critical care setting.[16]

Discharge planning

A recent North American prospective multicentre study[17] identified clinical factors that were useful in deciding whether a patient with CAP was sufficiently stable to be discharged from hospital. The presence of two or more features of clinical instability (based on temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, mental status, and oral intake) predicted a significant chance of re-admission or mortality. It is recommended that this assessment is considered when planning for discharge.

Antibiotics

Moxifloxacin has joined levofloxacin as the only licensed newer fluoroquinolones recommended for CAP in the UK, although the use of moxifloxacin is limited as it is not licensed for use in severe pneumonia, nor is it available in a parenteral formulation in the UK. As before, new fluoroquinolones are not recommended as first line agents or for community use for pneumonia, but can provide a useful alternative in selected hospitalised patients with CAP.[18 19]

FUTURE PRESENTATION OF GUIDELINE UPDATES

Like the 2001 guidelines, the update does not cover economic or quality assessment of CAP care—an area which is becoming increasingly important for audit and clinical governance[20] and will probably need to be included in future updates.

One challenge has been how to present updates of BTS guidelines. Various models are possible. In December the Infectious Diseases Society of America published the 2003 update of their 2000 guidelines on the management of CAP as a stand alone article on both their website and in *Clinical Infectious Diseases*[21]—a table summarising both the recommendations of 2000 and also the new recommendations for 2003 (printed in bold). For this update the BTS is using a web based article linked to a pdf document of the full 2001 guidelines available from the BTS website. It is expected that readers will download and view both documents together, but feedback will be welcome to guide the BTS in the best way of presenting future updates for its numerous published clinical guidelines. Ultimately, dissemination of the guideline will require respiratory physicians to inform and educate their colleagues, both in hospital and primary care. It is hoped that these few important recommendations will be incorporated easily into clinical practice.

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Authors' affiliations

J T Macfarlane, Chairman of the BTS Pneumonia Guidelines Committee, Nottingham City Hospital, Nottingham NG5 1PB, UK
D Boldy, Chairman of the BTS Standards of Care Committee, Pilgrim Hospital, Boston PE21 9QS, UK

Correspondence to: Dr J T Macfarlane, Nottingham City Hospital Nottingham NG5 1PB, UK; jmacfar1@ncht.trent.nhs.uk

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LUNG ALERT

Obesity associated hypoventilation in medical patients is common, potentially dangerous and under-recognised

▲ Nowbar S, Burkart KM, Gonzalez R, *et al*. Obesity-associated hypoventilation in hospitalized patients: prevalence, effects, and outcome. *Am J Med* 2004;**116**:1–7

The authors studied consecutive severely obese patients (BMI $\geqslant$35 kg/m^2) admitted to the medicine services of three teaching hospitals. Arterial blood gas tensions were measured to assess the prevalence, predictors, and outcomes of patients with obesity associated hypoventilation (OAH), defined as $Paco_2$ $\geqslant$43 mm Hg and pH $\leqslant$7.42, with no other obvious cause of hypoventilation. Of 4332 consecutive admissions, 277 (6%) had a BMI of $\geqslant$35 kg/m^2 and were screened. 127 were excluded for various reasons: 85 were unwilling to have an arterial blood gas measurement or could not provide consent, 32 used opiates, and 10 had a prior lung resection or a reduced FEV_1/FVC ratio ($<$50%).

Of the remaining 150 patients, OAH was found in 47 (31%). Compared with severely obese patients without OAH, patients with OAH were heavier, sleepier, more likely to have erythrocytosis, and had a lower FVC. They were more likely to require invasive mechanical ventilation (6% *v* 0%) and to require discharge to a long term care facility (19% *v* 2%). They also had a greater 18 month mortality rate (23% *v* 9%) which persisted after controlling for a variety of potential confounders. Surprisingly, only 23% of patients (n = 11) were given a discharge diagnosis of OAH, and only six of these were discharged with a recommendation to receive long term treatment (non-invasive nocturnal ventilation or tracheostomy).

In severely obese patients admitted to a medical service, OAH is common, associated with adverse outcomes, and under-appreciated. Clinicians should recognise the possibility of OAH in severely obese patients and consider performing arterial blood gas analysis.

N T Ayas
Assistant Professor of Medicine, University of British Columbia and the Centre of Clinical Epidemiology and Evaluation, Vancouver General Hospital, Vancouver, Canada;
ayasnajib@pol.net

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