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Sleep Apnea Syndrome: Symptomatology, Associated Features, and Neurocognitive Correlates

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This article reviews the essential features, types, prevalence, pathophysiology, and neuropsychological correlates associated with the sleep apnea syndrome. Persons who experience the intermittent hypoxia and fragmented sleep characteristic of the sleep apnea syndrome tend to exhibit moderate symptoms of diffuse cognitive dysfunction as well as multiple emotional and psychosocial sequela. It is concluded that more research is required in order to elucidate the relationship between the hypoxic parameters and neurocognitive deficits seen in the sleep apnea syndrome, and that neuropsychological assessment might represent a means whereby the effectiveness of various treatments for sleep apnea may be evaluated.

KEY WORDS: apnea; sleep-related breathing disorders; hypoxia; cognitive dysfunction.

INTRODUCTION

For the maintenance of life the body must be supplied with a large number of different substances, but the most urgent need is a continual supply of oxygen. Oxygenation of all bodily tissues is accomplished by means of the reciprocal exchange of oxygen and carbon dioxide via blood flow through the lungs. Proper oxygenation of cerebral tissues is particularly critical. The brain accounts for 2% of total body mass yet uses approximately 20% of the body's oxygen in the resting state. Cessation of

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oxygen to cerebral tissues (anoxia), such as experienced in cardiac arrest, can have a devastating effect on the brain. Sustained diminution of oxygen supply (hypoxia or hypoxemia) results in reduced tissue oxygen tension that can also impair brain functioning. Chronic pulmonary obstructive disease (COPD), which includes severe chronic bronchitis, chronic obstructive asthma, and emphysema, is a major clinical example of a disease that progressively deprives cerebral tissues of oxygen, resulting in impairments in neurocognitive functioning (Grant *et al.*, 1987; McSweeney *et al.*, 1985). Although operating through different mechanisms, carbon monoxide poisoning and prolonged exposure to high altitude provide further examples of conditions that produce oxygen desaturation in the blood, leading to neurocognitive dysfunction (Adams *et al.*, 1980; Hornbein *et al.*, 1989; Smith and Brandon, 1970; Townes *et al.*, 1984; Veil *et al.*, 1970).

Less well understood are the effects of intermittent hypoxia, such as seen in the sleep apnea syndrome (SAS). Formerly called Pickwickian syndrome after the character in the Charles Dickens story who could not stay awake on the job, the term sleep apnea was coined in the early 1970s in conjunction with research undertaken by such persons as Christian Guilleminault and colleagues at the Stanford University Sleep Laboratory. There is increasing evidence that persons who suffer from SAS manifest neurocognitive impairments as a consequence of the intermittent hypoxia they experience.

ESSENTIAL FEATURES AND TYPES OF SLEEP APNEA

An apneic episode is defined as an involuntary cessation of airflow at the nose and mouth lasting at least 10 seconds. Sleep apnea syndrome is diagnosed when at least 30 apneic episodes occur over seven hours of rapid eye movement (REM) and nonrapid eye movement (NREM) sleep. Alternatively, some researchers diagnose sleep apnea syndrome when there are at least 5 apneas per hour. These are conservative parameters inasmuch as some individuals may have apneas lasting over 3 min (Cirignotta *et al.*, 1989) or hundreds of episodes per night (Anch *et al.*, 1988; Guilleminault *et al.*, 1976). During such periods, significant oxygen desaturation can occur, occasionally to below 50% of preapneic levels. McCarty and Holmes (1985) evaluated 23 patients with sleep apnea and found that they averaged 35 apneic episodes per hour of sleep (range, 6–74), with the average apnea lasting 22 seconds.

As oxygen decreases, there is a corresponding rise in carbon dioxide tension, resulting in a condition termed hypercapnia. As a result, the

diaphragm increases effort to resolve the imbalance, leading to the development of more negative intrathoracic and oropharyngeal pressures in most cases (Guilleminault, 1987). Persons with SAS typically hyperventilate immediately following an apneic episode in response to the hypoxemia and hypercapnia that develop during the episode. Because of this, carbon dioxide is eliminated, and the individual then becomes relatively hypocapnic. Below a certain CO_2 threshold, ventilation ceases altogether, resulting in further apneas (Hudgel, 1989). The cyclical quality of the process accounts for the large number of episodes experienced in an average night's sleep. The repetitive apneas also change sleep structure. Persons with sleep apnea spend abnormal amounts of time in Stage 1 or Stage 2 sleep, whereas NREM Stages 3 and 4 are significantly reduced or absent. Restless and fragmented sleep tends to increase the duration of apneic episodes, further reinforcing the continuous feedback loop.

The Diagnostic Classification of Sleep and Arousal Disorders (Sleep Disorders Classification Committee, 1979) places sleep apnea syndrome both under disorders of initiating and maintaining sleep and under disorders of excessive somnolence, with the latter representing the more frequently observed manifestation. In addition, most researchers distinguish three types of SAS. In obstructive sleep apnea (OSA), upper respiratory airflow is reduced despite adequate and persistent diaphragmatic effort, with a concomitant collapse of the upper airway. The most important factor responsible for obstructive sleep apnea appears to be a small or inordinately narrow pharynx (Stradling, 1986). Central sleep apnea is defined by an absence of respiratory effort. Although the upper airway appears open, no air flows through it, and the CNS fails to activate the muscles that produce respiratory movements. Mixed apnea is defined by cessation of airflow and absence of respiratory effort early in the episode, followed by the resumption of unsuccessful respiratory effort in the latter part of the episode. In some cases, an obstructive apnea may give rise to a central apnea. While OSA is more common than either the central or mixed types, in many individuals the three types are not easily distinguished (Cherniak, 1981). According to Hudgel (1989), obvious upper airway narrowing is not found in more than half of obstructive sleep apnea cases, and evidence exists that the upper airway is more collapsible in OSA than in control patients, during both normal wakefulness and sleep. Periodic, Cheyne- Stokes breathing, characterized by rhythmic waxing and waning of the depth of respiration, also occurs in OSA, which may contribute to the development of airway collapse during sleep. Partial airway obstruction results in a phenomenon known as hypopnea. There is disagreement regarding the definition and significance of sleep-related hypopneas. Some researchers believe sleep apnea syndrome may occur in the absence of complete cessation of airflow

(Gould *et al.*, 1988), while others, such as Douglas *et al.* (1982), note that hypoventilation and mild hypoxia occur normally during sleep in healthy persons, particularly during REM.

NOCTURNAL SYMPTOMS

Snoring is a near-universal feature of sleep apnea and one of the most common causes of referral for evaluation for SAS, usually due to longstanding complaints from a bed partner. As hypoxia and hypercapnia worsen during an apneic episode, respiratory efforts become vigorous. Noisy pharyngeal snoring, associated with staccato-like snorts, serves to break the apnea, albeit temporarily. In some cases the intensity of snoring reaches 65 decibels or greater, which is above the noise level deemed safe in the workplace by the Occupational Safety and Health Administration (Guilleminault, 1987). Other nocturnal manifestations of SAS include motor restlessness, excessive sweating, enuresis, sleeptalking, sleepwalking, and cerebral hypoxic attacks resembling seizures. The first two of these symptoms occur in up to 2/3 of afflicted adults. The others are less common, although enuresis is usually present in children with SAS. Clinical features and electroencephalogram (EEG) differentiate nocturnal hypoxic attacks from epileptic seizures (Cirignotta *et al.*, 1989). Motor restlessness often takes the form of myoclonus, in which the individual may unwittingly kick a bed partner. Not surprisingly, separate bedrooms is a frequent consequence of SAS.

DIURNAL SYMPTOMS AND PSYCHOSOCIAL SEQUELA

Excessive daytime sleepiness (hypersomnia) is another ubiquitous feature of the syndrome, making such activities as driving or operating machinery particularly hazardous. Findley *et al.* (1988) compared the driving records of 29 patients with obstructive sleep apnea with those of 35 subjects without sleep apnea, and found that the former had a sevenfold greater rate of automobile accidents than the latter. In addition, 24% of the patients with sleep apnea reported falling asleep at least once per week while driving.

The individual with SAS is in a "twilight zone" much of the time, having difficulty differentiating sleep and quiet wakefulness (Browman and Mitler, 1988). There may be symptoms of altered awareness and hypnagogic hallucinations not unlike those observed in narcolepsy. The dramatic sleep attacks characteristic of narcolepsy are absent in SAS, and for this

reason the excessive daytime sleepiness seen in SAS may be more insidious and potentially more dangerous. Hypersomnia in SAS may produce an automatic behavior syndrome with retrograde amnesia similar to that seen in complex-partial seizure activity. The individual can carry out routine, undemanding tasks but will appear absentminded for periods lasting from minutes to hours, be unable to appreciate the passage of time, and may even display occasional involuntary outbursts of meaningless words (Guilleminault, 1987; Strub and Black, 1988). Again, EEG readily distinguishes this syndrome from that produced by epileptiform disorders (Hess, 1989).

Other manifestations associated with SAS include persistent headaches, irritability and mood disturbance, personality changes, and severe vocational and marital problems. Impotence in males and decrease in sex drive in both sexes is common (Hirshkowitz *et al.*, 1989). Mosko *et al.* (1989) found that hypersomniacs self-reported high rates of depressive symptomatology on the Profile of Mood States. In a sample of 25 consecutive sleep apneics, Reynolds *et al.* (1984) found that 40% met research diagnostic criteria for either affective disorder or alcohol abuse. The more depressed patients tended to complain of excessive daytime sleepiness, whereas the less depressed patients complained more often of insomnia. Kales *et al.* (1985b) reported that sleep apnea patients had significantly higher scores than matched controls on most of the clinical scales of the Minnesota Multiphasic Personality Inventory and Symptom Checklist-90-Revised, with predominant patterns reflecting depression and somatization in response to perceived chronic illness. In the absence of complaints from a bed partner, most individuals who experience apneas do not realize that they do so. Persons may seek or be referred for evaluation of psychiatric problems that initially may be thought to be primary but rather are secondary to SAS. The clinician needs to consider the contribution of SAS in the differential diagnosis of conditions presenting symptoms of affective disorder, cognitive dysfunction, characterological disturbance, seizure disorder, and even psychosis.

PREVALENCE, COURSE, AND ASSOCIATED FEATURES

Men exhibit SAS much more often than women. Even among persons who do not meet criteria for diagnosing the full syndrome, males outnumber females by at least a 6:1 ratio (Guilleminault *et al.*, 1976), although the prevalence is more similar between men and postmenopausal women. Female sex hormones may be protective and/or male sex hormones may be detrimental to breathing difficulties during sleep (Hudgel,

1989). The estimated prevalence of SAS in adult males ranges from 1 to 10%. However, there is a strong age relationship—the prevalence can increase to 50% in males over age 65 (Guilleminault, 1987; Lavie, 1983; Stradling, 1986). The generally accepted criteria for the diagnosis of sleep apnea syndrome is exceeded by elderly persons with such frequency that the validity of its application to this age group has been questioned (Knight *et al.*, 1987). Ancoli-Israel *et al.* (1987) performed home sleep recordings on 358 random elderly volunteers with a mean age of 72 years. Thirty-one percent of the males and 19% of the females exceeded the apnea index of 5 per hour. When the sexes were combined, 17% of the subjects showed symptoms of obstructive apnea, 6% showed symptoms of central apnea, and 1% manifested mixed symptoms. Age was most strongly related to frequency of apneic episodes within the obstructive group. There also is evidence that the severity of medical complications increases with age from cardiovascular phenomena associated with SAS and that sleep-related breathing disorders may contribute to the nocturnal peak observed in human mortality. Nocturnal hypoxemia has been associated with serious ventricular tachyarrythmias as well as life-threatening bradyarrythmias. The increased prevalence of heart and lung disease in the population as it ages contributes to sleep-related breathing disorders. Systemic hypertension has been reported in 50–90% of apneics. Conversely, sleep apnea is present in approximately 30% of hypertensives (McGinty, 1987; Shepard, 1987).

Other factors that aggravate SAS include obesity and CNS depressant drugs. Early "Pickwickian" patients were invariably obese, and a number of writers have commented on the relationship between increased body weight and sleep apnea syndrome, particularly the obstructive variant. In many cases of obstructive sleep apnea fatty infiltration of the upper airway is readily apparent. Alcohol, particularly when consumed immediately prior to bedtime, increases the frequency of apneas and prolongs their duration. Depressants such as sedative-hypnotics and tranquilizers have effects similar to those of alcohol. Any medication that retards respiratory activity tends to aggravate the affliction, and overmedication greatly raises the risk of mortality.

Sleep apnea syndrome is usually chronic in nature. Kales *et al.* (1985a) found that in a group of 50 adults afflicted with SAS whose condition warranted recommendations for tracheostomy (mean age = 46) apneic symptoms had been present for several years. Excessive daytime sleepiness was often an early symptom, beginning at a mean age of 36. In half of the patients hypertension or obesity preceded excessive daytime sleepiness by at least one year.

Symptoms of sleep apnea are also evident in many children and adolescents. Many adult patients recall family members making repeated comments about loud nightly snoring originating years before. The mother of a young boy with sleep apnea evaluated at the Stanford University Sleep Disorders Clinic reported the onset of such snoring when the child was only 4 months of age (Guilleminault *et al.*, 1976). It has been hypothesized that sleep apnea is involved in sudden infant death syndrome (SIDS). Premature infants with prolonged apneas and "near-miss" infants—those who survived episodes of cessation of breathing like those leading to crib death—have a much higher risk of subsequently dying of SIDS. Moreover, near-miss infants typically manifest more persistent neurological abnormalities than normal infants, and follow-up studies of near-miss infants have revealed frequent incidence of learning disabilities in elementary school (Ariagno *et al.*, 1980; Guilleminault *et al.*, 1975; Korobkin and Guilleminault, 1979; McGinty and Sterman, 1980).

A possible genetic basis for obstructive sleep apnea is suggested by the studies of Ancoli-Israel *et al.* (1987) and Strake *et al.* (1978), which found higher reported rates of breathing cessation during sleep and SIDS among blood relatives of OSA patients than among patients with other types of SAS or controls. Manon-Espaillant *et al.* (1988) described a familial "sleep apnea plus" syndrome consisting of sleep apnea, anosmia, color-blindness, partial-complex seizures, and cognitive dysfunction. The phenotypic expression of the syndrome suggested an autosomal dominant inheritance. Arkinstall *et al.* (1974) found genetic differences in the ventilatory response to inhaled CO_2, accounting for 80–90% of the variability in tidal volume response to CO_2 in terms of genetic factors. They proposed that unstable respiration during sleep could eventually generate overt pathology and that an unstable group might represent a population at risk for the development of sleep apnea syndrome.

In summary, the individual most at risk to develop SAS is likely (1) to snore, (2) to be male, (3) to be overweight, (4) to have systemic hypertension, (5) to be middle-aged or older, (6) to have a positive family history of sleep-disordered breathing, and (7) to use sedative-hypnotics or drink excessively, particularly immediately prior to bedtime.

PATHOPHYSIOLOGY AND POSSIBLE BRAIN MECHANISMS

Upper airway apneas can occasionally result from purely structural abnormalities such as excessive fat deposits, abnormally thick soft palate, or a narrow mandible. Other variants can be secondary to the "sleep

apnea plus" syndrome described by Manon-Espaillant *et al.* or to a variety of neurological conditions, including bulbar poliomyelitis, bilateral cordotomy, Shy-Drager syndrome, Ondine's curse, and myotonic dystrophy (McCarty and Holmes, 1985; Strub and Black, 1988). Most often, however, the symptomatology is idiopathic. The exact pathophysiology of the syndrome is frequently unclear, as well as which of the accompanying phenomena are antecedents and which are consequences. The sudden cessation of respiratory effort in central apnea strongly suggests some lesion or abnormality in the lower respiratory centers. The dramatic, and apparently reflexive, collapse of the upper airway seen in obstructive apnea also points to CNS dysfunction. Currently, most investigators consider OSA to be more of a "central" than totally a "peripheral" problem (Hudgel, 1989). It is likely that there is CNS involvement in all three types of sleep apnea.

Gadoth *et al.* (1988) found an abnormal prolongation of the late phase of the orbicularis oculi reflex response (OORR) in 1 patient with obstructive sleep apnea due to acromegaly and 2 other patients with sleep apnea without acromegaly. The OORR was normal in another patient with acromegaly who did not experience sleep apnea. Following surgery for the upper airway obstruction, the sleep apnea disappeared in the acromegalic patient but the OORR failed to normalize. The authors suggested that the presence of abnormal OORR in sleep apnea may reflect a basic defect in pontomedullary control of respiration during sleep. Meyer *et al.* (1987) studied measurements of regional cerebral blood flow (rCBF) during relaxed wakefulness and different stages of sleep in normal age-matched volunteers, narcoleptics, and sleep apneics. They found that in the awake state, rCBF values were reduced in both narcoleptics and sleep apneics in the brainstem and cerebellar regions. During sleep onset, whether REM or Stage I-II, rCBF values were paradoxically increased in narcoleptics but decreased severely in apneics, while in normals they became diffusely but more moderately decreased. Other studies suggest that SAS is related to the overall integrity of the brain. Sleep-related apneas and hypopneas occur more frequently in older than in younger persons, and elderly individuals with Alzheimer's disease and multi-infarct dementia experience a higher frequency of SAS than nondemented controls. Furthermore, the more severe the dementia, the greater the number of apneic/hypopneic episodes (Erkinjuntti *et al.*, 1987; Hoch *et al.*, 1986; Smallwood *et al.*, 1983).

Neurotransmitter imbalance may also play a role in SAS (Blass and Gibson, 1979; Davis *et al.*, 1979; Grant *et al.*, 1987). Acetylcholine generally stimulates ventilation, while norepinephrine and dopamine depress ventilation. Mild hypoxia in rats produces decreases in the synthesis of

acetylcholine, particularly in the hippocampal region (Gibson and Duffy, 1981; Shimada, 1981), suggesting that a similar imbalance may occur in humans who experience hypoxia. In sleep apnea blood-gas values fluctuate repeatedly and abruptly throughout the night. The metabolic changes induced by the unstable state of blood-gas values in sleep apnea may be of greater severity than those observed in other pathological but stable conditions (e.g., alveolar hypoventilation). It is also likely that neurotransmitters and cerebral blood flow in the brain are affected significantly by the blood-gas and hemodynamic changes characteristic of SAS (Guilleminault *et al.*, 1976). More investigation is required to elucidate the anatomic and physiologic mechanisms leading to SAS.

TREATMENT

Modifying any factors that aggravate SAS is always a reasonable initial treatment approach but does not constitute a cure. Sleep position adjustment and weight loss are examples. Obstructive sleep apnea is twice as severe while the individual is sleeping on the back as in the side position (Cartwright, 1984). Simply changing the sleeping position from supine to prone eliminated or reduced apneas in 5 of 23 patients studied by McCarty and Holmes (1985), even 2 with central apnea. Smith *et al.* (1985) reported that 15 obese OSA patients who lost 10 kg. over five months experienced a 47% reduction in the number of apneas, along with improved oxygenation during sleep. Eight obese OSA patients who did not lose weight showed no improvement. However, after weight loss the first group still averaged 29 apneas per hour of sleep.

Individuals with identifiable obstructive abnormalities may benefit from surgery. Uvulopalatopharyngoplasty (UPP) is usually recommended as the initial surgical procedure. It consists of trimming the soft palate and removing any tonsillar or redundant tissue in the pharynx. In general, the success rate of UPP is 50% (Hudgel, 1989). Tracheostomy bypasses the upper airway and provides a pathway for airflow during sleep. Although it has proven helpful in the past for many patients with severe OSA, it usually requires the individual to occlude or cover the surgical orifice for speaking during the day, and is currently considered a procedure to be utilized only when others have failed. Patients in whom OSA has been relieved by tracheostomy sometimes still experience periodic central apneas (Cherniak, 1981), illustrating the complex etiology of SAS. Other surgical procedures, such as repositioning of the mandibular, maxillary, or hyoid bones, are more complicated, and are performed only in selected cases.

Nasal continuous positive airway pressure (nCPAP) is a technique that provides pressures from an air compressor delivered through a nasal mask to maintain the upper airway open. This procedure is relatively noninvasive and is effective in most cases of SAS. However, when the pressure is discontinued, apneas resume. Also, many patients dislike wearing the mask night after night. Twenty-nine percent of 130 patients followed for at least 18 months in the Stanford University Sleep Disorders Clinic stopped using nCPAP and requested another treatment (Guilleminault, 1987), indicating that patient compliance may be a significant problem with this procedure.

Respiratory stimulant therapy with aminophylline, theophylline, naloxone, and medroxyprogesterone have all been used with varying degrees of success (Guilleminault and Dement, 1977). Tricyclic antidepressants, primarily protriptyline, have also been used. These agents stimulate upper airway inspiratory muscle activity, thereby widening the upper airway or stabilizing the pharyngeal walls against the collapsing force generated by diaphragm contraction (Hudgel, 1989). Bonora *et al.* (1985) found protriptyline to be effective in approximately half of a small sample of sleep apnea patients they studied. The potential usefulness of this drug is limited by its significant anticholinergic properties, producing side effects such as urinary hesitancy and erectile difficulties (Hudgel, 1989).

In summary, while useful in some cases, none of the above treatments have proven effective for all sufferers of SAS, or are without deleterious side effects or complications. With the exception of tracheostomy, few have received long-term follow-up evaluations.

COGNITIVE DYSFUNCTION IN SLEEP APNEA SYNDROME

Persons suffering from the effects of anoxia or hypoxia typically exhibit one or more aspects of a constellation of symptoms suggesting diffuse cognitive dysfunction. These include a decrease in new learning ability, impaired attention and concentration, visual-spatial deficits, and reduced capacity for planning, initiating, and executing activities. Affective dullness or disinhibition is frequently present as well (Lezak, 1983). The effects of sustained hypoxia on cognitive functioning, such as seen in prolonged exposure to high-altitude, carbon monoxide poisoning, and COPD, may provide a model for the effects of intermittent hypoxia. Symptoms may be transient or enduring, depending upon the degree of the oxygen reduction, its chronicity, and other factors.

In neuropsychological studies of young, fit mountaineers before and after an expedition to climb Mt. Everest, effects from exposure to extremely high altitude were found to include mild deterioration in the ability to learn, remember, and express information verbally. These impairments were present during the first three days after return to low altitude but not one year later. A bilateral reduction in the ability to maintain the speed of finger tapping did persist, however (Hornbein *et al.*, 1989; Townes *et al.*, 1984).

Veil *et al.* (1970) studied 108 victims of carbon monoxide poisoning one year later. The patients were compared with a control group of patients who had experienced loss of consciousness not caused by CO intoxication. All poisoned subjects had some symptoms that could be identified with sequela. The abnormalities were diverse, subtle, and variable, depending upon the premorbid personality and social role of the individual. They included structural-spatial problems, decreased attention span, recent memory deficits, sleep disturbance, and fatigue. In a three-year follow-up of 67 survivors of CO poisoning, Smith and Brandon (1970) noted that 33% exhibited personality deterioration as characterized by irritability and violent behavior, and 43% had persistent memory impairment.

McSweeney *et al.* (1985) administered an expanded version of the Halstead-Reitan Neuropsychological Test Battery and a battery of instruments measuring the quality of everyday life functioning to 303 patients with COPD and 99 matched healthy controls. Neuropsychological status was significantly more impaired in the COPD group, and was consistently related to activities of daily living and basic social role performance. Decreased motor speed, tracking, and attention/concentration were deficits evident in the COPD group. The authors found that complex multifunctional neuropsychological tasks were the best overall predictors of everyday life functioning. In a subsequent study combining neuropsychological test data from two multicenter trials (Grant *et al.*, 1987), three groups of patients with COPD whose hypoxemia was mild ($N = 86$), moderate ($N = 155$), or severe ($N = 61$) were compared with age- and education-matched nonpatients ($N = 99$). The rate of neuropsychological deficit rose from 27% in the group with mild hypoxemia to 61% in the group with severe hypoxemia, and multivariate analyses revealed a consistently significant relationship between degree of hypoxemia and neuropsychological impairment. Various neuropsychological abilities declined at different rates, suggesting differential vulnerability of cognitive functions to the progression of COPD. Perceptual learning and problem solving appeared most sensitive in differentiating the above subject groups. Conversely, simple motor skills, alertness, and psychomotor speed showed less consistent

decrement across the subject groups, and declined precipitously only with severe hypoxemia.

In general, neuropsychological studies of persons with sleep apnea syndrome have revealed moderate cognitive impairments similar to those reported above for persons who have experienced periods of more prolonged hypoxia. Apneics typically perform worse on neuropsychological tests than do those individuals with other sleep disorders or healthy controls, substantiating the relationship between intermittent hypoxic events and cortical dysfunction.

Kales *et al.* (1985b) reported that the majority of 50 apneic patients they studied showed some degree of impairment in thinking, perception, or memory on the Bender Gestalt, Wechsler Memory Scale, and Wechsler Adult Intelligence Scale—Revised (WAIS-R). They state that the Bender data indicated spatial disorganization, poor visual perception, and a potential for being distractible, confused, and irritable. Performance on the Wechsler Memory Scale indicated deficits in short-term memory, the ability to learn new information, and visual-perceptual skills. Discrepancies in the subtests of the WAIS-R were felt indicative of global organic involvement. Moreover, the cognitive difficulties revealed during testing were felt consistent with patients' behavior in general during the evaluation process. The apneic patients often displayed speech problems, inappropriate attire, poor hygiene, and inadequate recollection of recent events.

Fox *et al.* (1989) demonstrated a relationship between disordered speech and obstructive sleep apnea in a small subject sample and subsequently replicated their results with a larger group. In the second study, 10 graduate students in speech pathology rated speech samples produced by 27 SAS patients, 27 matched COPD patients, and 27 matched normal controls. The judges found abnormalities in resonance, articulation, or phonation in 74% of the SAS patients, 53% of the COPD patients, and only 7% of the normals. Discriminant function analysis correctly identified 96.3% of the normals and 63% of the sleep apnea subjects on the basis of speech abnormalities.

Findley *et al.* (1986) compared the cognitive functioning of 9 apneic patients who had associated hypoxemia with that of 17 apneic patients who were relatively nonhypoxic. The apneic patients with hypoxemia had more severe cognitive impairments than those without hypoxemia. Tests that were the most sensitive in differentiating the two groups included Trails B, the Paced Auditory Serial Addition Test, and the delayed component of the Wechsler Memory Scale, suggesting impairments in sustained concentration, problem solving, and delayed recall of verbal and visual information in the hypoxic group. The degree of hypoxemia during sleep and wakefulness, as measured by median oxygen saturation (SaO_2) and arterial

partial pressures of oxygen (PaO_2), correlated significantly with degree of overall cognitive impairment as rated by a neuropsychologist. On the other hand, measures of sleep fragmentation did not correlate significantly with overall cognitive impairment.

Using selected subtests of the WAIS-R, Trails B, Purdue Pegboard, the Controlled Oral Word Association Test, a letter cancellation task, the Wechsler Memory Scale, and Bender Gestalt, Greenberg *et al.* (1987) compared 14 SAS patients, 10 patients who were hypersomnolent due to other causes, and 14 controls. They found no cognitive impairment in the latter two groups, whereas the apneics had lower scores on 15 of 17 measures and were rated as more globally impaired by an independent neuropsychologist. In contrast with the findings of Findley *et al.* (1986), overall neuropsychological status did not correlate significantly with severity of hypoxia (i.e., total time not breathing and lowest oxygen saturation), although tests measuring motor and spatial skills did. Of note is the fact that Greenberg *et al.* utilized somewhat different indices of severity of hypoxia than did Findley *et al.*, suggesting that some hypoxic parameters may be more sensitive than others in contributing to the neuropsychologic deficits associated with SAS.

The cognitive functioning of habitual snorers has also been studied. Block *et al.* (1986) administered a battery of neuropsychological tests to 46 male subjects (mean age = 50 years) prior to sleep. Although apneics were specifically excluded, 28 subjects had at least 1 episode of apnea, and 6 subjects had more than 5 episodes. Lower test scores were related to increasingly abnormal breathing and oxygenation during sleep. Diminished performance on the Wechsler Memory Scale delayed visual, Rey Complex Figure delayed, the Wisconsin Card Sorting Test, and the WAIS Performance IQ was strongly related to the number of oxygen desaturations greater than 4% from the baseline established prior to sleep.

Telakivi *et al.* (1988) studied the association of snoring and cognitive functioning in 46 habitually snoring men ages 41–52 and 60 occasional or never snoring men of the same age group. A measure of excessive daytime sleepiness was associated with poor performance on neuropsychological tests requiring concentration, memory retention, and verbal and visual skills in the habitual snorers group. There was a mild relationship between number of oxygen desaturation episodes greater than 4% per hour of sleep and delayed recall of Logical Stories of the Wechsler Memory Scale and with spatial orientation (the Clock Test) in the habitual snorers, even after adjusting for age and obesity. When subjects with desaturation episode greater than 4% were excluded, there was no association between desaturation and any of the cognitive tests. The authors concluded that mild

desaturation in otherwise healthy snorers seems to have less of an effect on cognitive function than does sleep fragmentation and daytime alertness. While Telakivi *et al.* studied snorers rather than apneics, their results are somewhat in contrast with those of Findley *et al.* (1988), who found that measures of sleep fragmentation did not correlated with overall cognitive impairment.

Although sleep apnea is common in the elderly and medical complications reportedly increase with age (McGinty, 1987; Shepard, 1987), Knight *et al.* (1987) found that sleep apnea per se may not necessarily result in adverse physiologic or neuropsychologic consequences. Ten elderly subjects with more than 5 apneic episodes per hour of sleep were compared with 17 elderly subjects with fewer than 5 apneic episodes per hour on a protocol evaluating cardiac arrhythmias, systemic hypertension, or pulmonale (i.e., heart disease with associated ventricular enlargement), daytime sleepiness, and cognitive dysfunction. Neuropsychological tests administered included the Wechsler Memory Scale, California Verbal Learning Test, Controlled Oral Word Association Test, finger tapping and fingertip number writing, and selected subtests of the WAIS-R. In the group with the more frequent apneas, no excessive incidence of cardiovascular complications was found, and no appreciable differences in cognitive performance were demonstrated despite an increase in daytime sleepiness. Moreover, the two groups did not differ significantly on the Zung Depression Inventory. It is possible that the assessment battery used by Knight *et al.* was not sufficiently sensitive to evaluate the effects of sleep apnea on life functioning in this population, or that different results might have been obtained had a higher apnea index been utilized in distinguishing the two subject groups.

SUMMARY AND DISCUSSION

Persons who experience the intermittent hypoxia characteristic of the sleep apnea syndrome exhibit moderate symptoms of diffuse cognitive dysfunction similar to that seen in instances of more continuous hypoxia, as well as multiple emotional and psychosocial sequela. There is also evidence that the full syndrome produces more dysfunction than associated conditions do (e.g., habitual snoring) in the absence of the syndrome.

While degree of hypoxia appears the major factor in the pattern of cognitive dysfunction demonstrated, sleep fragmentation and hypersomnia also are contributory. The correlation between hypoxia and sleep fragmentation is likely to be high. Additional research is needed to separate the differential effects, if any, of these factors in SAS. Moreover,

some indices of hypoxia may be more consistently associated with neuropsychologic deficit than others, and various cognitive abilities are likely to be differentially vulnerable to the effects of both hypoxia and sleep fragmentation.

The relationship between age, sex, and pattern of cerebral dysfunction also needs to be addressed. Apneic episodes increase dramatically in the elderly, but it is unclear whether they induce additional cerebral dysfunction other than that attributable to aging per se or to other neuropathological conditions also correlated with age. It is possible that persons of varied ages are affected differentially by SAS or that the degree of chronicity of the syndrome is a primary determinant. Also, males present with SAS much more frequently than females, except when compared with elderly females, but research on cognitive correlates has focused almost exclusively on men. Sex differences have not been studied and clearly need to be investigated.

According to Greenberg *et al.* (1987), deriving valid relationships between neuropsychological test scores and indices of apnea may be problematic because of nightly variability in the respiratory status of some apneic individuals. Researchers who have used neuropsychological batteries have generally administered testing only once and at different times in the sleep–wake cycle. Some subject groups have received testing before going to sleep, and others, after awakening. Although it might be expected that neuropsychological impairment would be greater following a night of repeated apneas than beforehand, it is not clear whether testings at different times would yield different results in the typical sleep apnea patient. Perhaps a repeatable series of tests would help answer this question.

With the exception of only a few studies, systematic neuropsychological evaluation of a patient population before and after treatment for SAS has not been performed. If effective in reducing the number of apneas and improving oxygenation, successful treatment should also result in improvements in neuropsychological functioning, with corresponding benefits to affective and psychosocial adjustment. Martin and Lefebvre (1981) and Fleming *et al.* (1985) present case studies in which surgical correction of upper airway obstructions resulted in significant reductions in the symptomatology of a 13-year-old psychotic boy and a 52-year-old woman with bipolar affective disorder, respectively. Klonoff *et al.* (1987) found that the cognitive impairment in a group of 11 patients with obstructive sleep apnea improved with successful UPP treatment of the airway obstruction, but reported that both the presurgical level of impairment and the improvements noted postoperatively were no different than those found in an age-matched group of patients undergoing coronary artery

bypass surgery. The authors concluded that the cognitive abnormalities identified represented a generalized reaction to severe organic disease and were not specific to sleep apnea. It is possible, however, that the coronary bypass patients experienced some degree of hypoxia secondary to congestive heart failure, rendering their conclusion somewhat tenuous. Because of the high prevalence of sleep apnea in demented elderly persons, it may be hypothesized that hypoxemia occurring secondary to the sleep apnea contributes to and represents a potentially reversible cause of the demented stat (Hudgel, 1989; Smallwood *et al.*, 1983). This hypothesis could be substantiated if successful treatment of SAS led to an improvement in the observed dementia, but it apparently has not yet been adequately tested.

For the neuropsychologist in practice, an increased awareness of the risk factors for SAS and accompanying neuropsychological deficits will help identify those individuals who may benefit from appropriate medical treatment. Early intervention has the potential to arrest the insidious cognitive deterioration resulting from chronic intermittent hypoxia and serve to protect integrity of cortical functioning. Due to the complex etiologies, risk factors, and potential neurocognitive deficits typically associated with SAS, a screening type assessment approach would appear inadequate. Rather, a more comprehensive neuropsychological approach encompassing the evaluation of such factors as sustained attention, speed of information processing, speech production, memory (with particular emphasis on visual memory and delayed retention), and complex problem-solving clearly appears warranted.

Finally, some of the available studies are lacking in research rigor. Kales *et al.* (1985b) serve as an example. They probably overstate the data when they report that the Bender Gestalt indicated a potential for being distractible, confused, and irritable in their sleep apnea patients. Also, the authors did not administer neuropsychological tests to a control group and do not mention whether or not other neuropathological events were present in the histories of the subject group. Similarly, Cirignotta *et al.* (1989) describe a case of a 52-year-old man presenting with obstructive apneas lasting up to 220 seconds and cerebral anoxic attacks resembling seizures. They state that in this patient the arousal mechanism in the brain seemed sufficiently impaired to lead to the anoxic attacks. While this may have been true, the subject's 30-year history of exposure to industrial solvents was probably also a significant factor in contributing to impaired arousal mechanisms or even in causing the apneic episodes. Case studies are useful in presenting the clinical features associated with SAS, but it is difficult to derive general statements regarding cognitive functioning in individuals with SAS from uncontrolled observations of this sort. Future research on

the sleep apnea syndrome obviously needs to consider carefully the medical histories of its subjects, to exclude or adequately control for neurobehavioral risk factors, to use appropriate controls, and to minimize speculatory interpretations. It is possible that the neuropsychological deficits found in SAS could be partially attributable to complications arising from closely associated conditions, such as systemic hypertension, alcohol abuse, and obesity, rather than from sleep apnea per se.

According to Adams *et al.* (1980), the concordance between complex behaviors and first-order parameters of cerebral activity is frequently not as consistent as hoped or expected. While this certainly applies in the case of the sleep apnea syndrome, additional research along the lines presented above may help us better understand this phenomenon and to select the most efficacious treatments so as to reduce the risk of progressive cognitive impairment and associated affective and psychosocial sequela.

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