Sleep related movement disorders – common causes of chronic daytime sleepiness one has never heard of:
A review

ZSUZSANNA VIDA

Ministry of Defence, State Health Center, Sleep Department, Budapest, Hungary

Expectations towards the modern army (like peace force, guarding and protecting services) require sustained performance that cannot comply with the symptoms of sleep-related disorders. Chronic daytime sleepiness interferes with mental functioning and performance and is a potential cause of human error, catastrophic failures and accidents. The underlying causes of chronic daytime sleepiness include primary sleep disorders (such as obstructive sleep apnea, sleep-related motor disorders, narcolepsy, idiopathic hypersomnia, abnormalities of the circadian rhythm of sleep/wakefulness). Periodic Limb Movement Disorder (PLMD) and Restless Legs Syndrome (RLS) are types of sleep disorders that are not very well known and often not recognized in clinical practice, although they can cause severe impairment of sleep and lead to impairment in cognitive performance, mental health problems such as tension, depression, aggression.

Introduction

Network-centric doctrine and the proposed C4ISR (command, control, communications, computers, intelligence, surveillance and reconnaissance) distributions to the individual war fighter require sustained cognitive performance, judgment, and decision making in the forward operating environment, where various physiological and psychological stressors abound, in order to reduce human errors and catastrophic failures.

The US-led conflict in Iraq demonstrated the need for the military to manage chronic daytime sleepiness during long combat operations. For example, soldiers of the 3rd Infantry Division reported instances when columns of tanks and armoured vehicles would idle in gigantic bottlenecks behind a sleeping driver. According to the Los Angeles Times, “Crew members from a nearby vehicle would scramble out to awaken the stalled driver”. By the time the column started moving, someone farther back would have fallen asleep, and the process would start all over again.
The knowledge of primary sleep disorders that are common cause of chronic daytime sleepiness is essential in order to help the soldiers be alert when needed and to get rest when necessary.

Recognising this, the National Sleep Foundation helps to create a sleep education program for soldiers and pilots in Iraq, as part of a comprehensive preventative medicine and public health program. NSF sent copies of easy-to-use toolkit created for health and safety professionals interested in providing sleep information to their staff, crew, or soldiers.

The Sleep Department of Ministry of Defence, State Health Centre has already presented some important primer sleep disorder.1–3 In this article we would like to call attention to another important disease, which can be hidden for a long time and cause severe sleep deficit.

Periodic Limb Movement Disorder (PLMD) and Restless Leg Syndrome (RLS) are among the most common disorders seen in sleep clinics. The prevalence of these disorders is higher than that of epilepsy. They cause tremendous distress and affect the quality of life of those afflicted. Generally speaking, these disorders are not well understood in terms of the pathophysiology and symptomatology. Ironically, RLS can be described as the most common condition one has never heard of.

**Periodic Limb Movement Disorder**

Periodic limb movements are a type of motor disorder that occurs typically in sleep. The term for periodic limb movements during sleep, originally called nocturnal myoclonus, was defined as a phenomenon characterized by repetitive flexions and extensions involving the toes, ankles, and occasionally the knee and hip. These frequent movements occur in one or both legs during sleep, and often produce brief arousals and, in some cases, full awakenings from sleep. Periodic Limb Movement Disorder (PLMD) is defined by the *International Classification of Sleep Disorders* (ICSD) as periodic leg movements >15/h accompanied by a clinical sleep disturbance or a complaint of daytime fatigue.4 Recent studies have demonstrated that nearly all Periodic Limb Movements during sleep (PLMs) are accompanied by autonomic arousal.5–7 In addition, evidence is emerging that PLMs are associated with increases in blood pressure.8–11

Periodic limb movements most commonly involve the lower limbs12 (extension of the big toe and fanning of the other toes). Movements are typically bilateral but are not necessarily symmetrical or occur simultaneously. They may predominate in one leg or alternate between legs.12 Periodic involving the upper extremities often manifest as repetitive flexion at the elbow. They can occur either during sleep or during
wakefulness. When occurring during relaxed wakefulness [periodic leg movements of wakefulness (PLMW)], they appear as jerk-like movements with an appearance and distribution similar to PLMs affecting the lower limbs, but with greater intensity and speed.\textsuperscript{13}

The diagnosis is based on polysomnographic findings. The universally accepted criteria for diagnosis of PLMD are summarized in Table 1.\textsuperscript{14}

\begin{table}
\centering
\begin{tabular}{|l|}
\hline
There should be at least four leg movements in a 90-s period. \\
Contractions should be more than 0.5-s and less than 5-s. \\
When they are recorded from both anterior tibialis muscles, they should be separated by an interval of at least 5-s for them to be counted as two separate movements. They can either be associated with EEG arousals or in severe cases even overt arousals. \\
The PLM Index (PLMI) is calculated by dividing the total number of PLMs by sleep time in hours. Periodic Limb Movements Index of more than 5 and less than 25 is considered mild; PLMI of >25 and <50 is considered moderate and >50 is severe. \\
\hline
\end{tabular}
\end{table}

The diagnosis of PLMD can be made when patients present with insomnia, tiredness and daytime sleepiness in the presence of a high PLM index (PLMI). Sometimes spouses can complain that their partners kick their legs during sleep. Patient may report sleep onset problems or frequent arousals because of these movements. In contrast, those who are unaware of these movements may simply complain of un-refreshing sleep, ‘leg tiredness’ on awakening in the morning. The diagnosis of idiopathic PLMD is made when no other psychiatric, medical or sleep disorders can be found to account for the symptoms, and patients are not on medications that can result in PLMs.

\textbf{Epidemiology of PLMD}

PLMD are rare in children and are more common with advancing age.\textsuperscript{15,16} They can be found in >34\% of patients over 60 years of age. They are common in a variety of sleep disorders including Sleep-Related Breathing Disorders (SRBD) (20–30\%), Restless Leg Syndrome (RLS) (80–90\%), REM Behavioral Disorder (RBD) (70\%) and narcolepsy (45–60\%) and have been reported in 1–15\% of patients with insomnia. The actual prevalence of this disorder in the general population is not known, as this requires polysomnography for the diagnosis. While 80–90\% of patients with RLS have PLMs, only 30\% of PLM patients have RLS.
Restless Leg Syndrome

Unlike PLMD, Restless Leg Syndrome is a clinical diagnosis. The first description of RLS is attributed to Thomas Willis in 1685. Ekborn coined the term restless legs. In 1945, he gave a full description of the syndrome based on a large series of patients. This condition is sometimes referred to as Ekborn’s syndrome.

The most recent diagnostic criteria for RLS developed by National Institute of Health with members of IRSSLG (International Restless Leg Syndrome Study Group) require four essential criteria for the diagnosis of RLS:\17

1. Undesirable sensations in the legs that occur before sleep onset;
2. Irresistible urge to move the limbs;
3. Partial or complete relief of the symptoms on movement of the limbs and
4. Return of symptoms on cessation of the movements.

The sensory symptoms may include pricking, crawling, aching, burning, pulling, itching and tingly sensations.\18 Sometimes they could be as unique as ‘colas in my veins’. Patients usually are aware of these symptoms in the evening when they have finished with the day’s work and are relaxing, such as sitting on the sofa and watching television. The symptoms may prevent patients from going to bed. Patients may complain of having to get up from the bed either to stretch their legs or walk a few paces before they can return to the bed, only to be troubled by the same symptoms.

There are two types of RLS:

1. The early onset: Age of onset is less than 45 years, tends to cluster in families and progresses slowly with a female to male ratio of 2:1.
2. Late-onset RLS: Age of onset over 45, has an equal male to female ratio, more rapid progression, more severe and more frequent symptoms, no familial clustering and are more commonly associated with radiculopathy, neuropathy or myelopathy.

Prevalence of RLS

Ekborn estimated the prevalence of RLS to be 5% in the general population. Subsequent surveys have estimated the prevalence to be 1–29%.\18–22 The RLS Epidemiology, Symptoms and Treatment (REST) trial is the largest survey till date to study the prevalence of RLS.\18
Medical evaluation and diagnostic test RLS and PLMD

The diagnosis of RLS relies upon a good clinical interview and medical history documenting the four essential features of the disorder and a careful differential diagnosis. A routine physical and brief neurologic examination is recommended, particularly checking for signs of neuropathy and a complete blood count and an iron level. The occurrence of PLMD can be proved with a full-night polysomnographic examination in the sleep laboratory. A specific test, the Suggested Immobilization Test (SIT) has been developed to evaluate the sensory and motor symptoms of RLS during a period of rest. It is usually done in the hour before sleep onset, in the sleep laboratory.

Pathophysiological aspects of RLS

The basic pathophysiological mechanisms of RLS remain elusive. Pharmacological, physiological, pathological and new imaging studies have implicated dopaminergic systems, brain iron metabolism and the endogenous opioid system. The nigrostriatal dopaminergic system has been implicated in the pathogenesis of RLS and PLMD. The role of iron in RLS has been supported by demonstrated therapeutic benefit of iron in both RLS and PLMD. MRI and autopsy studies have shown lower iron levels in substantia nigra of RLS patients. Other studies have even found lower CSF ferritin levels with normal serum iron stores in RLS patients. The inability to store iron in the brain is more profound in early onset RLS than in patients with late-onset RLS. Akpinar in 1982 accidentally came across the beneficial effects of levodopa on RLS. Since then levodopa and other dopaminergic agents have been used effectively in the treatment of RLS and PLMD. This has led to the conclusion that dopaminergic systems must play some role in the pathophysiology of RLS. It has been hypothesized that there is a dysfunction in the central processing of sensory stimuli. There is a defective D2 binding in the medial thalamus and anterior cingulate gyrus that are involved in central sensory processing. The dienecephalo-spinal dopaminergic tract has received much attention as the potential anatomic site of dopaminergic dysfunction in RLS. The system projects proximally to the limbic system, sensory cortex and spinal cord. The proximity to the circadian control centers in the hypothalamus may offer some explanation for the circadian pattern of symptoms observed in RLS. Iron deficiency has long been associated with RLS, and iron therapy has been found to be effective in some cases. Earley et al. demonstrated markedly reduced cerebrospinal fluid ferritin levels and elevated transferrin levels in RLS patients compared with controls, even though there was no difference in serum ferritin levels. It is possible that even in the absence of total body iron deficiency; defective iron
metabolism in the brain could be responsible for RLS. A large study using MRI found decreased regional brain iron concentration in early onset RLS patients relative to controls. Based on the fact that transferrin receptor quantity is decreased (the opposite of what is seen in iron deficiency state) and iron regulatory protein 1 (IRP1) is deficient, it has been hypothesized that a primary protein dysfunction in the brain iron regulation system is responsible for RLS.

**Treatment**

Treatment of RLS and PLMD shares a lot of similarities.

In PLMD treatment is justified only if the patient has daytime sleepiness. If the patient has a low ferritin level (less than 50 mcg/l) oral iron treatment should be taken. Caffeine, alcohol, nicotine and medications that aggravate RLS should be avoided. Physical and mental activity may help ameliorate symptoms in mild cases.

The most commonly used dopaminergic agents are levodopa, dopamine agonist such as ropinirole, pramipexole and in some countries the ergot-derivative pergolide. The efficacy of dopaminergic agents has been shown to be 90% in randomized placebo-controlled trials. They are generally effective in both relieving symptoms and decreasing the number of movements at night. Levodopa/carbidopa generally works better for intermittent symptoms and as prophylaxis prior to car rides and plane trips. For daily symptoms, either ropinirole or pramipexole can be used. These are longer acting in comparison with levodopa. They should be administered at least 2 hr prior to the onset of symptoms. For RLS symptoms that occur mostly in the early part of the night, taking these medications with dinner maybe helpful. In cases of PLMS, they should be given an hour prior to going to sleep. Both pramipexole and ropinirole can be started at 0.25 mg and increased as tolerated. The maximum dose of these medications his generally 3 mg. In patients who are intolerant to dopaminergic medications, the ergot-derivative pergolide can be used. The starting dose is a 0.025 mg and increased up to 0.5 mg.

**Discussion**

RLS and PLMD are not well known and rarely recognized causes of chronic daytime sleepiness. The prevalence of RLS, severe enough to cause impairment in cognitive functions and warrant medical treatment is probably around 2–3%. This makes clinically significant RLS 2 to 6 times as common as epilepsy in developed countries (estimated prevalence of epilepsy 0.5–1%). The fact, that the prevalence of RLS and
PLMD is increasing with age and the signs and symptoms can be hidden for a long time increases the importance of the knowledge these sleep disorders.

A comprehensive discussion of the epidemiology, pathophysiology, symptomatology and treatment as attempted in this article should improve the awareness of these entities among civil and military persons, health and safety professionals and help them manage these cases more effectively.

References

3. SZTERNÁK, N.: Screening, diagnosis and therapy of narcolepsy that has a crucial effect on military service. AARMs, 2007, Vol. 6, No. 4. pp 575–585.


