

Fatigue and Sleep Disorders in Multiple Sclerosis

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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

Fatigue and Sleep Disorders in MS

Metabolic disorders and fatigue

- Effect of medication (next slide)
- Hypothyroidism (? interferons)
- Hepatic or renal dysfunction
- Anemia
- Chronic fatigue syndrome/fibromyalgia
- Many others

Fatigue and Sleep Disorders in MS

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 Disorders in MS

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

	MS	Controls
OSA	58%	47%
RLS	27%	6%
Severe/Very Severe RLS	19%	3%
REM behavior disorder	3%	0%
Narcolepsy	2%	0%
Severe hypersomnia	18%	16%
Any hypersomnia	45%	78%

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

Sleep Disorders

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

Sleep disorders in multiple sclerosis. Review. Veuthier, C. Curr Neurol Neurosci Rep 2015 May;15(5):21.

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
- 1990, 1997, 2001, 2005, 2014—revisions of sleep disorders classification system
- 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



Specific Sleep Disorders

Obstructive Sleep Apnea (OSA)

- 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

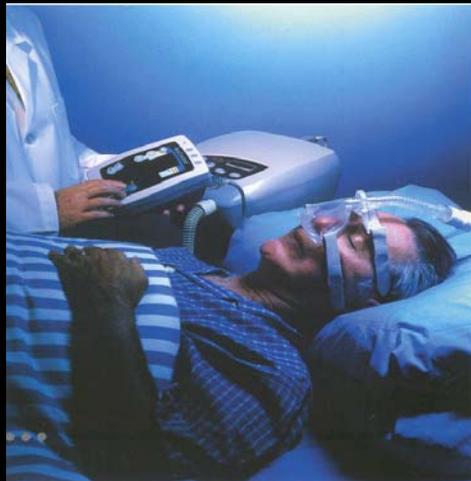


Photo Courtesy of T Weaver and C Guilleminault, AASM

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
- Hypnagogic/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

NARCOLEPSY: Genotype (cont)

- 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

NARCOLEPSY: Anatomic Basis

- 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, spino-cerebellar 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 tricyclics, 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

REM-SLEEP BEHAVIOR DISORDER

- 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

INSOMNIA-- MEDICAL TREATMENT

Classification

- Sleep onset insomnia
- Sleep maintenance insomnia
- Both

INSOMNIA-- MEDICAL TREATMENT

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

INSOMNIA-- MEDICAL TREATMENT

- 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

INSOMNIA-- MEDICAL TREATMENT

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 MT_1 and MT_2 receptors



Do MS plaques cause sleep disorders?

Sleep Disorders in MS

- 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 (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

Sleep Study or Sleep Specialist Consultation?

- 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 in MS Patients

- 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 a patients with insomnia.

MS Factors Disturbing Sleep

- 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

