Sleep disordered breathing and stroke

Sleep disordered breathing and the outcome of stroke

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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

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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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

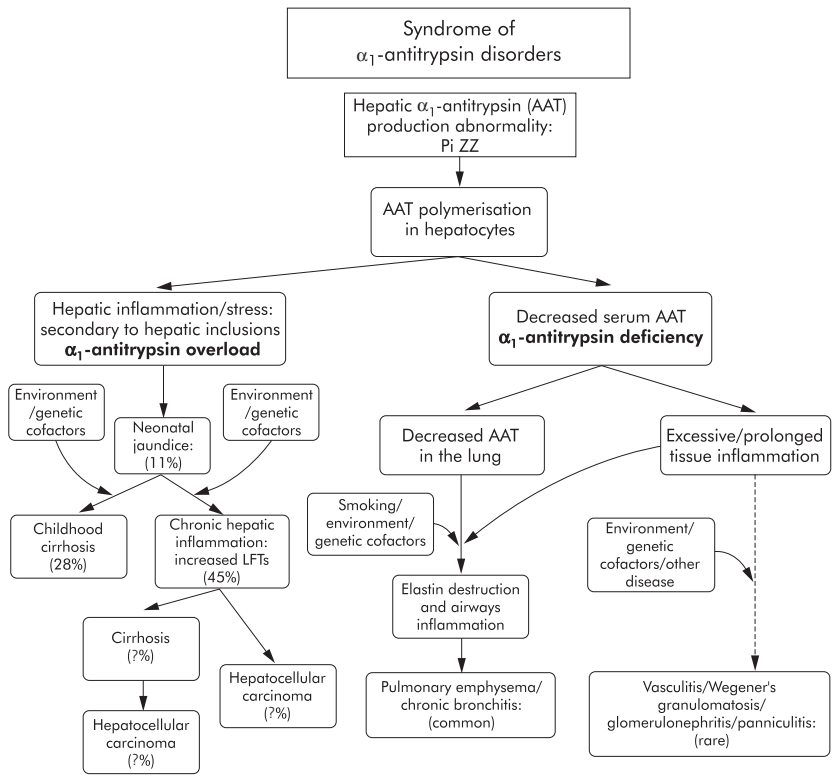

Figure 1 Hepatic polymerisation of the α_1-antitrypsin (Pi ZZ) protein results in both hepatocyte inclusions and decreased serum concentration. The low serum level is reflected in a low lung level of α_1-antitrypsin which is insufficient to protect the tissue from inflammation generated, for example, 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.