



Sleep Disorders in Multiple Sclerosis

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Sleep Disorders in MS

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

Doctor: “What do you mean by ‘tired’, Mrs. Smith?”

Sleep Disorders in MS

The meaning of “tired”

- Fatigued—lack of energy, easily physically fatigued with exertion
 - Sleepy—need to close eyes and sleep
 - 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
 - Combination of above—not mutually exclusive
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Sleep Disorders in MS

Causes of “fatigue”

- MS-related
 - Chronic
 - Acute exacerbation
 - Depression
 - Infection (e.g., UTI, viral syndrome)
 - Metabolic disorders
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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
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Sleep Disorders in MS

Medications and fatigue/sleepiness

- Side effects of β -interferons
 - Flu-like syndrome
 - Sleep deprivation
 - 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)
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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
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Outline

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

- 1979—first classification of sleep disorders
 - 1990, 1997—revisions of sleep disorders classification system
 - Physician training in medical school is very limited—average time is 20 minutes in 4 years of medical school
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Why Do We Sleep?

- Resting the body rejuvenates the biological processes
 - Resting the brain rejuvenates the biological processes in the CNS
 - For the brain to rest, we must sleep.
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How Do We Sleep?

- Reticular activating system—brainstem
 - RAS controlled by light, hormonal regulatory systems
 - Delicate system—easily disturbed and can cause sleep disturbance or sleep disorder
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How Do We Study Sleep?

- Correlate EEG sleep stage with biochemical and imaging studies in animals and humans
 - Correlate patient histories with known sleep disorders
 - Polysomnography
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Types Of Sleep Disorders

- Hypersomnias (excessive daytime sleepiness)
 - Insomnias
 - Parasomnias
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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
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Specific Sleep Disorders

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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
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Polysomnography

- Multi-channel recording of sleep with video
 - Recording includes:
 - Brainwave activity (EEG)
 - Muscle tone at chin
 - Airflow, oxygen saturation
 - Chest, abdominal, and limb movements
 - Eye movement
 - Cardiac rhythm
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Multiple Sleep Latency Test (MSLT)

- Usually immediately after a polysomnogram
 - 4-5 naps attempted for 20 minutes each through the day for 20 minutes
 - Study to determine if excessive sleepiness and if sleep episodes are associated with REM Sleep (Dream Sleep)
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Normal Sleep

- Sleep is divided into non-rapid eye movement (NREM) and rapid eye movement (REM) states
 - REM Sleep is characterized by vivid dreams, rapid eye movements, and faster brain wave activity
 - During REM sleep, muscle activity is inhibited (atonia)
 - NREM is divided into 4 stages
 - Stages 3 and 4 are often grouped together as deep, delta or slow wave sleep
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Normal Sleep Structure

- Sleep begins in NREM
 - Sleep cycles from NREM to REM every 90-120 minutes 3 to 6 times per night
 - NREM is 75-80% of sleep
 - 45-55% is stage 2
 - 3-8% stage 3
 - 10-15% stage 4
 - REM is 20-25%
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Normal Sleep: Timing of Events

- Delta or deep sleep is concentrated in the first half of the sleep cycle
 - REM sleep is concentrated in the last half of the last half of the sleep cycle
 - Wakefulness may briefly occur at transitions in the cycle between REM and NREM
 - Wakefulness should be less than 5% within sleep time
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Obstructive Sleep Apnea (OSA)

- Most common hypersomnia—affects 2.5 million people.
 - Men > women, obesity
 - Recurrent airway obstruction while asleep resulting in brief arousals (microarousals)
 - Daytime sleepiness, snoring
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Obstructive Sleep Apnea

- Diagnosis made in Sleep Laboratory
 - Apnea or apnea-hypopnea index
 - Oxygen desaturation
 - Treatment
 - CPAP or BIPAP (positive airway pressure applied through a mask)
 - Dental appliances
 - Surgery
 - CPAP Clinic—compliance
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CPAP

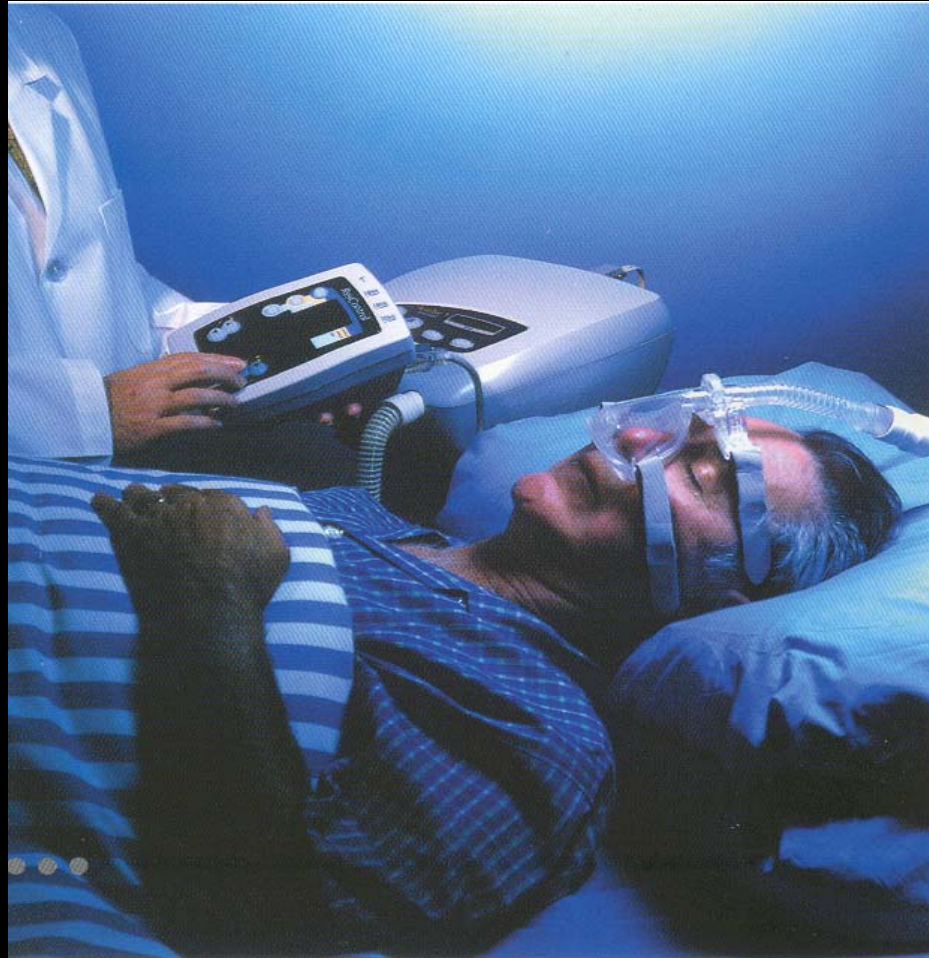


Photo Courtesy of T Weaver and C Guilleminault, AASM

Central Sleep Apnea (CSA)

- A loss of muscular effort to breath
 - Can be seen with neuromuscular disorders but is very very rare
 - Loss of unconscious respiratory drive is called Ondine's Curse
 - Reported in 2 MS patients with medullary lesions by Auer et al 1996
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Neurological Sleep Disorders

- Narcolepsy
 - Periodic limb movements of sleep
 - Restless legs syndrome
 - REM sleep behavior disorder
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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/hypnapompic hallucinations
 - Sleep paralysis
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NARCOLEPSY

- Prevalence
 - 26/100,000 in Caucasians (0.05%)
 - Onset varies from childhood through 50's with peak in second decade
 - Genetics
 - Men = (or slightly greater than) women
 - HLA genotype
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NARCOLEPSY: HLA Genotype

- 85% of Caucasians and Japanese have genotype HLA*DR1501 (formerly DR15 or DR2) and DQB1*0602 (formerly DQ1 or DQ6)
- 85% of African-Americans have the DQB1-0602 genotype, only 65% have D*1501
- The DQB1-0602 is most likely the HLA-associated narcolepsy susceptibility gene
- HLA-DR2 (prob DR*1501) increases the risk of developing MS. It is found in 56% of MS pts and only 26% normals of Northern European descent.

NARCOLEPSY: Genotype (cont)

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 environmental factors are necessary

Inheritance is most consistent with autosomal dominant pattern with incomplete penetrance

NARCOLEPSY: Biological Basis

- Cells in the hypothalamus that secrete orexin (hypocretin) are diminished or absent
 - CSF orexin is also measurably diminished
 - Involves both monoamine and acetylcholinergic pathways
 - No convincing evidence of autoimmune dysfunction (although suspected)
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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
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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
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NARCOLEPSY: Treatment

- Stimulant drugs: methylphenidate (Ritalin), pemoline (Cylert), amphetamines
 - Modafinil (Provigil, Alertec), an alpha-1-adrenergic agonist with alerting properties
 - Xyrem (gamma hydroxybutyrate)
 - Protriptyline (Vivactil) and selegiline (Eldepryl)
 - Behavioral treatment, such as planned daytime naps
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Modafinil: Provigil, Alertec

- Stimulates the arousal centers in the brainstem
 - Less agitation & anorexia than amphetamines
 - No addiction potential
 - 100-200mg daily or twice daily
 - Less effective with prior exposure to stimulants
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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 hours
 - Result in arousals from sleep (>5/hour)
 - Hundreds per night may occur
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PLMS: Epidemiology

- 5% of people ages 30-49
 - 35% of people 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
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PLMS 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
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PLMS: Diagnosis

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

- Dopamine agonists (pramipexole (Mirapex), ropinirole (Requip), pergolide (Permax))
 - Levodopa with Carbidopa (Sinemet especially the CR form with or without COMT inhibitor (entacapone), such as Comtan, Stalevo)
 - Clonazepam (Klonopin)
 - Opioids (especially codeine)
 - Anticonvulsants (gabapentin (Neurontin))
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RESTLESS LEG SYNDROME: RLS

- Similar to PLMS, but occurs during the waking hours
 - Affects 2%-5% of the population
 - Prevalence increases with age
 - May be associated with an abnormality of iron metabolism
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RLS Types

- 1° Restless Leg Syndrome
 - 33-92% hereditary
 - Autosomal dominant, variable penetrance
 - 2° Restless Leg Syndrome
 - Neuropathy, PD, SCA, uremia, low ferritin, PVD, DM, RA, CHF
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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
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RLS: Treatment

- Benzodiazepines: Clonazepam
 - Dopaminergics: pramipexole, ropinirole, carbidopa/levodopa
 - Opioids
 - Anticonvulsants: gabapentin, carbamazepine
 - Others: baclofen, clonidine, tizanidine
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PLMS 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
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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
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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
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REM-SLEEP BEHAVIOR DISORDER

- Biological Basis
 - Most commonly seen with degenerative brain diseases (dementias)
 - Treatment
 - Clonazepam (Klonopin)
 - Tether self to bed
-

Insomnia

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INSOMNIA-- MEDICAL TREATMENT

- Up to 27% of healthcare clinic attendees worldwide
 - One of most common complaints in primary practice
 - Cost to medicine and society is high
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INSOMNIA-- MEDICAL TREATMENT

Classification

- Sleep onset insomnia
 - Sleep maintenance insomnia
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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
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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
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INSOMNIA-- MEDICAL TREATMENT

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

Worldwide, 3-10% of the population
uses sleep agents

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

Ideal sleep agent

- Promotes uninterrupted, restful, nightlong sleep
 - Normal sleep architecture
 - No tolerance or addiction
 - No withdrawal or rebound
 - No side effects or hangover
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INSOMNIA--

MEDICAL TREATMENT

- Benzodiazepine hypnotics
 - Dalmane, Restoril
 - Halcion
 - Nonbenzodiazepine hypnotics
 - Ambien (zolpidem)
 - Sonata (zaleplon)
 - Lunesta (Eszopiclone)
 - Tricyclic antidepressants
 - Anti-histamines
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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
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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.

INSOMNIA--

Drug dependence

Management Of Dependence

- About 3/4 of insomniacs use their drugs many months
 - 1/3 of elderly patients were still taking hypnotics after 4 years
-

INSOMNIA--

Drug dependence

- Primary goal is withdrawal of hypnotics entirely
 - Substitution with nonpharmacologic treatments
 - Slow withdrawal may be possible
 - Substitute with tricyclics
-

INSOMNIA--

Drug dependence

Not all patients
can be withdrawn

INSOMNIA--

Drug dependence

- Some studies show less tolerance with at least two drug-free nights per week
 - Maximum of 3-4 nights per week according to patient choice results in even less tolerance
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INSOMNIA--

Drug dependence

- Combination therapy
 - Nightly sedating tricyclic antidepressants
 - Intermittent benzodiazepine receptor agonists
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Do MS plaques cause sleep disorders?

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Sleep Disorders in MS

- Do MS plaques cause sleep disorders?
 - 1987—no association of narcolepsy & MS
 - 1993—intractable hiccups and SAS 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.
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Summary

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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
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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 can be important factors in the evaluation of a patients with insomnia
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MS Factors Disturbing Sleep

- Spasticity and spasms may require different management at night
 - Neuropathic pain can lower sleep efficiency
 - Nocturia and bladder function at night are important for quality of life
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THE END

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