Fatigue and Sleep Disorders in Multiple Sclerosis

David W. Brandes, MS, MD, FAAN
Hope MS Center, Knoxville, TN
Director, Rest Analysis, Los Angeles, CA
Asst. Clinical Professor, UCLA

Fatigue and Sleep Disorders in MS

Mrs. Smith: “Doctor, I’m tired all the time.”

Doctor: “What do you mean by ‘tired’, Mrs. Smith?”
Fatigue and Sleep Disorders in MS

The meaning of “tired”

- Fatigued—lack of energy, easily physically fatigued with exertion
- Depression—diminished desire to do things, no “psychic” energy, lack of interest mentally
- Cognitive dysfunction—can’t think clearly, difficulty with multi-tasking, fatigue with mental exertion
- Sleepy—need to close eyes and sleep
- Combination of above—not mutually exclusive

Fatigue and Sleep Disorders in MS

Causes of “fatigue”

- MS-related
  - Chronic (continuous and episodic)
  - Acute exacerbation
- Depression
- Infection (e.g., UTI, viral syndrome)
- Metabolic disorders
Metabolic disorders and fatigue
- Effect of medication (next slide)
- Hypothyroidism (? interferons)
- Hepatic or renal dysfunction
- Anemia
- Chronic fatigue syndrome/fibromyalgia
- Many others

Medications and fatigue/sleepiness
- Side effects of disease modifying drugs
  - Sleep worse on injection nights of interferon
  - Glatiramer patients also noted to have decreased sleep compared to untreated patients (Mendozzi et al, 2009)
- Side effects of other MS medications (e.g., AED’s, antidepressants, anti-spasticity drugs)
- Side effects of non-MS medications (e.g., anti-hypertensives, anti-histamines)
Sleep disturbance in patients with MS may occur for many reasons:
- Leg spasms
- Pain
- Immobility
- Nocturia
- Medication side effects
- Primary or secondary sleep disorders

Outline
- General overview of sleep disorders
- Specific sleep disorders
- Insomnia
- Do MS lesions cause sleep disorders?
- Summary
Sleep Disorders

Obstructive sleep apnea is associated with fatigue in multiple sclerosis; M Kaminska, et al.; Multiple Sclerosis Journal; December 19, 2011.

Sleep disorders may occur in up to 60% of patients with multiple sclerosis.

History Of Sleep Disorders

- 20th century—systematic study of sleep began
- Last half of the 20th century—recognized that sleep disorders are common, serious and treatable
- 1970’s—first sleep disorder centers
- 1975—Association of Sleep Disorders Centers

History Of Sleep Disorders

- 1979—first classification of sleep disorders
- Physician training in medical school is very limited—average time is 1 hour in 4 years in about 1/3 of medical schools
- Subsequent training is also minimal without special interest courses
Types Of Sleep Disorders

- Hypersomnias (excessive daytime sleepiness)
- Insomnias
- Parasomnias

Definitions

Hypersomnias

Uncontrollable drowsiness

Unwanted sleep episodes during the waking hours
Definitions

Insomnias

- Difficulty falling asleep
- Difficulty staying asleep
- Awakening too early
- Non-restorative sleep

Definitions

Parasomnias

Undesirable physical phenomena occurring primarily during sleep
Hypersomnias

- Obstructive sleep apnea
- Periodic limb movements of sleep
- Narcolepsy
- Other causes—medication effects, medical disorders, Pickwickian, central hypoventilation, nocturnal GERD, voluntary sleep restriction

How Sleep Disorders Are Evaluated

- History
  - Familial factors, substance use
  - Sleepiness rating scales
- Physical Exam
  - Airway, jaw, tongue, neurologic exam
- Sleep Diary
- Polysomnography (PSG)
- Multiple Sleep Latency Test
- Actigraphy
Most common hypersomnia—affects 2.5 million people in the U.S.

Men > women, obesity, snoring, small airway

Recurrent airway obstruction while asleep resulting in brief arousals (micro-arousals)

Daytime sleepiness, lack of energy, cognitive impairment
Obstructive Sleep Apnea

- Diagnostic testing--Sleep Laboratory vs. home testing
- Apnea-hypopnea index (>5 events per hour)
- Oxygen desaturation (especially <85%)
- Treatment
  - CPAP or BilevelPAP (positive airway pressure applied through a mask)
  - Dental appliances, nasal patches (Provent)
  - Oxygen
  - Surgery
- Follow-up---compliance counseling

CPAP

Photo Courtesy of T Weaver and C Guilleminault, AASM
Central Sleep Apnea (CSA)

- A loss of muscular effort to breath
- Associated with congestive heart failure
- Can be seen with neuromuscular disorders but is very rare
- Severe decrease in respiratory drive while asleep is called Ondine's Curse
  - Reported in 2 MS patients with medullary lesions by Auer et al 1996

Neurological Sleep Disorders

- Narcolepsy
- Periodic limb movements of sleep
- Restless legs syndrome
- REM sleep behavior disorder
NARCOLEPSY: Clinical Diagnosis

- Overwhelming attacks of daytime sleepiness (despite adequate night-time sleep)
- Brief daytime refreshing naps
- Cataplexy—sudden loss of postural tone, especially precipitated by strong emotional events, heavy meals and fatigue
- Hypnogogic/hypnopompic hallucinations
- Sleep paralysis

NARCOLEPSY

- Prevalence
  - 1 in 3000 in Caucasians
  - Onset varies from childhood through 50’s with peak in second decade
- Genetics
  - Men = (or slightly greater than) women
  - HLA genotype
    - HLA-DR*1501 found in 85% of narcolepsy patients (most common gene “causing” MS); however, DQB1*0602 is the most likely cause of narcolepsy
• However, DQB1*0602 is present in 15-35% of the normal population, thus it is not the only cause of narcolepsy

• Identical twin studies show discordance, suggesting that polygenic and/or environmental factors are necessary

• Inheritance is most consistent with autosomal dominant pattern with incomplete penetrance

• MRI and PET scans have not shown visible abnormalities, although the hypothalamus is now thought to be the primary site of the pathological process.

• Classical narcolepsy + cataplexy vs. non-classical narcolepsy
  ◦ Genetic basis applies primarily to the former
NARCOLEPSY: Laboratory Diagnosis

- Polysomnogram followed by MSLT (Multiple Sleep Latency Test) showing 2 or more REM onset naps out of five attempts
- HLA typing
- Medication issues/ drug screening

PERIODIC LIMB MOVEMENTS IN SLEEP (PLMS): Clinical

- Repetitive extension of the big toe with ankle dorsiflexion (occasionally hips, knees, rarely arms)
- Lasting 0.5-5 seconds, occurring in a pseudo-periodic pattern every 20-40 sec
- Episodes last from minutes to rarely hours
- Result in (micro-)arousals from sleep (>5/hour)
- Hundreds per night may occur
PERIODIC LIMB MOVEMENTS IN SLEEP (PLMS): Clinical (cont’d)

- Periodic limb movement disorder (PLMD)
- Same as PLMS, but associated with significant arousals and excessive daytime sleepiness

PLMS/PLMD: Epidemiology

- 5% of normals ages 30-49
- 35% of normals over age 50
- Associated with restless legs syndrome, narcolepsy, sleep apnea
- Associated with Parkinson’s disease, peripheral neuropathy, multiple sclerosis, spinal cord injury, ALS and other neurological diseases
PLMS/PLMD in Multiple Sclerosis

- Seen in up to 65% of MS patients
- Symptomatic in fewer, perhaps 15-20% of the MS patients who have PLMS
- A potential cause of daytime sleepiness, fatigue

PLMS/PLMD: Diagnosis

- Characteristic history from bed-partner
- Therapeutic medication trial
- Complete polysomnogram if uncertain diagnosis by history or lack of response to medication trial
PLMD: Treatment

- Dopamine agonists (pramipexole (Mirapex), ropinirole (Requip), rotigotine (Neupro))
- Levodopa with Carbidopa (Sinemet, especially the CR form with or without COMT inhibitor [entacapone], such as Comtan, Stalevo)
- Anticonvulsants: gabapentin (Neurontin), pregabalin (Lyrica)
- Clonazepam (Klonopin)
- Opioids (especially codeine)

RESTLESS LEG SYNDROME: RLS

- Often associated with PLMS, but occurs while awake
- Affects 2%-5% of the population
- Prevalence increases with age
- May be associated with an abnormality of iron metabolism
**RLS Types**

- 1° Restless Leg Syndrome
  - 33-92% hereditary
  - Autosomal dominant, variable penetrance

- 2° Restless Leg Syndrome
  - Multiple sclerosis, neuropathy, Parkinson’s, spinocerebellar ataxias, uremia, low ferritin, vascular disease, diabetes, rheumatoid arthritis, CHF

**RLS: Diagnosis**

- A desire to move the extremities, often associated with sensory phenomena
- Motor restlessness
- Worsening at rest & temporary relief by physical activity
- Worsening in the evening or night
**RLS: Treatment**

- Benzodiazepines: clonazepam, diazepam
- Dopaminergics: pramipexole, ropinirole, rotigotine, carbidopa/levodopa
- Anticonvulsants: gabapentin, pregabalin, carbamazepine
- Opioids
- Others: baclofen, clonidine, tizanidine

**PLMD and RLS: Aggravating Conditions and Medications**

- Iron deficiency may cause a marked or abrupt increase in symptom severity
- Pregnancy may cause, maximal in third trimester
- Antidepressant medications may aggravate PLMS/RLS including the tricylics, SSRI’s, and SNRI’s
- Bupropion may alleviate
- Withdrawal from anticonvulsants, benzodiazepines, or barbiturates may worsen
- Less with fever/heat
**RLS: Biologic Basis**

- Unknown, ? subcortical or brainstem

- Disorder of dopaminergic dysfunction with enhanced spinal cord excitability
  - Bara-Jimenez et al Neurology 2000

- Increased motor cortex excitability and decreased subcortical inhibition
  - Tergau et al Neurology 1999

**RLS and MS**

- Increased frequency in MS (19-36%)

- Impairs sleep quality and increases daytime fatigue in MS (Moreira et al)

- Associated with cervical spinal cord damage
  - Manconi et al 2007

- Associated with severe pyramidal and sensory disability
  - Manconi et al 2008
**REM-SLEEP BEHAVIOR DISORDER (RBD)**

- Clinical manifestations may include dramatic, violent, potentially injurious motor activity during REM sleep

- The behaviors include talking, yelling, swearing, grabbing, punching, kicking, jumping, or running out of the bed

**Biological Basis**
- Most commonly seen with degenerative brain diseases (dementias); often precursor to Parkinson’s disease

**Treatment**
- Clonazepam
- Tether self to bed
Insomnia

**INSOMNIA—MEDICAL TREATMENT**

- Up to 27% of healthcare clinic attendees worldwide
- One of most common complaints in primary practice
- Costs to medicine and society are high
Classification

- Sleep onset insomnia
- Sleep maintenance insomnia
- Both

Causes

- Medical problems (muscle spasms, nocturia, pain, immobility and medications are common offenders in MS patients)
- Psychiatric/psychological
- Substance-induced
- Circadian disturbance
- Inadequate sleep hygiene
- Misperception
- Idiopathic
INSOMNIA--MEDICAL TREATMENT

- Initial treatment decision depends on the diagnosis
- Up to 49% of chronic insomniacs may benefit from polysomnography to fully elucidate the diagnosis

INSOMNIA--MEDICAL TREATMENT

- Multi-dimensional approach to treatment
- Often requires separate office visit just for this problem
INSOMNIA--MEDICAL TREATMENT

• Treatment of causative conditions
  ▫ Medical conditions
  ▫ Psychiatric conditions (especially anxiety and depression)

• Behavioral treatments
  ▫ Relaxation techniques, incl. Biofeedback
  ▫ Sleep hygiene improvement

• Alternative treatments
  ▫ Melatonin
  ▫ ? Others

INSOMNIA--MEDICAL TREATMENT

• Benzodiazepine hypnotics
  ▫ Dalmane, Restoril
  ▫ Halcion

• Nonbenzodiazepine hypnotics
  ▫ Ambien (zolpidem)
  ▫ Sonata (zaleplon)
  ▫ Lunesta (eszopiclone)

• Tricyclic antidepressants

• Anti-histamines
Benzodiazepine hypnotics have detectable effects on daytime performance.

The new short acting and ultra-short acting non-benzodiazepine hypnotics have little or no such effect.

Non-benzodiazepine hypnotics:
- Tricyclic antidepressants
  - Less dependence
  - Reasonable efficacy/side effects
  - Possible serious side effects
- Trazodone
- Anti-histamines—morning hypersomnolence, rapid tolerance
- Melatonin—must be used several hours before desired sleep onset. Only 1 mg dose is needed.
- Rozerem (ramelteon)—prescription melatonin analogue, stimulates MT₁ and MT₂ receptors
Do MS plaques cause sleep disorders?

- 1987—no association of narcolepsy & MS
- 1993—intractable hiccups and sleep apnea syndrome in 2 pts, both had medullary tegmentum lesions
- 1994—3 MS pts with OSA had brainstem lesions, but no different from 17 pts without OSA
- 1994—PLMS in 36% of MS pts, greater lesion loads in brainstem and cerebellum
- 1996—medullary plaques associated with fatal sleep apnea (Ondine’s curse) in 2 pts.

Sleep Disorders in MS

- Do MS plaques cause sleep disorders?
Sleep Disorders in MS

- Do MS plaques cause sleep disorders (cont’d)?
  - 1996—13 yo girl with acute onset of MS with hypersomnia resembling narcolepsy associated with incontinence, strabismus, weakness, incoordination, ataxia. All sx improved with dexamethasone.
  - 1998—13 yo boy with prior ON developed classical narcolepsy with SOREM; no brainstem lesions on MRI. Sx resolved with steroids.
  - 2002—RBD in 25 yo woman with MS, resolved with steroids. MRI—DWM and pontine lesions.

Summary
Many facilities offer polysomnograms without consultation with a specialist trained in sleep medicine.

Consultation offers the ability to better define a differential diagnosis, identify and remediate aggravating or complicating factors, focus the polysomnogram if needed, and fine tune treatment.

Sleep disorders are common and may complicate the presentation of MS “fatigue.”

Be aware of obstructive sleep apnea and Periodic Limb Movements of Sleep as potential causes of excessive daytime sleepiness.

Restless legs syndrome and mood disorders are often important factors in the evaluation of patients with insomnia.
Spasticity versus PLMD may require different management at night

Neuropathic pain can lower sleep efficiency

Nocturia and bladder function at night are important for quality of life
  - DDAVP an option for some

THE END