EDITORIAL

Sleep and ESRD: A Wake-Up Call

IN AN EXTENSIVE, well-conducted, and nicely presented study, Chen et al report the extraordinarily high prevalence of subjective sleep complaints in a huge sample of hemodialysis (HD) patients. This presents a special and timely opportunity to reflect on the current state of knowledge, therapeutic implications, and future research directions in the arena of sleep complaints, sleep disorders, and chronic renal failure (CRF).

This study should serve as a “wake-up call” to all nephrologists and other professionals caring for this patient population. The bad news is that sleep complaints are ubiquitous in this CRF, and may result in untold misery and medical complications. The good news is that most wake/sleep complaints are diagnosable and, more importantly, treatable. All too often, complaints of excessive daytime sleepiness and insomnia are summarily attributed to the fact that patients with CRF are undergoing dialysis and/or are receiving multiple medications.

For perspective, sleep disorders are extremely prevalent in the general population. Therefore, at least 10% to 20% of patients with CRF had insomnia, 4% had obstructive sleep apnea (OSA), and 10% had restless legs syndrome (RLS)—even before they developed CRF. Things go downhill from there.

INSOMNIA

This and other studies found an astonishing number (67%) of HD patients complained of insomnia. Recent advances in insomnia research have clearly indicated that in many cases there are physiologic underpinnings to insomnia, and that most cases of insomnia are not due to underlying significant psychiatric or psychologic problems. Insomnia is best thought of as a constitutional symptom, like pain, fever, or weight loss. An underlying etiology can usually be identified. Once identified, the underlying cause can be treated. Frequent causes in this population include conditioned insomnia, RLS, and medication-induced insomnia.

Long-Term (Chronic) Conditioned Insomnia

This common form of insomnia develops after an event that triggered acute situational insomnia (anxiety, excitement, bereavement, pain, medication, etc). This short-term insomnia then becomes conditioned, or “learned.” The inciting event disappears, but the insomnia persists, and remains until treated by behavioral and/or pharmacologic means. The behavioral treatments include sleep restriction, sleep consolidation, sleep hygiene, and cognitive behavioral therapy. Effective pharmacologic treatment includes benzodiazepines (temazepam, clonazepam, triazolam, or estazolam) or the newer nonbenzodiazepine medications (zaleplon, zolpidem, or eszopiclone). Many medications commonly prescribed to treat insomnia (antihistamines, tricyclic antidepressants, or trazodone) are generally ineffective.

Restless Legs Syndrome

There is a fascinating relationship between CRF and RLS. Although RLS is most often idiopathic or familial, it has long been known that conditions associated with iron abnormalities (anemia, pregnancy, and CRF) are associated with RLS. RLS is actually a neurologic sensory motor disorder that presents as severe insomnia resulting from a difficult-to-describe discomfort in the lower extremities, which is relieved only by moving or rubbing the legs, or by getting up and walking about. The discomfort returns when the patient attempts to return to sleep. There is now overwhelming evidence that the primary abnormality in many patients with RLS is a defect of iron metabolism in the central nervous system. Many RLS patients have low serum ferritin levels (despite normal hemoglobin, hematocrit, iron, and iron binding capacity determinations). Some have low cerebrospinal fluid ferritin levels despite normal serum ferritin levels. Functional neuroimaging studies support the concept.
of abnormal central nervous system iron metabolism.\textsuperscript{5,7}

The prevalence of RLS is much greater in CRF than in the general population. It results in often incapacitating insomnia, and may be present during sedentary wakeful activities. In some HD patients, the waking restlessness is severe enough to actually interfere with dialysis sessions. RLS has been associated with increased morbidity in patients with end-stage renal disease.\textsuperscript{8}

Fortunately, RLS tends to respond nicely and often dramatically to a number of medications including dopaminergic agonists (pramipexole and ropinirole), benzodiazepines (clonazepam), opiates, and gabapentin.\textsuperscript{5}

\textit{Medication-Induced Insomnia}

Relatively few medications are known to cause insomnia. Those pertinent to the CRF population include phenytoin and steroids (taken by a number of CRF patients). Steroid-induced insomnia may be severe, and often responds nicely to effective sedative/hypnotic medication.\textsuperscript{9}

\textbf{EXCESSIVE DAYTIME SLEEPINESS}

\textit{Sleep Apnea}

This and other studies have found a very high prevalence of sleep apnea in patients with CRF.\textsuperscript{10} The reason for this high association is elusive. That many patients with CRF and OSA are not overweight serves as a reminder that being overweight is not a necessary accompaniment of OSA. But clearly, identification and treatment of any underlying OSA is important. Untreated OSA results in daytime sleepiness and is a known risk factor for hypertension, cardiac disease, stroke, and type 2 diabetes\textsuperscript{11,12}—all of which may already be problematic for many CRF patients.

\textit{Hypersomnia Not Related to OSA}

Daytime sleepiness is common in HD patients, and is not always attributable to OSA.\textsuperscript{13} The cause and treatment of this currently are unknown.

\textbf{WHAT TO DO?}

Wake and sleep function should be viewed as a vital sign: every patient should be asked about sleep and daytime alertness. Any complaint should be taken seriously and not simply attributed to the underlying renal disease and/or medications.

Complaints of insomnia can be evaluated with sleep diaries or actigraphy. An actigraph is a wristwatch-like device that records movement over prolonged periods (weeks). The movement is highly correlated with wake/sleep patterns. Actigraphy provides an “at a glance” overview of the wake/sleep pattern over prolonged periods.\textsuperscript{14} RLS can be identified simply by asking if, while having trouble falling asleep, the patient lies quietly in bed awaiting sleep, or is compelled to move the legs or get out of bed to walk about. Patients with RLS are virtually unable to lie still in bed trying to fall asleep. Formal sleep studies are rarely indicated in the evaluation of insomnia.

Patients with unexplained hypersomnia should undergo formal sleep studies. If significant OSA is found, nasal continuous positive airway pressure is the treatment of choice. If hypersomnia unrelated to OSA is documented, stimulant medication may be of value, however this remains undocumented.

\textbf{FUTURE DIRECTIONS}

Documentation of the staggering prevalence of sleep complaints in patients with CRF (including children)\textsuperscript{15} is overwhelming.\textsuperscript{16,17} Impaired quality of sleep likely impairs quality of life in CRF patients.\textsuperscript{18} Applying this information to our patients with CRF can markedly improve their quality of life. Already, there is evidence that renal transplantation can reduce the prevalence of insomnia in dialysis patients to that seen in the general population.\textsuperscript{19} Careful analysis of objective data regarding the specific relationships among CRF, sleep apnea, insomnia, and RLS will advance the fields of both sleep medicine and nephrology. Close collaboration among the fields of basic science and clinical sleep medicine and nephrology will provide important scientific and clinical information that will serve to benefit our patients.

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