Spinal Cord (1998) 36, 231–239

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Sleep apnoea related hypoxia is associated with cognitive disturbances in patients with tetraplegia

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Sleep disordered breathing is common in patients with tetraplegia. Nocturnal arterial hypoxemia and sleep fragmentation due to sleep apnoea may be associated with cognitive dysfunction. We therefore studied the influence of sleep disordered breathing on neuropsychological function in 37 representative tetraplegic patients (mean age 34 ± 9.7 years). Thirty percent (11 of 37 patients) had clinically significant sleep disordered breathing, defined as apnoea plus hypopnoea index (AHI) greater than 15 per hour of sleep. Most apnoeas were obstructive in type. Seven patients (19%) desaturated to $<80\%$ during the night. Neuropsychological variables were significantly correlated with measures of sleep hypoxia, but not with the AHI and the frequency of sleep arousals. The neuropsychological functions most affected by nocturnal desaturation were: verbal attention and concentration, immediate and short-term memory, cognitive flexibility, internal scanning and working memory. There appeared to be a weak association between the presence of severe sleep hypoxia and visual perception, attention and concentration but no association was found between sleep variables and depression scores. We concluded that sleep disordered breathing is common in patients with tetraplegia and may be accompanied with significant oxygen desaturation. The latter impairs daytime cognitive function in these patients, particularly attention, concentration, memory and learning skills. Cognitive disturbances resulting from sleep apnoea might adversely affect rehabilitation in patients with tetraplegia.

Keywords: tetraplegia; sleep apnoea; hypoxia; cognitive impairment

Introduction

Sleep disordered breathing appears to be common in patients with tetraplegia.[1–4] A recent population based study by our group[1] indicated that the predominant type of sleep disordered breathing amongst patients with tetraplegia with C4–C8 lesions was obstructive sleep apnoea (OSA) and that the prevalence of sleep apnoea was two to three times higher than that reported in normal populations. The majority of the patients in our study had mild-moderate severity sleep apnoea. A small subgroup had evidence of severe disease. None of the patients had been recognised clinically as suffering from the OSA syndrome.

Obstructive sleep apnoea causes arterial oxygen desaturation and sleep disruption[2,5,6] and patients with OSA commonly present with daytime sleepiness. In our previous study[1] we found that subjective complaints of daytime sleepiness were related to the frequency of sleep arousals. Experimental sleep fragmentation in normal subjects has been shown to result in abnormalities of daytime cognitive functioning.[7,8] Hypoxia also has been shown to have deleterious effects on neuropsychological functioning in patients with hypoxemic lung disease.[9] Previous studies in severely affected, untreated non-tetraplegia OSA patients have demonstrated a range of neuropsychological deficits that are reversible following successful treatment of the sleep apnoea.[10,11]

The purpose of the present study was to determine whether the presence of sleep apnoea in tetraplegic patients is associated with abnormalities of neuropsychological functioning. Further we wished to explore whether neuropsychological abnormalities were influenced more by the presence of sleep hypoxia, or sleep fragmentation. We considered this information to be important for the following reasons. Treatment of moderate to severe obstructive sleep apnoea often involves wearing a nasal CPAP mask in sleep. This presents special difficulties and challenges in those who are tetraplegic. If neuropsychological functioning was intact or only minimally impaired as a result of OSA in those with tetraplegia a more conservative approach

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to treatment might be justified. On the other hand, special significance is attached to the preservation of cognitive function in this population because of their severe physical restrictions. Significant neuropsychological deficits due to sleep apnoea that were unsuspected or untreated could have a major negative impact on quality of life.

In this study we report the results of tests of neuropsychological function conducted in the 37 tetraplegic patients included in our previous study and relate these results to the patients' polysomnographic findings. A more detailed description of the sleep disordered breathing and sleep disturbance found in the original 40 patients subjected to polysomnography, and from whom the present 37 patients were recruited for neuropsychologic testing, is found in our earlier report.

Methods

Patient selection
We targeted the tetraplegic population in the state of South Australia who met the following selection criteria: (1) age between 18 and 60 years inclusive; (2) spinal cord injury level C8 or above classified as Frankel A, B or C; and (3) injury sustained 6 months or more before study. Frankel category A refers to complete motor function and sensory loss below the level of the lesion; category B, complete motor function loss with some sensory sparing and; category C, some sensory sparing and some non-functional motor sparing. Patients were excluded if they had chronic cardio-pulmonary disease, alcohol or drug abuse at the time of the study, or a history of head injury resulting in post traumatic amnesia greater than 24 h. Patients with other neurologic diseases or a history of psychiatric illness were also excluded.

Patient recruitment A national registry of spinal injured patients was used to identify all patients who sustained a spinal cord injury C8 or above in South Australia between 1976 and 1990 and who met the age and time-since-injury criteria. These patients were then sent a letter inviting them to participate in the study and were asked to complete and return a questionnaire regardless of whether or not they wished to proceed to the overnight sleep study. The questionnaire asked a number of questions concerning sleep, choking episodes in sleep, snoring, daytime sleepiness, current medications, alcohol consumption and past head injury. In addition, we searched records for the same period (1976–1990) in the two institutions in South Australia that were likely to have had contact with other patients who sustained their injury in another State but subsequently moved to South Australia. Those patients who returned questionnaires and agreed to participate in sleep studies were then personally visited and examined by one of the investigators (HF) to confirm that they currently met all selection criteria.

Sleep studies
Night-time polysomnographic studies were performed on patients in their own homes using a portable device that recorded multiple channels of physiological information on magnetic tape (Oxford, Medilog MPA-2, Oxford, UK). Sleep scoring (screen-by-screen) using this device has been shown to be as reliable as polygraph chart paper scoring.[12] The following parameters were recorded: electroencephalogram (C3/A2), submental electromyogram, bilateral oculograms, abdominal respiratory movement (inductive plethysmography), airflow (oronasal thermistor), and finger-probe pulse oximetry (SaO_2). A single channel of respiratory effort was used because of the limitation of total channels available for recording and because we reasoned that paradoxical thoraco-abdominal motion is always present in this population and, therefore, is unhelpful in detecting upper airway obstruction.

A polysomnographer (IM) attached the electrodes and transducers prior to the patient's usual 'lights out' time and activated the recording device. She then returned early the following morning to remove the electrodes after the usual patient 'wake time'. There was no trained polysomnographer in attendance for any of the studies and nine out of 42 patients (21% of cases) were entirely alone at night. In one study the SaO_2 signal was lost, but none of the studies failed.

Analysis of sleep disordered breathing and sleep fragmentation
The polysomnographic recordings were played back through an Oxford Medilog 9200 computer system and displayed on a VDU screen in 30 s epochs for manual scoring of sleep using the standard criteria of Rechtschaffen and Kales.[13] The respiratory signals were used to identify apnoeas (absence of airflow for 10 s or more) which were then classified as either central (absence of respiratory motion or effort), obstructive (presence of respiratory effort) or mixed (central and obstructive components). Hypopnoeas were defined as a reduction in airflow of 50% or more from baseline, lasting 10 s or more. Apnoea-hypopnoea index (AHI), which represents an average number of apnoeas plus hypopnoeas per hour of sleep, was used as a primary measure of sleep disordered breathing.

In addition to the standard polysomnographic criteria for sleep staging, brief arousals from sleep were scored according to recently published criteria.[14] In general, an arousal requires an abrupt increase in EEG frequency (eg, return of alpha rhythm) that lasts for 3 s or more. Such an arousal is often accompanied by other physiological changes such as head movement artefact on the EEG, EOG or EMG signals. In this study we also identified sudden runs of K complexes or slow waves that were associated with a sudden increase in the rate or depth of breathing, and/or movement artefacts. These changes were interpreted

and scored as arousals although they did not strictly meet the definition of an arousal mentioned above. Arousal index (AI, average number of arousals per hour of sleep) was then calculated and used as a measure of sleep fragmentation.

Neuropsychological assessment

On the evening of the polysomnographic recordings a battery of neuropsychologic tests was administered by our sleep technician (IM), who had been trained to administer the tests by the neuropsychologist involved in the study (JW). The neuropsychological tests used in this study are summarised in Table 1 according to the various functions (eg, memory, perception, attention and concentration) that they assess. A more detailed description of the individual tests that were administered is as follows.

(1) Rey Auditory Verbal Learning Test (RAVLT)[15] Each patient was read a list of 15 words (list A) and then asked to recall as many of the words as he/she could. The number of words correctly recalled on trial one (List Learning 1, LL1) was taken as a measure of attention and immediate memory. The list was repeated to each subject four more times and at the completion of each reading the patient was asked to recall as many words as they could. The fifth recall (List Learning 5, LL5) was used as a measure of learning and short term memory. A different list of 15 words (list B), used as an interference task, was then read to patients and the number of correctly recalled words was recorded (List Learning B, LLB). Following this patients were again asked to recall as many of the list A words as possible (delayed recall). The difference between the fifth trial and the delayed recall (Learning Loss, LLoss) was used as a measure of short-term memory loss/retention. The difference between LL5 and LL1 (LLDif) was used as a measure of learning.

(2) Digit Span sub-test of the Wechsler Adult Intelligence Scale Revised (WAIS-R)[16] The first part of this test, digits forward (DForw), required patients to correctly repeat, in the same order, a series of random digits which were read to them. Patients were presented with two trials at each span length (initial span length contained two digits). They were required to successfully complete one of two trials before being presented with the next pair in the series with a one digit increment. The test was terminated when the subject failed two trials at the same span length or successfully repeated two nine digit sequences. The score recorded (DForw) was the number of correctly recalled sequences. This test is considered primarily as a test of attention and immediate memory span.[15]

The second part of the test, digits backwards (DBack), followed the same procedure as digits forward except patients had to repeat the digits in reverse order. The digits backward score (DBack) was the number of correct reverse sequences given. Although a measure of attention, it is also viewed as a measure of cognitive flexibility, internal scanning and working memory.[15]

(3) Paced Auditory Serial Addition Test (PASAT)[17] This test was presented to patients by the playing of the standardised audio tape. Sixty one random digits were presented at four different rates: 1.2, 1.6, 2.0 and 2.4 s between each digit. Patients were required to add each digit to the digit preceding it. The score recorded (PASAT) was the number of correct responses. The test is a measure of auditory attention and concentration.[15]

(4) Symbol Digit Modality Test (SDMT)[18] Only the oral form of this test was administered. Patients were presented with a random sequence of 110 nonsense symbols (nine different types of symbols) printed in four rows of boxes on a sheet of paper. On top of the sheet was a key which paired each symbol with the numbers from 1–9. Patients were required to verbalise the number which corresponded with each symbol in the sequence and this was recorded on another sheet by

Table 1 Neuropsychological tests and functions measured

	Rey Auditory Verbal Learning Test					*Digit Span Test*				
Function	*LL1*	*LL5*	*LLB*	*LLoss*	*DForw*	*DBack*	*DDiff*	*SDMT*	*PASAT*	*BDI*
Short-term memory	+	+	+	+						
Attention/concentration	+				+	+	+	+	+	
Immediate memory span	+		+		+	+	+			
Cognitive flexibility						+	+			
Internal scanning						+	+			
Working memory					+	+				
Visual perception								+		
Visual attention and concentration								+		
Depression										+

LL1-list learning 1; LL5-list learning 5; LLB-list learning B; LLoss-learning loss (derived score); DForw-digit forward; DBack-digit backwards; DDiff-digit difference (derived score); SDMT-symbol digit modality test; PASAT-paced auditory serial addition test; BDI-the Beck depression inventory

the investigator. The number of correct responses in 90 s was recorded (SDMT). This test is considered a measure of visual perception, visual attention and concentration.[15]

(6) New Adult Reading Test (NART)[19] Patients were required to pronounce a list of 50 phonetically irregular words. The number of incorrect responses was equated with WAIS-R full-scale IQ scores. This test is used as a measure of pre-morbid intellect.

The Beck Depression Inventory (BDI)[20] Due to subject's physical impairment only the 13 questions from the cognitive sub-scale of the BDI were administered. Each of the subject's responses was recorded on a separate sheet.

Subjective Daytime Sleepiness
The patients were asked about their level of daytime sleepiness and were required to indicate how often they 'felt sleepy in the day' by answering 'never', 'rarely', 'sometimes' or 'often'.

Other measurements
Prior to commencing the sleep study, awake arterial oxygen saturation was recorded (pulse oximetry). Spirometry was performed including forced and slow vital capacity manoeuvres using a calibrated spirometer (Vitalograph, Buckingham, UK).

Data analysis and statistics
A preliminary examination of the data to test for possible subject selection bias with respect to age and gender was performed using the Student *t*-test and the Chi-square test respectively. The relationships between variables of sleep disordered breathing and neuropsychological function were examined using two statistical approaches. First, simple tests of correlation (Spearman) were performed to determine which of the phenomena associated with sleep apnoea (eg, sleep disturbance, oxygen desaturation) were most closely related to disturbances of daytime cognitive function. Second, to enable a clinically useful interpretation of the data, the patients were stratified into two groups according to widely reported cut-off criteria for the presence of abnormal levels of: (a) sleep disordered breathing; (b) sleep fragmentation, and (c) sleep desaturation. These groups were compared using the Mann Whitney U-test. A P value less than 0.05 was considered statistically significant.

The severity of sleep disordered breathing is usually first described by the frequency of abnormal breathing events (ie, number of apnoeas plus hypopnoeas per hour of sleep, apnoea-hypopnoea index, AHI), and then further characterised by the effects of these abnormal events on sleep architecture and gas exchange. Sleep disturbance is described in a number of ways, the most widely reported being the frequency of sleep arousals.[14] Oxygen desaturation is usually defined in terms of the frequency of transient desaturations below the baseline oxygen saturation or the time spent below a given threshold level. The commonly accepted threshold for moderate to severe levels of sleep disordered breathing which we have adopted for this report is an AHI of 15 or greater.[21] A baseline of sleep arousals of approximately 15–20/h has been reported in healthy young normal subjects[8,22] and is observed commonly in our clinical laboratory in patients who prove on sleep testing not to have a significant sleep disorder. We therefore used a cut off of 30 arousals per hour of sleep in the present study to signify the presence of clinically relevant sleep fragmentation. This corresponds to a level of experimental sleep fragmentation that has been shown to cause daytime neuropsychological dysfunction.[8] Severe sleep desaturation was defined as occurring at SaO_2 levels of 80% or below and patients were classified as severe desaturators if they spent $\geqslant 1\%$ of their total sleep time below this level. Frequent desaturators were defined as those with >10 episodes of desaturation ($\geqslant 4\%$ from baseline) per hour of sleep.

Results

Patient selection
Ninety-one (91) apparently eligible patients were sent a questionnaire and asked to participate in the study. Of these, 65 (71%) replied. Two patients were excluded at this stage because their replies to the questionnaire indicated a significant head injury, or alcohol and drug abuse. Six of 65 patients indicated that they were unwilling to participate in the sleep studies. Eight of the remaining 57 patients were excluded because they were now residing in another State. This left 49 potentially eligible patients who were willing to participate. On close clinical examination nine patients were subsequently excluded because there had been substantial neurological recovery since their injury and they no longer met the inclusion criteria. Therefore, of the initial 91 patients approached, 40 patients (44%) were confirmed to meet the entry criteria and proceeded to overnight polysomnography. Neuropsychological tests were successfully completed in 37 patients. Therefore this report is on a sample population of 37 tetraplegic patients in whom sleep study and neuropsychological data could be compared.

Representativeness of the sample
To determine whether our sample was representative of the South Australian tetraplegic population, we compared the mean age and the gender ratios of the 37 patients studied (Group I) with the other 54 patients (Group II) who were either excluded from the study or did not participate for any reason. There were no

significant differences in these parameters (Mean age. *Group I* 34.1 ± 1.5 years, *Group II* 32.2 ± 1.4, NS; Gender ratio (M : F). *Group I* 34 : 3, *Group II* 45 : 9, NS). Unfortunately, the information from the national patient registry was not sufficiently complete or up-to-date to enable us to compare parameters of body mass and medication use in the 37 patients studied with those that did not participate. Questionnaire responses of the six patients who refused polysomnography did not differ from the questionnaire responses of the participants with respect to the frequency of witnessed apnoeas, choking episodes or daytime sleepiness.

Clinical, anthropomorphic and lung function data of the 37 tetraplegic patients participating in the study are provided in Table 2. Predictable reductions in lung function were observed, but mean awake SaO_2 was normal. Most of the patients took antispastic medications.

Spectrum of severity of sleep disordered breathing
Data on sleep disordered breathing are presented in Table 3 and compared with recently published data in a normal population.[21] Findings in the 37 patients included in the present study are virtually the same as those reported earlier for the slightly larger sample size.[1] Namely, 30% (11 of 37 patients) had AHI $\geqslant$15. Most apnoeas were obstructive in type. Sixteen percent (six of 37) had an apnoea index $\geqslant$20/h, which is a level of breathing disturbance shown in an early study to be associated with increased mortality.[23]

Among the 11 patients with AHI $\geqslant$15, the average nadir SaO_2 was 76.1 ± 12.6% (mean ± SD; range 49% (indicating severe O_2 desaturation) to 95% (insignificant desaturation)). Seven patients (19%) desaturated to <80% during the study night and spent 1–33% of their total sleep time with SaO_2 <80%. Awake SaO_2 correlated with sleep time spent below SaO_2 of 80% but not with the frequency of nocturnal desaturations $\geqslant$4% from baseline.

Sleep complaints and sleep fragmentation
Six patients (16%) 'often' felt excessively sleepy in the day, 12 (32%) 'sometimes', five (14%) 'rarely' and 14 patients (38%) 'never' complained of daytime sleepiness. The degree of self reported daytime sleepiness was directly related to the frequency of sleep arousals of all types ($P<0.05$) but not with respiratory arousals alone (ie, arousals following apnoeas or hypopnoeas). Sleep architecture for various age categories in the present study is shown in Table 4 and compared with normative data from the literature.[24] There was evidence of marked sleep disturbance in the tetraplegic population studied: there was a consistent increase in the percentages of Stage 1 and a corresponding decrease in the percentage of Stage 2 and REM sleep across all age groups compared with a control population. REM sleep appeared to be reduced both in minutes and as a percentage of total sleep time. Total sleep time was increased compared with previously published normal values.[24]

Table 2 Clinical, anthropmorphic and lung function data on sample population of tetraplegic patients, $n=37$

	Mean ± SD	*Range*
Age (yrs)	34.1 ± 9.69	19–60
Patients taking diazepam (*n* (%))	22 (59)	
Patients taking baclofen (*n* (%))	28 (76)	
Patients consuming alcohol (*n* (%))	14 (38)	
Neck Circumference (cm)	41.5 ± 4.58	33–60
Chest Circumference (cm)	95.8 ± 13.2	74–146
Abdominal Circumference (cm)	94.2 ± 20.1	30–160
FEV_1 (L)	2.55 ± 0.79	1.1–4.5
FEV_1 (% predicted)	62.2 ± 17.0	26–101
FVC (L)	2.86 ± 0.93	1.2–5.2
FVC (% predicted)	53.8 ± 15.9	21–88
FEV_1/FVC (%)	90.0 ± 8.45	67–100
Awake SpO_2 (%)	96.8 ± 1.61	91–99

Table 3 Respiratory Disturbance Index (AHI)

	Percent of patients (95% confidence intervals)	
	Tetraplegics (current study)	*Able bodied population*[21]
AHI $\geqslant$ 5	57 (46–67) ($n=21$)	24 (19–28)
AHI $\geqslant$ 10	38 (32–51) ($n=14$)	15 (12–19)
AHI $\geqslant$ 15	30 (19–33) ($n=11$)	9.1 (6.4–11)

Ref.#21: 352 males, aged 30–60 yrs, randomly selected from a working population

Relationships between sleep variables and neuropsychological functioning

Correlations (Table 5)
There was no relationship observed between the frequency of apnoea plus hypopnoeas (AHI) and neuropsychological variables. Similarly there was no relationship observed between the frequency of sleep arousals and neuropsychological function. However, there were associations between cognitive disturbance and sleep hypoxia. This was only observed when examining for severe levels of desaturation (ie, SaO_2 <80%) and, to a lesser extent, the frequency of desaturations $\geqslant$4% from baseline. Awake saturation correlated with only one of the neuropsychological variables measured: the digits forward component of the WAIS-R test.

Comparisons using clinical cut-offs (Table 6)
Patients with moderate-severe sleep disordered breathing (ie, AHI $\geqslant$15 per hour of sleep) did not differ with

Table 4 Sleep architecture in quadriplegic patients compared with normal subjects

	Age (years)							
	18–29		*30–39*		*40–49*		*50–60*	
	Present Study n=13	*Normal* Subjects n=44*	*Present Study n=14*	*Normal* Subjects n=23*	*Present Study n=7*	*Normal* Subjects n=49*	*Present Study n=3*	*Normal* Subjects n=41*
Total Sleep Time (TST, min)	393±18.0	347±9.4	393±19.7†	340±14.8	383±23.8†	329±7.8	386±57.2	332±9.9
Non REM Sleep								
min	334±5.9‡	275±3.8	340±6.6‡	267±5.9	331±9.4‡	265±4.5	340±11.2‡	263±4.6
% of TST	85±1.5†	79±1.1	87±1.7†	79±1.7	86±2.4	81±1.4	88±2.9	79±1.4
Stage 1								
% of NREM	30±6.1‡	6±0.7	50±7.8‡	5±0.7	41±7.0†	8±0.7	35±3.0†	8±0.7
Stage 2								
% of NREM	37±4.4‡	72±2.3	35±5.1‡	73±3.7	44±5.7‡	79±2.7	32±5.6‡	81±2.9
Stage 3+4								
% of NREM	18.1±4.8	23±1.2	16±2.6	22±2.3	16±2.4	13±1.7	22±4.3†	11±1.6
REM Sleep								
min	59±5.9	72±4.4	53±6.6	73±7.5	53±9.4	64±3.9	46±11.1	69±3.9
% of TST	15±1.5†	21±1.3	13±1.7†	21±2.2	14±2.4	19±1.2	12±2.9†	21±1.2

Values are given as means±SE. *Normal subjects (first night sleep laboratory) data derived from reference#24. †$P<0.05$ and ‡$P<0.001$, cf normal subjects from the same age group

Table 5 Correlations of overall cognitive impairment with sleep study variables in 37 patients with tetraplegia

	LL1	*LL5*	*LLB*	*LLoss*	*DForw*	*DBack*	*DDiff*	*SDMT*	*PASAT*	*BDI*
Sleep disordered Breathing										
Apnoea-Hypopnoea Index	−0.17	−0.27	−0.10	0.6	0.22	0.15	0.05	−0.17	−0.04	0.06
Sleep Fragmentation										
Arousal Index	−0.05	−0.02	−0.12	−0.09	0.29	0.15	0.17	0.01	−0.02	0.12
Sleep Desaturation										
Episodes (⩾4% from baseline)										
per hour of sleep	−0.34*	−0.29†	−0.39*	0.23	−0.04	−0.14	0.14	−0.30†	−0.26	0.15
% of total sleep time spent with:										
$SaO_2<90\%$	−0.18	−0.23	−0.16	0.11	−0.10	−0.23	0.17	−0.11	−0.25	0.30†
$SaO_2<80\%$	−0.22	−0.53*	−0.30†	0.08	−0.09	−0.44*	0.39*	−0.31†	−0.56*	0.18
Awake SaO_2	0.17	−0.002	0.19	−0.14	0.34*	0.12	0.15	0.06	0.28	−0.28

*$P<0.05$, †$0.1>P>0.05$

respect to cognitive function from those with mild or absent sleep disordered breathing. Similarly, patients with a high level of sleep fragmentation (Arousal index >30/hour of sleep) did not have more cognitive dysfunction than those with low levels of sleep disturbance. However, patients experiencing severe nocturnal oxygen desaturation (ie, ⩾1% time spent with SaO_2 <80%) or frequent desaturations (ie, ⩾10 desaturation dips (>4% from baseline) per hour of sleep) did have reduced neuropsychological function.

The neuropsychological functions most affected by nocturnal desaturation were: verbal attention and concentration, immediate and short-term memory, cognitive flexibility, internal scanning and working memory. There appeared to be a weak association between the presence of severe sleep hypoxia and visual perception, attention and concentration but no association was found between sleep variables and depression scores. We found no associations between cognitive dysfunction and the use of baclofen, diazepam and alcohol, or with age (results not shown).

Discussion

In our previous study sleep disordered breathing was found to be frequent amongst tetraplegic patients.[1] The new finding reported in this study is that sleep hypoxia, which is a consequence of the sleep apnoea-hypopnoea, is associated with reductions in neuropsychological function. Attention, concentration, memory and learning were the main cognitive tasks affected by nocturnal hypoxia. We minimised other potential confounding causes of cognitive disturbance such as alcohol and drug abuse by our selection process and no

Table 6 Influence of sleep disordered breathing on neuropsychological functioning in patients with tetraplegia

Groups	*LL1*	*LL5*	*LLB*	*LLoss*	*DForw*	*DBack*	*DDiff*	*SDMT*	*PASAT*	*BDI*	
AHI <15 ($n=27$) vs AHI $\geqslant 15$ ($n=10$)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
ArI <30 ($n=20$) vs ArI $\geqslant 30$ ($n=17$)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Sat80 <1 ($n=29$) vs Sat80 $\geqslant 1$ ($n=7$)	NS	0.002	NS	NS	NS	NS	0.001	0.002	NS	0.001	NS
DesI <10 ($n=28$) vs DesI $\geqslant 10$ ($n=8$)	0.03	0.001	NS	NS	NS	NS	0.047	NS	0.009	0.02	NS

Nonparametric Mann-Whitney U test used for group comparison

statistical associations were found between medication or alcohol consumption and neuropsychological function.

There are relatively few previously published studies on cognitive functioning in non head-injured tetraplegic patients. These studies have focussed on the effects of a loss of the normal somatosensory input to the central nervous system. It has been proposed that this may enhance cortical reactivity and subsequent cognitive task efficiency.[25] The studies found some evidence for increased or equivalent levels of auditory attention/concentration in ambulatory tetraplegics compared with able bodied populations.[25,26] Our results are different and suggest that in tetraplegic patients who have sleep apnoea the effects of sleep hypoxia override any positive effects of the loss of somatosensory inputs on attention/concentration.

Impaired cognitive functioning has been previously documented in able bodied populations of sleep apnoea patients.[27–32] Cognitive dysfunction in patients with sleep apnoea has been related to both nocturnal hypoxemia[27–32] and sleep fragmentation/disruption.[28,31] There is uncertainty about the relative importance of hypoxemia and sleep fragmentation in the development of neuropsychological dysfunction and the two are difficult to separate in the clinical disorder of sleep apnoea. Hypoxia appears to be a major determinant and may be the predominant cause of cognitive disturbance. Nocturnal hypoxemia, in heavy snorers without clinically significant sleep apnoea/sleep fragmentation has been shown[33] to result in decrements of general intelligence, verbal and nonverbal memory, and expressive verbal fluency. Also, Findley *et al*[32] showed more impairment of cognitive function in hypoxemic *versus* non-hypoxemic sleep apnoea patients. Similarly, cognitive disturbance has been related to chronic hypoxia in patients with obstructive pulmonary disease.[9] Our results are in concordance with these findings and showed relationships between cognitive disturbance and sleep hypoxemia but not with sleep fragmentation. This does not mean that sleep fragmentation is not potentially important. Several studies have shown[7,8] in young healthy volunteers that sleep fragmentation alone (ie, without oxygen desaturation) can adversely affect daytime cognitive functioning. Others have shown in sleep apnoea patients[28] associations between cognitive impairment and both sleep hypoxemia and sleep fragmentation.

We found that awake SaO_2 correlated with sleep time spent below SaO_2 of 80% but not with the frequency of nocturnal desaturations $\geqslant 4\%$ from baseline. The relationship between awake SaO_2 and the severity of sleep desaturation in patients with sleep disordered breathing is expected. Baseline SaO_2 determines the position on the oxyhaemoglobin dissociation curve and is a major determinant of the level of nocturnal desaturation. The frequency of desaturation episodes is determined by the frequency of apnoeas and hypopnoeas. The relationship between awake and sleep oxygenation raises the question as to their relative effects on cognitive function. Our data suggest that severe levels of desaturation (SaO_2 $<80\%$) accompanying repetitive sleep apnoeas appeared to be most strongly associated with cognitive abnormalities. Awake SaO_2 had only a weak association with cognitive disturbance affecting just one cognitive measure.

There are a number of possible reasons for the significant effects of sleep hypoxia, but not sleep arousals, on cognitive function in our study. We speculate that the use of sedative or GABA agonist medications in tetraplegic patients may change the nature of sleep arousals thereby protecting patients from the negative effects of sleep arousal on neuropsychologic function. We have previously shown, for example, that a single oral 25 mg dose of baclofen in able bodied snorers prolongs total sleep time and decreases the awake time after sleep onset.[34] Alternatively, patients with tetraplegia may sleep longer at night[1] or in the day thereby compensating for the sleep fragmentation effects on cognitive

function. It is also possible that, by virtue of the abnormal lung function in tetraplegic patients and their use of sedatives, that the degree of hypoxemia will be greater at any level of apnoea severity than occurs in non-tetraplegic populations. A recent study in an able bodied population of sleep apneics[26] showed that 40% of apnoea/hypopnoea episodes were accompanied by desaturations of >4%. In our study 60% of apnoeas and hypopnoeas were associated with desaturations >4%.

Depression may affect the performance of subjects during neuropsychological testing. We think this is an unlikely explanation for the decrements in cognitive function found in the present study since Beck Depression Inventory scores correlated with only one neuropsychological measure (List Learning B from Ray auditory verbal learning test). Other parameters within the Ray Auditory test appeared not to be affected. Furthermore, while the subset of questions from the Beck Depression Inventory used in our study was necessarily limited (because of their physical handicap), the scores did not indicate that our patients were clinically depressed.

Methodological considerations

Because of the neuromuscular impairment in our patients, neuropsychological tests which assessed simple motor and psychomotor function (eg, trail making, finger tapping) could not be administered. These tests have been found to be the most sensitive to acute hypoxia.[27] It is possible therefore, that our results may represent a conservative estimate of the detrimental effects of sleep hypoxia on cognitive function.

We found no association between sleep apnoea variables and the Beck depression inventory. However, we were limited to the cognitive subscale of this test. Other parts of the test reflect motor functionality. A test of depression specifically developed for patients with severe motor disability might reveal other associations.

Clinical implications

The major associations that have been found in this study are between sleep hypoxia and decreased memory and attention. These functions play a vital role in higher order (executive) cognitive functioning (eg, ability to plan and organise; abstract thought processing).[35] Compliance with rehabilitation programmes and their success amongst tetraplegic patients may therefore be adversely affected by sleep hypoxia.

The associations found between sleep hypoxia and cognitive function found in this study do not address the question of the severity of individual patient cognitive impairment. To provide some assessment of the level of 'clinical' neuropsychologic impairment a *post hoc* review of individual patient data was undertaken. Clinically significant decrements in function (ie >1 SD below mean values reported for normal subjects) were found amongst our study population. For example, seven patients showed LL1 responses that were clinically abnormal[36] and four demonstrated abnormal LL5 responses.

In conclusion, sleep disordered breathing is common in patients with tetraplegia and may be accompanied by significant oxygen desaturation. Nocturnal oxygen desaturation appears to impair daytime cognitive function in these patients, particularly their attention, concentration, memory and learning skills. Clinicians treating these patients should be alert to these possible cognitive disturbances, particularly as they are potentially reversible with sleep apnoea treatment.[10]

Acknowledgements

Supported by a grant from the Julia Farr Centre Research Foundation Inc.

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