Diagnosis and Management of Sleep Apnea Syndrome and Restless Legs Syndrome in Dialysis Patients

Marta Novak,*† David Mendelssohn,‡ Colin M. Shapiro,† and Istvan Mucsi*§¶

*Institute of Behavioral Sciences and §1st Department of Internal Medicine, Semmelweis University, Budapest, Hungary; †Sleep Research Laboratory and Department of Psychiatry, and ¶Division of Nephrology, Faculty of Medicine, University of Toronto, and ‡Department of Nephrology, Humber River Regional Hospital, Toronto, Ontario, Canada

ABSTRACT

Sleep complaints are very common in patients with end-stage renal disease (ESRD) and contribute to their impaired quality of life. Both obstructive and central sleep apnea syndromes are reported more often in patients on dialysis than in the general population. Impaired daytime functioning, sleepiness, and fatigue, as well as cognitive problems, are well known in patients with sleep apnea. Increasing evidence supports the pathophysiological role of sleep apnea in cardiovascular disorders, which are the leading cause of death in ESRD patients. Uremic factors may be involved in the pathogenesis of sleep apnea in this patient population and optimal dialysis may reduce disease severity. Furthermore, treatment with continuous positive airway pressure may improve quality of life and may help to manage hypertension in these patients. Secondary restless legs syndrome is highly prevalent in patients on maintenance dialysis. The pathophysiology of the disorder may also involve uremia-related factors, iron deficiency, and anemia, but genetic and lifestyle factors might also play a role. The treatment of restless legs syndrome involves various pharmacologic approaches and might be challenging in severe cases. In this article we review the diagnosis and treatment of sleep apnea and restless legs syndrome, with a focus on dialysis patients. We also briefly review current data regarding sleep problems after transplantation, since these studies may indirectly shed light on the possible pathophysiological role of uremia or dialysis in the etiology of sleep disorders. Considering the importance of sleep disorders, more awareness among professionals involved in the care of patients on dialysis is necessary. Appropriate management of sleep disorders could improve the quality of life and possibly even impact upon survival of renal patients.

Sleep problems are common in medically ill populations (1), including those with end-stage renal disease (ESRD). There is limited information regarding sleep disorders and their impact in chronic kidney disease (CKD) patients who are not yet on dialysis and after renal transplantation. However, a number of studies suggest that the majority of patients on dialysis suffer from at least one sleep disorder (2–7). Sleep disorders have profound effects on quality of life and also have significant socioeconomic impacts (4,5,8,9).

In a previous article in this journal, we focused on the diagnosis and treatment of insomnia in patients with renal disease. Here we discuss issues related to two additional clinically significant sleep disorders that are particularly common in CKD patients: sleep apnea syndrome (SAS) and restless legs syndrome (RLS).

Sleep apnea syndrome has a special significance, as it has been suggested to contribute to cardiovascular morbidity and mortality in ESRD patients (10,11). Neuropsychiatric symptoms of sleep apnea (fatigue and cognitive impairment) may be mistakenly attributed to uremia, and these symptoms might also overlap with the symptoms of depression. RLS leads to severe initiation insomnia and greatly impaired quality of life (4,5). In one study, RLS was associated with premature discontinuation of dialysis and a significantly increased risk of mortality after 2.5 years follow-up (12).

Despite the impact of sleep disorders, these conditions often remain undiagnosed and untreated (13,14). Our two articles (parts 1 and 2) aim to raise awareness among professionals involved in the management of dialysis patients and provide guidance concerning the detection and treatment of these sleep disorders. We will also briefly discuss whether kidney transplantation eliminates or diminishes the frequency of sleep disorders in ESRD patients.

Sleep Apnea Syndrome

Sleep apnea syndrome is characterized by disordered breathing during sleep, resulting in heavy snoring in most cases, repetitive apnea, restless sleep, fragmented sleep structure, frequent arousals, morning headache, personality and mood changes, and daytime sleepiness. Based

Address correspondence to: David Mendelssohn MD, Humber River Regional Hospital, Room 2024, 200 Church St. Weston, Ontario, M9N 1N8, Canada, or e-mail: dmendelssohn@hrrh.on.ca.

Seminars in Dialysis—Vol 19, No 3 (May–June) 2006 pp. 210–216

on different criteria of disease severity and the age of the studied population, the prevalence of the disorder in the general population varies between 2% and 24% (15).

Central sleep apnea is characterized by unstable, decreased, or even absent regulatory motor activity of the respiratory centers in the central nervous system during sleep, leading to apneic episodes (16). It is most frequently associated with neurologic disorders or with congestive heart failure. The condition is greatly underdiagnosed, as it can only be recognized by polysomnography. Several authors have suggested that it may be quite common in patients with renal disease (10,17,18).

Most central apneas occur at sleep onset, establishing a cycle of decreased or absent respiratory effort terminated by ongoing arousals. Snoring may or may not be present, and often the clinician suspects obstructive apnea prior to testing. Daytime sleepiness is the dominant symptom due to the high-grade fragmentation of sleep.

Obstructive sleep apnea syndrome (OSAS), on the other hand, is characterized by repetitive closure of the upper airways during sleep, usually at the pharyngeal level, which produces apnea. Increasing respiratory effort against the collapsed airway with asphyxiation induces repetitive arousals. The most obvious symptoms are loud snoring interrupted with apneic episodes ("malignant snoring") and excessive daytime sleepiness (EDS) (hypersomnolence). Apneic episodes lead to microarousals, sleep fragmentation, and activation of the sympathetic nervous system. Sleep fragmentation and hypoxemia result in excessive daytime sleepiness, cognitive impairment, and impaired quality of life. There is an interesting, but not well-studied relationship between apnea and depression. Symptoms of depression and sleep apnea do overlap, and there is an increased prevalence of depression in sleep apnea patients (19). The association of insomnia with OSAS has also been emphasized, with the suggestion that the presence of insomnia may lead to an amplification of OSAS symptom severity. Patients with both conditions may experience more symptoms related to depression, anxiety, and stress (20) and poorer quality of life (6). A recent study suggested that depression predicted sleep quality in patients with OSAS (21). Sleep apnea is frequently associated with arterial hypertension, and it is also a suggested risk factor for cardiovascular morbidity and mortality (10,11).

The pathogenesis of OSAS is not fully understood. Anatomic changes caused by obesity or developmental problems play an important role. Some authors also suggest a role for pharyngeal neuropathy and myopathy (22). The potential role of uremia or uremic toxins in the pathogenesis of OSAS in CKD patients is supported by the results of Hanly and Pierratos (23), who showed that nocturnal hemodialysis significantly decreases the prevalence and severity of obstructive sleep apnea.

Diagnosis of SAS

Obstructive sleep apnea syndrome should be suspected in middle-aged and obese patients with hypersomnolence and loud snoring, usually reported by the sleeping partner of the patient. Importantly, neck size appears to be a stronger predictor of sleep apnea than body mass index. Additional clinical symptoms of OSAS are restless sleep, profuse sweating, dry mouth or sore throat in the morning, morning headaches and confusion, impotence, and intellectual impairment. OSAS is frequently associated with hypertension (Table 1). However, clinical features do not reliably predict sleep apnea (24).

TABLE 1. Clinical Features Suggestive of Sleep apnea

Nighttime symptoms:
Loud snoring
Awakening from sleep feeling breathless or gasping for air or choking
Restless, nonrestorative sleep (grogginess, lack of energy)
Apneas witnessed by a bed partner
Frequent urination at night
Dry mouth or sore throat upon awakening
Daytime symptoms:
Morning headaches
Unintentional lapses into sleep, especially in boring situations
Excessive daytime sleepiness and tiredness
Difficulty maintaining daytime alertness
Difficulty concentrating and memorizing
Unrefreshing naps
Mood changes (depression, irritability)
Other clinical features:
Increased body mass index, increased neck size
Sexual dysfunction, impotence
Cardiovascular disorders, especially hypertension
Diabetes
Coexisting sleep disorders: insomnia, PLMS, RLS

Several models have been developed to help the clinician decide which patients need to be referred for more definitive testing (25,26). The Berlin questionnaire, for example, which has been validated against polysomnography, asks about risk factors for sleep apnea, namely snoring behavior, wake-time sleepiness or fatigue, and the presence of obesity or hypertension (27). Scoring high risk on this instrument yielded a sensitivity of 0.86, a specificity of 0.77, and a positive predictive value of 0.89 in attempting to detect OSAS in a primary care setting.

A definitive diagnosis of sleep apnea, however, requires polysomnographic sleep studies, although the extent and location of the examination are still the subjects of considerable debate. There is still no clear consensus on the following important issues: Is one full night of diagnostic polysomnographic assessment in a sleep clinic necessary to establish the diagnosis of OSAS? Given the night-to-night variability, is a one-night assessment enough? Is home monitoring acceptable for the diagnosis? Is oximetry alone enough, or do we need electrophysiologic recording and other measures during sleep? Home monitoring may be appealing for dialysis patients who already spend much of their week in the dialysis center.

Defining the presence and extent of excessive daytime sleepiness is important in assessing patients with SAS, but in some cases this task can be challenging. Both clinicians and patients often confuse fatigue or tiredness with sleepiness. Disorders such as chronic insomnia, depression, fibromyalgia, and organic problems often induce fatigue, but not necessarily sleepiness (28). Furthermore, CKD patients may experience the above symptoms, or even excessive sleepiness, for reasons other than SAS. Sleepiness and alertness can be evaluated objectively using the Multiple Sleep Latency Test

(MSLT) (29) and the Maintenance of Wakefulness Test (MWT) (30) in the sleep laboratory, or using a subjective sleepiness scale, such as the Epworth Sleepiness Scale, Karolinska Sleepiness Scale, or Stanford Sleepiness Scale (31–33).

SAS in Dialysis Patients

Except a recent study involving eight CKD patients, no polysomnographic study has been reported in the CKD population not yet on dialysis. Results obtained in that work suggest that sleep problems of patients with CKD and those receiving chronic intermittent daytime hemodialysis might have different etiologies (34). The authors suggest that functional and psychological factors might play a greater role in the development of sleep disruption in CKD patients. In a recent survey we found that 29% of CKD patients scored "high risk" for SAS on the Berlin questionnaire. These patients had a higher body mass index and lower serum albumin than patients with low risk (35).

The reported prevalence of SAS in the dialysis population varies between 30% and 80%. Most of the early studies used nonvalidated questions or scales in selected populations to assess the symptoms of sleep apnea. In a recent survey of unselected dialysis patients that used both a questionnaire and objective measures to assess the presence of OSAS, 16% of patients met the diagnostic criteria for OSAS (36). More recently we used the Berlin questionnaire in a group of nonselected hemodialysis patients and found that 30% scored high risk (37). The few studies that used polysomnography reported even higher prevalences of OSAS (30–80%) (18,38,39). However, these studies are criticized because the relatively few patients enrolled were usually preselected on the basis of clinical suspicion for apnea. Several authors have suggested that central apnea may be quite prevalent in CKD patients, but no large epidemiologic studies have been reported. The true prevalence of both central and obstructive apnea in the CKD population is still unknown. Although a few studies compared the prevalence of sleep apnea in patients on different dialysis modalities, there are not enough data to assess any possible differences (40,41).

Treatment of SAS in CKD Patients

Treatment of OSAS includes nonsurgical and surgical approaches. There is little evidence that treatment of asymptomatic sleep apnea (generally those patients with less than 15 apneic-hypopneic events per hour of sleep and with no daytime sleepiness) is beneficial, although the risk of cardiovascular disorders should be considered. Patients with mixed apnea, even when the predominant component appears to be central apnea, should be treated as if they have OSAS. This may be particularly important in CKD patients, where central or mixed apnea may be more prevalent.

The first step in the specific management of documented OSAS is to look for, and treat if present, any anatomic airway obstruction (enlarged tonsils, skeletal abnormalities, nasal obstruction). In mild cases of sleep apnea, weight loss, changing sleeping position (inserting a tennis ball in a pocket sewn into the back of the pajamas, for example), or special oral devices can bring some improvement. Lifestyle factors such as sleeping in the supine position or avoiding alcohol or sedatives close to bedtime should also be discussed with patients.

Although not a curative intervention, continuous positive airway pressure (CPAP) is the treatment of choice for moderate or severe cases of OSAS. With the help of a mask, CPAP provides airway pressure to keep the upper airways open during sleep. In mild cases, CPAP therapy should be used if daytime sleepiness or neurocognitive symptoms are present. It should also be considered in patients with significant cardiovascular disorders.

Continuous positive airway pressure ameliorates excessive daytime sleepiness and may also improve hypertension associated with apnea (42,43). Recent studies have also confirmed the beneficial cardiovascular effects of CPAP therapy (44).

It has been shown that CPAP improves the quality of life of sleep apnea patients and even that of their bed partners (45). CPAP also improves neuropsychiatric symptoms and depression, which are typically present in OSAS (46), as well as erectile dysfunction related to OSAS (47). A recent study showed that patients who benefit from CPAP are those who suffer from EDS (48).

Compliance with CPAP is far from optimal. It has been suggested that approximately 20–40% of patients will not use CPAP, and many others do not use it all night or every night. Some strategies, including education, regular follow-up, and the use of equipment with heated humidifiers have been shown to improve compliance (49). Using CPAP may be particularly challenging in dialysis patients, whose lives already depend on other mechanical equipment.

Several different oral appliances have been proposed to ameliorate OSAS. These devices protrude the mandible or hold the tongue away from the pharyngeal wall. There are very limited data available to support the effectiveness of these appliances. These devices may be acceptable treatments for some patients with mild OSAS (50,51).

Medroxyprogesterone acetate (MPA) may be effective in the few patients with obesity-hypoventilation syndrome (sleep apnea, obesity, and awake hypoventilation) who are not controlled with CPAP. Some patients on CPAP may still have residual sleepiness; these individuals may benefit from the use of modafinil, a wake-promoting agent.

Surgery may be indicated only in selected cases. Tracheostomy was the first uniformly successful treatment for OSAS. With the advent of CPAP therapy, the frequency of tracheostomy for OSAS has decreased to a negligible number.

Uvulopalatopharyngoplasty, maxillofacial surgery, or the less invasive radiofrequency tissue ablation (RFA) have all been used to treat sleep-related breathing disorders. The available evidence does not support the clinical effectiveness of these procedures (52,53), therefore they should be reserved for patients in whom CPAP is not an option. In fact, prior uvulopalatopharyngoplasty may compromise subsequent CPAP therapy.

The very few studies that have examined the effectiveness of CPAP in patients with renal failure found significant improvement in the apnea/hypopnea index, nocturnal oxygenation, and sleep quality (54). This may be particularly important in this population, as it has been reported that nocturnal hypoxemia predicts cardiovascular complications in dialysis patients (11). It is possible—although not investigated—that treating OSAS may reduce cardiovascular morbidity in the CKD population.

Restless Legs Syndrome

Restless legs syndrome is characterized by an urge to move the legs that is often hard to resist and is usually, but not always, associated with disagreeable leg sensations. The symptoms of RLS typically occur during inactivity and frequently interfere with sleep. RLS is almost invariably associated with another movement disorder, periodic limb movements in sleep (PLMS). However, the reverse does not apply, that is, many patients have PLMS and fragmented sleep and sleepiness or fatigue without having RLS.

Restless legs syndrome can occur in an idiopathic form or secondary to other conditions such as pregnancy, iron deficiency, rheumatoid arthritis, or ESRD. The cause of primary, idiopathic RLS is unknown, but genetic mechanisms are suggested by the fact that a family history consistent with dominant inheritance is present in more than 40% of these patients (55).

The pathogenesis of the disorder is still unclear, but it is widely accepted that it involves disruption of dopaminergic functions in the central nervous system. Several studies provide suggestive evidence pointing to dysfunction of subcortical brain areas in the condition (56). Finally, there is some evidence supporting a proposed relation between brain iron metabolism and RLS. Uremia may be one important pathogenetic factor in patients with ESRD, but there are other factors (neuropathy, anemia, iron deficiency, comorbidity, immobilization during therapy) involved in the pathogenesis of RLS in patients with renal disease.

Restless legs syndrome leads to severe initiation insomnia and greatly impaired quality of life (4,5,57). In one study, RLS was associated with premature discontinuation of dialysis and a significantly increased risk of mortality after 2.5 years follow-up (12). Benz et al. (58) found a similar association between PLMS and mortality.

Diagnosis of RLS

Restless legs syndrome is best diagnosed by an experienced clinician. Diagnostic criteria have recently been established (59). A specific questionnaire, based on the diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG), has also been developed and validated for screening in epidemiologic studies (3,12,60–62). There are four mandatory and some additional clinical features that support the diagnosis (Table 2). Additional clinical features that are typical but do not contribute to the diagnosis include a chronic, and in most cases progressive, clinical course and the presence of sleep disturbances, most frequently initiation insomnia. Polysomnography may be helpful for the diagnosis of resistant RLS (63). In such cases, coexisting PLMS may also be identified.

TABLE 2. Clinical Diagnosis of RLS (based on Allen et al. (59))

Essential diagnostic criteria for RLS, which are mandatory for clinical diagnosis:
An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
The urge to move or unpleasant sensations are partially or totally relieved by movement
The urge to move or unpleasant sensations are worse in the evening or at night than during the day or only occur in the evening or at night
Supportive clinical features:
Positive family history
Positive response to dopaminergic therapy
Presence of PLMS or periodic limb movements during wakefulness

RLS in Dialysis Patients

There is an almost complete lack of information about the prevalence of RLS in predialysis patients. In our survey involving CKD patients not yet requiring dialysis, we found RLS in 6% of individuals (35), a prevalence that is quite similar to that observed in the general population (2–15%) (64). Previous studies have shown a 12–62% prevalence in ESRD patients (3,4,6,12,65,66). These large variations may be attributed in part to the heterogeneity of the study populations and to differences in the definitions of RLS and the tools used to diagnose the syndrome. In more recent studies that applied the IRLSSG diagnostic criteria, the prevalence of the disorder in the ESRD population was 10–20%. However, the definitions of the disorder used in those reports were still quite variable (12,65). Based on the IRLSSG criteria, a self-report questionnaire (RLS Questionnaire [RLSQ]) was developed and validated by Allen and Early (67). The instrument may provide a relatively simple tool to detect RLS in a uniform manner.

Using the RLSQ in 333 dialyzed patients, we found that RLS was present in 14% of patients. RLS was associated with impaired overall sleep quality and poorer quality of life (5).

Recently a polysomnographic study involving 48 patients on dialysis showed that RLS was observed in 58% of the patients and PLMS was present in almost 90% of RLS patients. Patients with both disorders had significantly poorer subjective and objective sleep quality than those with neither disorder or with PLMS alone. Quality of life was also significantly worse in patients with RLS and PLMS compared to those without the disorders, and patients with PLMS alone also tended to have worse quality of life (68).

Treatment of RLS in Dialysis Patients

Although pharmacologic therapy is the mainstay of treatment efforts directed at RLS and PLMS, counseling

about sleep hygiene and lifestyle is also essential. There is a wide range of self-help information available (e.g., from the support group of the Restless Legs Foundation [NightWalkers Newsletter, http://www.rls.org/nwalkers]).

Not everybody with RLS requires treatment. The need for pharmacologic therapy depends on the frequency and severity of symptoms. Some patients need medication only for certain events, for example, when attending the theater or traveling, or when there are long periods of sitting still. In patients with severe insomnia and impaired quality of life, pharmacotherapy is necessary. Pharmacologic trials typically address the therapy of RLS, but in practice both RLS and PLMS are treated with the same groups of medications.

The first step is to rule out RLS caused by medications (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), lithium, dopamine antagonists). Caffeine, nicotine, and alcohol may also aggravate the symptoms of RLS.

Earlier studies frequently identified anemia as a risk factor for RLS in the ESRD population. It has repeatedly been shown that treatment of renal anemia with erythropoietin or intravenous iron reduces the prevalence or severity of RLS (69–71).

Current recommendations suggest dopaminergic therapy (levodopa or dopamine receptor agonists: pramipexol, ropinirole, pergolide, or caber goline) as first-line treatment of RLS. This option has been the most frequently studied, and these drugs are clearly effective in reducing RLS symptoms. On the other hand, daytime augmentation of RLS (i.e., worsening of daytime RLS symptoms with higher doses and long-term medication use), early morning rebound RLS, and insomnia are frequent side effects of levodopa, especially with continuous use. It appears from recent studies that the side effects of pramipexole and ropinirole may be less significant, self-limited, and better controlled than the side effects of levodopa (72) although properly designed comparative trials are still needed to address this question.

Other dopamine agonists and dopaminergic agents (e.g., amantadine and selegiline hydrochloride) and some other classes of medications, including benzodiazepines (especially clonazepam) and anticonvulsants (e.g., carbamazepine and gabapentin) may be also effective, but there are fewer data supporting the use of these agents. Several studies have reported a beneficial effect with different opioids. In some cases benzodiazepines are beneficial for the sleep disruption caused by RLS or PLMS. Gabapentin might be useful for those with painful RLS. There are some data supporting the use of clonidine in RLS, but the effectiveness of this medication is not confirmed in all studies.

An expert panel suggested differentiation of three particular types of RLS. "Intermittent RLS" is troublesome enough when present to require treatment, but it is not sufficiently frequent to require regular daily medication use. "Daily RLS" requires daily treatment, and RLS is considered "refractory" when daily RLS does not respond to a dopamine agonist or if intolerable adverse effects are experienced (73). In our own practice we also place an emphasis on the chief complaint of the patient. If the main problem is daytime fatigue or sleepiness, we are inclined to use selegiline hydrochloride, which has an alerting effect (74). If the major complaint is sleep disruption, we prefer clonazepam as a first step.

Levodopa with a decarboxylase inhibitor together with nonpharmacologic approaches are suggested as first-line therapy for intermittent RLS. Other options in the therapy of intermittent RLS are dopaminergic agonists (see below), low-potency opioids (propoxyphene, codeine, or tramadol), and benzodiazepines (primarily clonazepam) (72).

For daily RLS, the initial therapy should include a dopaminergic agonist (pramipexole or ropinirole) along with nonpharmacologic measures. Alternatives to these medications include gabapentin (although there are very little data supporting its effectiveness) or low-potency opioids.

Referral to a specialist for RLS management should be considered for patients suffering from refractory RLS. It is useful to perform a full sleep study for these patients to ensure that there is no other sleep disorder present. Sleep apnea often coexists with RLS and PLMS, and the symptoms of OSAS may be masked by RLS. The treatment of OSAS, if present, may alleviate RLS/PLMS symptoms. Changing treatment to a different dopamine agonist or to gabapentin, or adding another drug (gabapentin, benzodiazepine, or opioids) to the treatment may also be helpful in such cases (72).

In renal patients, several drugs have been suggested to be effective in treating RLS, however, most published studies suffer from short treatment periods and insufficient statistical power due to small sample sizes. Similar to the therapy of nonuremic RLS, dopaminergic drugs play an important role in the management of RLS in dialysis patients. Two small randomized studies as well as one cohort study showed a positive effect of L-dopa in renal patients (75–77). Based on the limited evidence available, ropinirole (78) and gabapentin (79) are effective for the treatment of RLS in renal patients as well.

Do Sleep Disorders of Dialysis Patients Improve After Renal Transplantation?

Renal transplantation partially restores renal function and alleviates many uremic symptoms and complications. As a consequence, sleep problems may be less prevalent in transplanted patients than in patients treated with maintenance dialysis. At the same time, the same biological, psychological, and social factors that interfere with sleep in the CKD and dialysis populations and the utilization of immunosuppressive medications may also contribute to the development of sleep disorders in this particular patient group.

Sabbatini et al. (80) compared 301 kidney transplanted patients to a group of normal control subjects and to patients on maintenance hemodialysis using the Pittsburgh Sleep Quality Index. Transplanted patients had significantly better overall sleep quality than did patients on maintenance hemodialysis, but their sleep was poorer than that reported by the healthy control group. A surprisingly high proportion (52%) of the transplanted patients were classified as "poor sleepers."

We recently completed a large cross-sectional study (TRANS-QOL study) enrolling 1067 transplanted and 214 wait-listed dialysis patients where validated questionnaires were used to assess sleep disorders. The prevalence of insomnia, assessed with the Athens Insomnia Scale (AIS), was significantly lower in transplanted than in dialyzed patients (8% versus 15%). In multivariate analysis, psychological distress, the presence of RLS and OSAS, comorbidity, and measures of social status were independently associated with the AIS score (81).

Little is known about the prevalence and potential consequences of sleep apnea in the kidney transplanted population. In two case reports, the symptoms of sleep apnea disappeared and the polysomnographic assessment became normal after successful transplantation (17,82). On the other hand, in a study by Unruh et al. (83), the severity of sleep apnea did not change in seven patients after successful kidney transplantation. Our yet unpublished results from the "TRANS-QOL study" suggest that the prevalence of SAS (assessed with the Berlin questionnaire) is similar in transplanted versus wait-listed patients: about 30% of the patients scored high risk for SAS in both populations.

The first case report about the improvement of RLS after renal transplantation was published in 1986 (84). More recently, Winkelmann et al. (85) followed 11 patients with uremic RLS after kidney transplantation. The symptoms of RLS disappeared in 1–21 days after transplantation, but the symptoms of RLS reappeared as the graft failed.

Recently our group published results obtained in the "TRANS-QOL study" using the RLSQ (86). The prevalence of RLS was significantly lower in transplanted patients than in wait-listed patients. RLS was associated with declining renal function, lower serum hemoglobin, higher comorbidity, and iron deficiency. Surprisingly the symptoms of RLS were significantly less frequent in patients taking steroids than in patients not taking this medication.

Conclusion

Sleep problems and sleep disorders are common complaints in renal patients, and evidence shows that this has a significant impact on quality of life, morbidity, and mortality. Surprisingly there is a lack of well-designed studies assessing different therapies in CKD and dialysis patients or in patients after renal transplantation. Most sleep disorders are treatable. Our aim is to raise awareness about the diagnosis and therapy of these important conditions, which we suggest may lead to improvements in the quality of life and rehabilitation of renal patients. Finally, it is still speculative, but entirely possible, that effective treatment of sleep disorders will improve survival.

Acknowledgments

The work of the authors was supported by grants from the National Scientific Research Funds (OTKA TS 040889, OTKA T038409, NKFP 1/002/2001), the Ministry of Health (218/2003), and TeT Foundation (2005/06, MN). Istvan Mucsi is a Bekesy Postdoctoral Fellow of the Hungarian Ministry of Education, Marta Novak is recipient of the Hungarian Eotvos Scholarship.

References

1. Moran MG, Stoudemire A: Sleep disorders in the medically ill patient. *J Clin Psychiatry* 53(suppl.):29–36, 1992
2. Holley JL, Nespor S, Rault R: Characterizing sleep disorders in chronic hemodialysis patients. *ASAIO Trans* 37:M456–M457, 1991
3. Sabbatini M, Minale B, Crispo A, Pisani A, Ragosta A, Esposito R, Cesaro A, Cianciaruso B, Andreucci VE: Insomnia in maintenance haemodialysis patients. *Nephrol Dial Transplant* 17:852–856, 2002
4. Unruh ML, Levey AS, D'Ambrosio C, Fink NE, Powe NR, Meyer KB: Restless legs symptoms among incident dialysis patients. association with lower quality of life and shorter survival. *Am J Kidney Dis* 43:900–909, 2004
5. Mucsi I, Molnar MZ, Ambrus C, Szeifert L, Kovacs AZ, Zoller R, Barotfi S, Remport A, Novak M: Restless legs syndrome, insomnia and quality of life in patients on maintenance dialysis. *Nephrol Dial Transplant* 20:571–577, 2005
6. Mucsi I, Molnar MZ, Rethelyi J, Vamos E, Csepanyi G, Tompa G, Barotfi S, Marton A, Novak M: Sleep disorders and illness intrusiveness in patients on chronic dialysis. *Nephrol Dial Transplant* 19:1815–1822, 2004
7. Shayamsunder AK, Patel SS, Jain V, Peterson RA, Kimmel PL: Sleepiness, sleeplessness, and pain in end-stage renal disease: distressing symptoms for patients. *Semin Dial* 18:109–118, 2005
8. Iliescu EA, Coo H, McMurray MH, Meers CL, Quinn MM, Singer MA, Hopman WM: Quality of sleep and health-related quality of life in haemodialysis patients. *Nephrol Dial Transplant* 18:126–132, 2003
9. Novak M, Mucsi I, Shapiro CM, Rethelyi J, Kopp MS: Increased utilization of health services by insomniacs—an epidemiological perspective. *J Psychosom Res* 56:527–536, 2004
10. Hanly P: Sleep apnea and daytime sleepiness in end-stage renal disease. *Semin Dial* 17:109–114, 2004
11. Zoccali C, Mallamaci F, Tripepi G: Nocturnal hypoxemia predicts incident cardiovascular complications in dialysis patients. *J Am Soc Nephrol* 13:729–733, 2002
12. Winkelman JW, Chertow GM, Lazarus JM: Restless legs syndrome in end-stage renal disease. *Am J Kidney Dis* 28:372–378, 1996
13. Meissner HH, Riemer A, Santiago SM, Stein M, Goldman MD, Williams AJ: Failure of physician documentation of sleep complaints in hospitalized patients. *West J Med* 169:146–149, 1998
14. Reuveni H, Tarasiuk A, Wainstock T, Ziv A, Elhayany A, Tal A: Awareness level of obstructive sleep apnea syndrome during routine unstructured interviews of a standardized patient by primary care physicians. *Sleep* 27:1518–1525, 2004
15. Stradling JR, Davies RJ: Sleep. 1: Obstructive sleep apnoea/hypopnoea syndrome: definitions, epidemiology, and natural history. *Thorax* 59:73–78, 2004
16. De Backer WA: Central sleep apnoea, pathogenesis and treatment: an overview and perspective. *Eur Respir J* 8:1372–1383, 1995
17. Langevin B, Fouque D, Leger P, Robert D: Sleep apnea syndrome and end-stage renal disease. Cure after renal transplantation. *Chest* 103:1330–1335, 1993
18. Kimmel PL, Miller G, Mendelson WB: Sleep apnea syndrome in chronic renal disease. *Am J Med* 86:308–314, 1989
19. Schroder CM, O'Hara R: Depression and obstructive sleep apnea (OSA). *Ann Gen Psychiatry* 4:13, 2005
20. Smith S, Sullivan K, Hopkins W, Douglas J: Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). *Sleep Med* 5:449–456, 2004
21. Wells RD, Day RC, Carney RM, Freedland KE, Duntley SP: Depression predicts self-reported sleep quality in patients with obstructive sleep apnea. *Psychosom Med* 66:692–697, 2004
22. Boyd JH, Petrof BJ, Hamid Q, Fraser R, Kimoff RJ: Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. *Am J Respir Crit Care Med* 170:541–546, 2004
23. Hanly PJ, Pierratos A: Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med* 344:102–107, 2001
24. Viner S, Szalai JP, Hoffstein V: Are history and physical examination a good screening test for sleep apnea? *Ann Intern Med* 115:356–359, 1991
25. Crocker BD, Olson LG, Saunders NA, Hensley MJ, McKeon JL, Allen KM, Gyulay SG: Estimation of the probability of disturbed breathing during sleep before a sleep study. *Am Rev Respir Dis* 142:14–18, 1990
26. Flemons WW, Whitelaw WA, Brant R, Remmers JE: Likelihood ratios for a sleep apnea clinical prediction rule. *Am J Respir Crit Care Med* 150:1279–1285, 1994
27. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP: Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. *Ann Intern Med* 131:485–491, 1999
28. Shapiro CM, Ohayon MM, Huterer N: *Fighting Fatigue and Sleepiness.* Thornhill, Ontario, Canada: Joli Joco Publications, 2005

29. Carskadon MA, Dement WC: The multiple sleep latency test: what does it measure? *Sleep* 5(suppl 2):S67–S72, 1982
30. Mitler MM, Gujavarty KS, Browman CP: Maintenance of wakefulness test: a polysomnographic technique for evaluation treatment efficacy in patients with excessive somnolence. *Electroencephalogr Clin Neurophysiol* 53:658–661, 1982
31. Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 14:540–545, 1991
32. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC: Quantification of sleepiness: a new approach. *Psychophysiology* 10:431–436, 1973
33. Akerstedt T, Gillberg M: Subjective and objective sleepiness in the active individual. *Int J Neurosci* 52:29–37, 1990
34. Parker KP, Bliwise DL, Bailey JL, Rye DB: Polysomnographic measures of nocturnal sleep in patients on chronic, intermittent daytime haemodialysis vs those with chronic kidney disease. *Nephrol Dial Transplant* 20:1422–1428, 2005
35. Mendelssohn D, Novak M, Dunai A, Ambrus C, Chan W, Shapiro C, Devins G, Molnar M, Mucsi I: Sleep disorders and quality of life in chronic kidney disease patients in the predialysis stage. *J Am Soc Nephrol* 15:132A, 2004
36. Kuhlmann U, Becker HF, Birkhahn M, Peter JH, von Wichert P, Schutterle S, Lange H: Sleep-apnea in patients with end-stage renal disease and objective results. *Clin Nephrol* 53:460–466, 2000
37. Kovacs Z, Molnar M, Ambrus C, Pap J, Mucsi I, Novak M: Prevalence of sleep apnea syndrome is not different in patients on hemodialysis vs. kidney transplanted patients. *J Sleep Res* 13(suppl 1):412, 2004
38. Wadhwa NK, Seliger M, Greenberg HE, Bergofsky E, Mendelson WB: Sleep related respiratory disorders in end-stage renal disease patients on peritoneal dialysis. *Perit Dial Int* 12:51–56, 1992
39. de Oliveira Rodrigues CJ, Marson O, Tufic S, Kohlmann O Jr, Guimaraes SM, Togeiro P, Ribeiro AB, Tavares A: Relationship among end-stage renal disease, hypertension, and sleep apnea in nondiabetic dialysis patients. *Am J Hypertens* 18:152–157, 2005
40. Hallett MD, Burden S, Stewart D, Mahony J, Farrell PC: Sleep apnea in ESRD patients on HD and CAPD. *Perit Dial Int* 16(suppl 1):S429–S433, 1996
41. Stepanski E, Faber M, Zorick F, Basner R, Roth T: Sleep disorders in patients on continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 6:192–197, 1995
42. Dhillon S, Chung SA, Fargher T, Huterer N, Shapiro CM: Sleep apnea, hypertension, and the effects of continuous positive airway pressure. *Am J Hypertens* 18:594–600, 2005
43. Dursunoglu N, Dursunoglu D, Cuhadaroglu C, Kilicaslan Z: Acute effects of automated continuous positive airway pressure on blood pressure in patients with sleep apnea and hypertension. *Respiration* 72:150–155, 2005
44. Doherty LS, Kiely JL, Swan V, McNicholas WT: Long-term effects of nasal continuous positive airway pressure therapy on cardiovascular outcomes in sleep apnea syndrome. *Chest* 127:2076–2084, 2005
45. Doherty LS, Kiely JL, Lawless G, McNicholas WT: Impact of nasal continuous positive airway pressure therapy on the quality of life of bed partners of patients with obstructive sleep apnea syndrome. *Chest* 124:2209–2214, 2003
46. Kawahara S, Akashiba T, Akahoshi T, Horie T: Nasal CPAP improves the quality of life and lessens the depressive symptoms in patients with obstructive sleep apnea syndrome. *Intern Med* 44:422–427, 2005
47. Goncalves MA, Guilleminault C, Ramos E, Palha A, Paiva T: Erectile dysfunction, obstructive sleep apnea syndrome and nasal CPAP treatment. *Sleep Med* 6:333–339, 2005
48. Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, Monasterio C, Bosch M, Ladaria A, Rubio M, Rubio R, Medinas M, Hernandez L, Vidal S, Douglas NJ, Agusti AG: Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness: a randomized, controlled trial. *Ann Intern Med* 134:1015–1023, 2001
49. Haniffa M, Lasserson TJ, Smith I: Interventions to improve compliance with continuous positive airway pressure for obstructive sleep apnoea. *Cochrane Database Syst Rev* Oct 18:CD003531, 2004
50. Ferguson KA, Ono T, Lowe AA, al-Majed S, Love LL, Fleetham JA: A short-term controlled trial of an adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. *Thorax* 52:362–368, 1997
51. Hoekema A, Stegenga B, De Bont LG: Efficacy and co-morbidity of oral appliances in the treatment of obstructive sleep apnea-hypopnea: a systematic review. *Crit Rev Oral Biol Med* 15:137–155, 2004
52. Keenan SP, Burt H, Ryan CF, Fleetham JA: Long-term survival of patients with obstructive sleep apnea treated by uvulopalatopharyngoplasty or nasal CPAP. *Chest* 105:155–159, 1994
53. Loube DI, Gay PC, Strohl KP, Pack AI, White DP, Collop NA: Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: a consensus statement. *Chest* 115:863–866, 1999
54. Pressman MR, Benz RL, Schleifer CR, Peterson DD: Sleep disordered breathing in ESRD: acute beneficial effects of treatment with nasal continuous positive airway pressure. *Kidney Int* 43:1134–1139, 1993
55. Montplaisir J, Boucher S, Poirier G, Lavigne G, Lapierre O, Lesperance P: Clinical, polysomnographic, and genetic characteristics of restless legs syndrome: a study of 133 patients diagnosed with new standard criteria. *Mov Disord* 12:61–65, 1997
56. Allen RP, Earley CJ: Restless legs syndrome. a review of clinical and pathophysiologic features. *J Clin Neurophysiol* 18:128–147, 2001
57. Allen RP, Walters AS, Montplaisir J, Hening W, Myers A, Bell TJ, Ferini-Strambi L: Restless legs syndrome prevalence and impact: REST general population study. *Arch Intern Med* 165:1286–1292, 2005
58. Benz RL, Pressman MR, Hovick ET, Peterson DD: Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. *Am J Kidney Dis* 35:1052–1060, 2000
59. Allen RP, Picchietti D, Hening WA, Trenkwalder C, Walters AS, Montplaisi J: Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med* 4:101–119, 2003
60. Allen R, Earley CJ: Validation of a diagnostic questionnaire for the restless legs syndrome (RLS). *Neurology* 56(suppl 3):4A, 2001
61. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C: Epidemiology of restless legs symptoms in adults. *Arch Intern Med* 160:2137–2141, 2000
62. Holley JL, Nespor S, Rault R: A comparison of reported sleep disorders in patients on chronic hemodialysis and continuous peritoneal dialysis. *Am J Kidney Dis* 19:156–161, 1992
63. Walters AS: Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord* 10:634–642, 1995
64. Zucconi M, Ferini-Strambi L: Epidemiology and clinical findings of restless legs syndrome. *Sleep Med* 5:293–299, 2004
65. Takaki J, Nishi T, Nangaku M, Shimoyama H, Inada T, Matsuyama N, Kumano H, Kuboki T: Clinical and psychological aspects of restless legs syndrome in uremic patients on hemodialysis. *Am J Kidney Dis* 41:833–839, 2003
66. Nichols DA, Allen RP, Grauke JH, Brown JB, Rice ML, Hyde PR, Dement WC, Kushida CA: Restless legs syndrome symptoms in primary care: a prevalence study. *Arch Intern Med* 163:2323–2329, 2003
67. Allen RP, Earley C: Validation of a diagnostic questionnaire for the restless legs syndrome (RLS) [abstract]. *Neurology* 58:A4, 2001
68. Rijsman RM, de Weerd AW, Stam CJ, Kerkhof GA, Rosman JB: Periodic limb movement disorder and restless legs syndrome in dialysis patients. *Nephrology (Carlton)* 9:353–361, 2004
69. Sloand JA, Shelly MA, Feigin A, Bernstein P, Monk RD: A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *Am J Kidney Dis* 43:663–670, 2004
70. Earley CJ, Heckler D, Allen RP: Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome. *Sleep Med* 6:301–305, 2005
71. Earley CJ, Heckler D, Allen RP: The treatment of restless legs syndrome with intravenous iron dextran. *Sleep Med* 5:231–235, 2004
72. Silber MH, Ehrenberg BL, Allen RP, Buchfuhrer MJ, Earley CJ, Hening WA, Rye DB: An algorithm for the management of restless legs syndrome. *Mayo Clin Proc* 79:916–922, 2004
73. Earley CJ: Clinical practice. Restless legs syndrome. *N Engl J Med* 348:2103–2109, 2003
74. Grewal M, Hawa R, Shapiro C: Treatment of periodic limb movements in sleep with selegiline HCl. *Mov Disord* 17:398–401, 2002
75. Trenkwalder C, Stiasny K, Pollmacher T, Wetter T, Schwarz J, Kohnen R, Kazenwadel J, Kruger HP, Ramm S, Kunzel M, et al. L-dopa therapy of uremic and idiopathic restless legs syndrome: a double-blind, crossover trial. *Sleep* 18:681–688, 1995
76. Walker SL, Fine A, Kryger MH: L-DOPA/carbidopa for nocturnal movement disorders in uremia. *Sleep* 19:214–218, 1996
77. Sandyk R, Bernick C, Lee SM, Stern LZ, Iacono RP, Bamford CR: L-dopa in uremic patients with the restless legs syndrome. *Int J Neurosci* 35:233–235, 1987
78. Pellecchia MT, Vitale C, Sabatini M, Longo K, Amboni M, Bonavita V, Barone P: Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis: an open randomized crossover trial versus levodopa sustained release. *Clin Neuropharmacol* 27:178–181, 2004
79. Micozkadioglu H, Ozdemir FN, Kut A, Sezer S, Saatci U, Haberal M: Gabapentin versus levodopa for the treatment of restless legs syndrome in hemodialysis patients: an open-label study. *Ren Fail* 26:393–397, 2004
80. Sabbatini M, Crispo A, Pisani A, Gallo R, Cianciaruso B, Fuiano G, Federico S, Andreucci VE: Sleep quality in renal transplant patients: a never investigated problem. *Nephrol Dial Transplant* 20:194–198, 2005
81. Novak M, Molnar MZ, Ambrus C, Kovacs AZ, Koczy A, Remport A, Szeifert L, Szentkiralyi A, Shapiro CM, Kopp MS, Mucsi I: Chronic insomnia in kidney transplant recipients. *Am J Kidney Dis* 47:655–665, 2006
82. Auckley DH, Schmidt-Nowara W, Brown LK: Reversal of sleep apnea hypopnea syndrome in end-stage renal disease after kidney transplantation. *Am J Kidney Dis* 34:739–744, 1999
83. Unruh M, Teehan G, D'Ambrosio C, Jaber B: The impact of kidney transplantation on sleep disorders. *J Am Soc Nephrol* 14:657A, 2003
84. Yasuda T, Nishimura A, Katsuki Y, Tsuji Y: Restless legs syndrome treated successfully by kidney transplantation—a case report. *Clin Transpl* 12:138, 1986
85. Winkelmann J, Stautner A, Samtleben W, Trenkwalder C: Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. *Mov Disord* 17:1072–1076, 2002
86. Molnar MZ, Novak M, Ambrus C, Szeifert L, Kovacs A, Pap J, Remport A, Mucsi I: Restless legs syndrome in patients after renal transplantation. *Am J Kidney Dis* 45:388–396, 2005