

# *Excessive Daytime Somnolence*

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**EXCESSIVE DAYTIME SOMNOLENCE (EDS)** - abnormal sleepiness during normal waking hours:

- A. **Secondary EDS** - due to insomnia.
- B. **Primary EDS** (independent of insomnia):
  1. Obstructive Sleep Apnea
  2. Narcolepsy
  3. Idiopathic Hypersomnia
  4. Restless Legs Syndrome and Periodic Limb Movement Disorder
  5. Kleine-Levin Syndrome
  6. Circadian rhythm disorders
  7. Brain lesions of pathways involved in sleep-wake regulation (e.g. tumors in 3<sup>rd</sup> ventricle area, obstructive hydrocephalus, certain viral encephalitis, mononucleosis).

**CLINICAL FEATURES**

- 1) susceptibility to *falling asleep*;
  - in *mild cases* - inadvertent napping during sedentary activities, during normal nadirs in daytime alertness in afternoon or evening.
  - in *severe cases* – **SLEEP ATTACKS** - unavoidable nodding off during active periods (e.g. driving car, conversing) → accidents and catastrophes.
- 2) apparent *increase in total sleep* during 24-hour day.
- 3) difficulty in achieving *full alertness after awakening* in morning.
- 4) impaired *performance* and diminished *intellectual capacity*.

Epworth sleepiness scale:

For each of situations outlined in recent everyday life, ask patient to grade likelihood of dozing off or falling asleep:  
 0 = Would never doze  
 1 = Slight chance of dozing

2 = Moderate chance of dozing 3 = High chance of dozing	
Situation	Chance of dozing
Sitting and reading	
Watching television	
Sitting inactive in a public place (e.g. a theatre or meeting)	
As passenger in a car for 1 hour without a break	
Lying down for a rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, whilst stopped for a few minutes in traffic	
<b>TOTAL</b>	

**DIFFERENTIAL DIAGNOSIS**

- 1) DEPRESSION - **dysphoric symptoms** (complaints of tiredness, lack of energy / motivation / drive) - may mimic sleepiness.
- 2) SEDATIVE DRUG use.
- 3) disorders of CONSCIOUSNESS
- 4) liver failure, uremia, chronic pulmonary disease (with hypercapnia), hypothyroidism (severe with myxedema).
- 5) POSTCONCUSSION syndrome
- 6) SYNCOPE
- 7) partial complex or absence SEIZURES
- 8) CHRONIC FATIGUE SYNDROME.

**DIAGNOSIS**

**Multiple sleep latency test** - shortened latency.

**TREATMENT**

**MODAFINIL** (Provigil®) – FDA approved for narcolepsy, obstructive sleep apnea, shift-work sleep disorder.

**NARCOLEPSY**

- incurable lifelong genetically based disorder of systems that regulate REM sleep expression.

- PREVALENCE (narcolepsy with cataplexy) in white population - 1 in 4000.  
5 times more prevalent in Japan;  
only 1 per 500,000 in Israel.
- **men = women.**

HLA-associated gene:

- 90% patients have *specific HLA haplotype* - **HLA-DQB1-0602** (present in 20-30% of general population); but no direct evidence that narcolepsy is autoimmune disease!
- **gene penetrance is low** - risk for narcolepsy in 1° relatives is only ≈ 1% (although it is 40 times greater than in general population) - unknown ENVIRONMENTAL FACTORS play important role.

No pathologic changes (macro- or micro-) are found in brain.

- narcolepsy may be rare symptom of lesions in region of 3<sup>rd</sup> ventricle and hypothalamus.

## CLINICAL FEATURES

Symptoms begin gradually in **2<sup>nd</sup> decade of life**;

- onset before age of 5 is rare;
- occasional onset after age 50.

1. **EXCESSIVE DAYTIME SLEEPINESS** with **INVOLUNTARY DAYTIME SLEEP EPISODES** (100%) – first symptom to appear; most prominent symptom; may be sole clinical manifestation - recognition that patient has medical disorder often takes years!
  - severity fluctuates during day and is variable among individuals.
  - *boring sedentary situations* and *warm afternoons following lunch* are especially difficult settings;
    - work performance is most affected in sedentary jobs requiring sustained vigilance.
    - physical activity provides relief, but sleepiness returns as soon as patient sits down.
  - brief daytime sleep episodes (**MICROSLEEPS**, s. **SLEEP ATTACKS**) are common.
    - may cause *amnesic episodes of automatic behavior* lasting seconds to hour (patients drift in and out of sleep while engaging in aimless or semipurposeful activity\* - observers may not realize that patient is asleep).
      - \*examples - getting lost while driving, typing or writing gibberish, misplacing things, walking into objects.
    - patients may *fall directly into REM sleep* and *report dreams* during these naps.
    - patient can be roused from narcoleptic sleep as readily as from normal sleep (ease of arousability – important diagnostic feature).
    - these spontaneous naps are usually brief and somewhat refreshing.
  - family members, friends, and even patient often *misinterpret symptoms* as indicating laziness, lack of ambition, delayed maturation, or psychologic defects; because these symptoms begin during crucial period of maturation (from puberty to adulthood), lack of diagnosis can greatly impact patient's personality!

N.B. narcoleptics do not sleep more, but *need to sleep more frequently!*

2. **CATAPLEXY** (76%) - brief episode of *bilateral weakness*, without altered *consciousness*, that is precipitated by strong, but normal *emotion* (laughter!!!, anger, fear, etc).
 

Cataplexy that responds to tricyclic antidepressants is pathognomonic for narcolepsy!

  - may develop simultaneously with sleepiness, or decades later (absence of cataplexy does not exclude diagnosis).
  - lasts few seconds.
  - **muscle atonia** (in sleep paralysis and cataplexy) is *similar to muscle atonia of REM sleep* and resemble loss of muscle tone that occurs in person who is "weak with laughter".
  - may be partial and affect only certain muscles - buckling of knees, sagging of jaw or face, drooping eyelids, mild dysarthria;
    - *twitching* in face may accompany weakness.
    - severe attacks produce *complete paralysis* (except muscles of respiration) → collapse.
    - prolonged episodes may be associated with *hallucinations* (auditory, visual, tactile).
3. **SLEEP PARALYSIS** (64%) - episodes of complete paralysis\* (as in cataplexy) at beginning or at end of sleep.
  - episode lasts few seconds ÷ minutes.
  - patients feel awake and aware of being in bed.
  - may be accompanied by struggle to move, to speak, or to wake up; *frightening hallucinations* and sense of suffocation.
  - despite intense very frightening psychic experience, *patients appear to be asleep* (eyes closed, occasional twitches, slight moans, irregular respirations).

- attack can be *aborted by external stimulus* (usually touch); sometimes patient himself can abort paralysis by imagining touch.
- 4. **HYPNAGOGIC & HYPNOPOMPIC HALLUCINATIONS** (68%) - represent **REM sleep imagery intrusion** into consciousness during transitions between wakefulness and sleep.
  - almost always include *visual imagery* (often frightening).
  - difference from dreams - thematic story is lacking and some awareness of surroundings is preserved.
  - hallucinations are so vivid and realistic that subject may take actions to escape from images.
- 5. **NOCTURNAL SLEEP DISRUPTION** (frequent awakenings) by vivid, frightening dreams (87%) - may be prominent complaint.

### Course

- **SLEEPINESS** is lifelong (chronic without remissions).
- **CATAPLEXY, SLEEP PARALYSIS**, and hypnagogic **HALLUCINATIONS** improve with age in 30% patients.
- longevity is unaffected.

## DIAGNOSIS

### Multiple Sleep Latency Test:

- 1)  $\geq 2$  *sleep-onset REM periods* - diagnostic criterion for narcolepsy!
  - 2) mean sleep latency < 5 minutes
- *false-positive results* occur with depression, drug withdrawal, sleep deprivation.

REM sleep begins within 10-15 minutes of sleep onset (instead of normal 85-100 minutes); this abnormal timing of REM sleep is called **sleep-onset REM period**.

**HLA typing** - limited value for diagnosis.

## MANAGEMENT

### **Medications and behavioral measures** *to enhance alertness during critical times of day!*

- important adjunctive treatment is rational scheduling of *daytime naps\** (15-20 min during lunch or other breaks) and maintenance of *proper sleep hygiene*.
  - \*each nap provides several hours of sleep-free performance!

**STIMULANTS** improve **EXCESSIVE DAYTIME SLEEPINESS**:

A. **AMPHETAMINES** – **DEXTROAMPHETAMINE, METHAMPHETAMINE**

B. **NONAMPHETAMINES**:

- 1) **METHYLPHENIDATE** - drug of choice! see A35 p.
- 2) **PEMOLINE**
- 3) **MAZINDOL**
- 4) **MODAFINIL** (Provigil®) (precise mechanism unknown;  $\alpha$ -adrenergic agonist?)
  - single morning dose 100-400 mg; no effect on ability to sleep when sleep is desired; adverse effects – serious rash (incl. Stevens-Johnson syndrome); anxiety, mania, hallucinations, suicidal ideation.

5) **ARMODAFINIL** (Nuvigil™) - R-enantiomer (longer-lived) of MODAFINIL; single morning dose 150 or 250 mg.

- stimulants should be initiated at low doses and *increased gradually* - until symptoms are controlled or side effects appear.
- chronic use of stimulants can lead to irritability, insomnia, hypertension, habituation, addiction, psychosis (risk for amphetamine abuse is no higher than in general population!).
- most narcoleptics take stimulants regularly for decades without harmful side effects.

**ANTIDEPRESSANTS** - potent REM-suppressants - effective for "REM phenomena" (**CATAPLEXY**, **SLEEP PARALYSIS**, **HYPNAGOGIC HALLUCINATIONS**):

- a) **nonsedating tricyclic** (esp. **IMIPRAMINE**, **CLOMIPRAMINE**)
- b) **SSRI** (e.g. **FLUOXETINE**).

**SODIUM OXYBATE**, s. **γ-HYDROXYBUTYRATE** (Xyrem®)

– FDA approved **CNS DEPRESSANT (SEDATIVE / HYPNOTIC)** for **EXCESSIVE DAYTIME SLEEPINESS** and **CATAPLEXY**.

- mechanism of action unknown.
- taken at bedtime and second dose 2.5-4 hours later (patient will need to set alarm to awaken for second dose).  
N.B. can cause sleep very quickly - both doses should be taken while seated in bed; after ingesting each dose patient should lie down and remain in bed.
- starting dose 4.5 g/night (divided into two equal doses of 2.25 g); titrated every 1-2 weeks up to 9 g/night.
- adverse effects:
  - 1) abuse potential with risk of dependence & severe withdrawal!!! (schedule III controlled substance)
  - 2) *combination with alcohol may be lethal!*  
overdose → supportive measures (rapid metabolism;  $T_{1/2} \approx 0.5-1$  h).
  - 3) sleep apneas
  - 4) urinary incontinence.
  - 5) contains a lot of sodium (concern in CHF, hypertension, renal failure).
- contraindications:
  - 1) other sedative / hypnotic use
  - 2) succinic semialdehyde dehydrogenase deficiency (drug is catabolized via Krebs cycle to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ ).

## IDIOPATHIC (PRIMARY) HYPERSONNIA

- chronic narcolepsy-like **DAYTIME SLEEPINESS** despite adequate amounts of normal sleep at night:

**CLASSIC TYPE** - increased need for sleep, nocturnal sleep is prolonged (up to 20 hrs during day and night) but not refreshing, difficulty awakening in morning, sleep drunkenness with disorientation and confusion in morning; daytime naps are long and *unrefreshing*.

**SECOND (NARCOLEPTIC) TYPE** - irresistible daytime sleepiness, but short naps are *refreshing*.

- cataplexy does not occur; no association with specific HLAs.
- less common than narcolepsy (1:10).
- pathogenesis unknown.
- gradual onset during adolescence or young adulthood.
- diagnosis of exclusion;

**PSG** - relatively normal sleep architecture (vs. narcolepsy);

**MSLT** - pathological sleepiness, but REM sleep does not occur during naps.

- **management** similar to narcolepsy (**NARCOLEPTIC TYPE** responds to stimulants, whereas **CLASSIC TYPE** may not).

## KLEINE-LEVIN SYNDROME

- rare PERIODIC (RECURRENT) **HYPERSOMNIA** (sleeping up to 20 hours per day) associated with **BULIMIA**.

- **psychologic changes** often accompany episodes (disorientation, forgetfulness, depression, depersonalization, hallucinations, irritability, aggression, sexual hyperactivity, etc).
- **pathology** – undiscovered (similar syndrome may be seen acutely in encephalitis involving hypothalamus).
- **onset** typically in early adolescent boys (rarely in girls and adults).
- **course** - episodes last up to several weeks (with interval of 2-12 months between episodes); episodes decrease in frequency and severity with age; rarely present after 4<sup>th</sup> decade.
- **treatment** - **stimulants** (amphetamines, **METHYLPHENIDATE**);  
because of similarities to bipolar depression, **LITHIUM** has been used.

## SLEEP APNEA

**Sleep Apnea** – apnea > 10 sec, sukelianti hipoksiją; at least 5 episodes/hour.

**Sleep Hypopnea** - reduction in airflow by > 50% for at least 10 seconds.

**CENTRAL SLEEP APNEA / HYPOPNEA** – nutrūkstanti *respiratory center* veikla.

**OBSTRUCTIVE SLEEP APNEA / HYPOPNEA** – periodiška *kvėpavimo takų* obstrukcija.

N.B. trumpi apnea epizodai yra normalaus miego reiškinys!

### OBSTRUCTIVE SLEEP APNEA

Common and treatable disorder with serious complications!

- dažniausia sleep apnea rūšis (PREVALENCE – 4% **men**, 2% women, 1% children).

#### PATHOPHYSIOLOGY

- dėl pharynx raumenų hipotonuso (ypač *m. genioglossus* – liežuvio šaknies protrakcija į priekį) miegant kai kuriems asmenims įvyksta **pilna kvėpavimo takų obstrukcija** → apnea → hypoxia → **ligonis nubunda**.

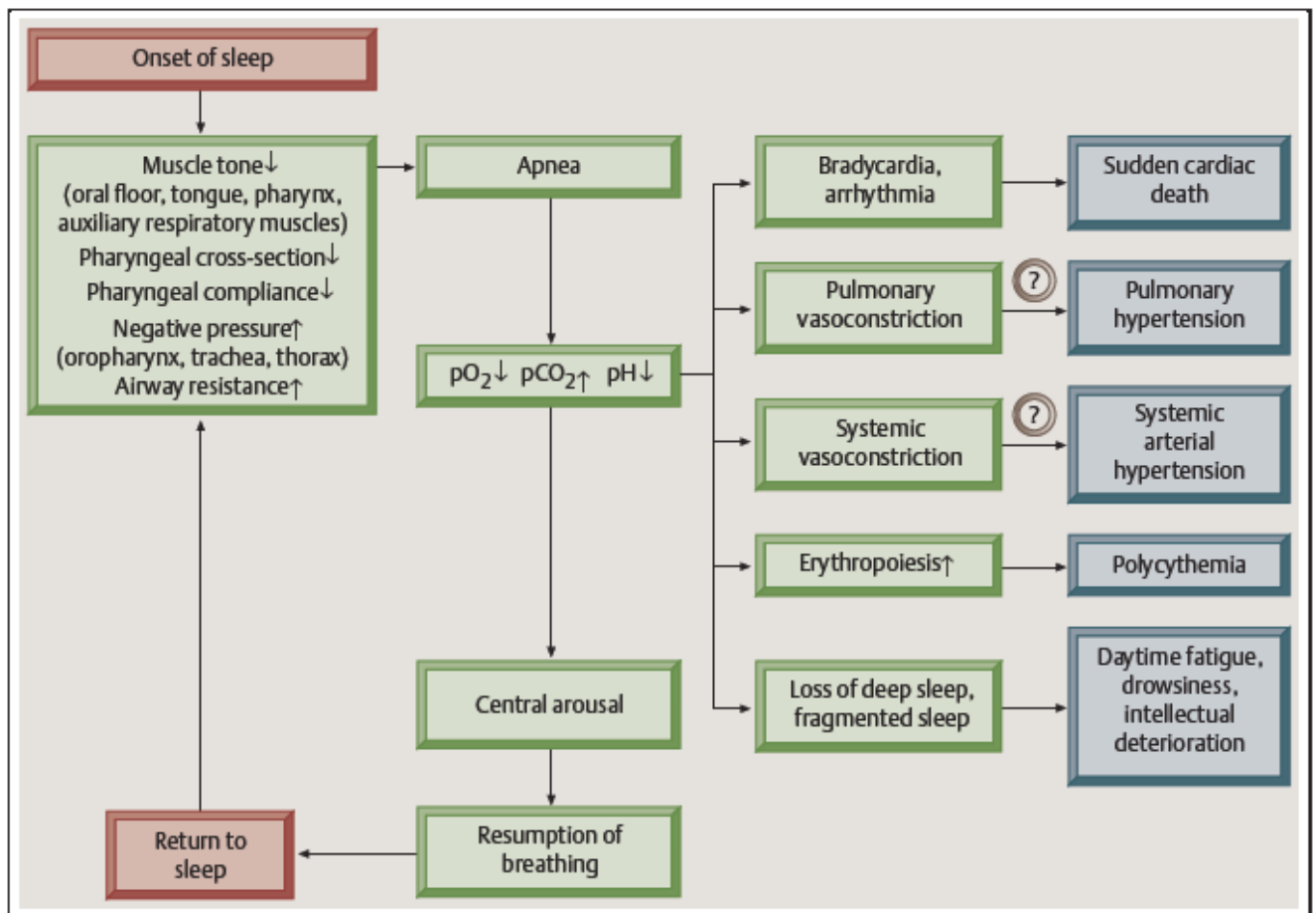
- **incomplete pharyngeal occlusion** (leads to **SNORING**) may cause decreased ventilation (hypopnea) → hypoxemia → arousals (sleep fragmentation), etc - *same functional effect as apnea!*
- obstruction occurs in pharynx (lacks supporting cartilage and bone).
- in severe cases, apnea-awakening epizodai kartojasi iki kelių šimtų kartų per naktį.
- SaO<sub>2</sub> falls at rate 0.1-1.6% per second (SaO<sub>2</sub> < 70% is common in severe obstructive sleep apnea).
- arteriolar constriction (as result of hypoxemia) → arterial hypertension.
- negative intrathoracic pressure (associated with attempts to breathe) → decreased cardiac output, increased vagal tone.
- apneas / hypopneas are longer **during REM sleep** (as long as 3 minutes) - associated with more severe hypoxemia.
- **ligonių gupės**:

1. **Obese with thick necks** (mégsta miegoti supine!)  $\approx$  65% patients
2. **Structural lesions** (e.g. **enlarged tonsils** and adenoids, pharyngeal tumors).
3. **Craniofacial malformations** (high arched palate, long low-placed soft palate, dental malocclusion, **retrognathia**).
4. **Abnormally compliant airway in Marfan syndrome**
5. **Neurological diseases** - incoordination of preinspiratory activation of upper airway dilators, mouth breathing with posterior mandible displacement, weakness of bulbar muscles.
  - differentiate from neurological diseases causing **diaphragmatic weakness** which is exacerbated by supine sleep (esp. REM sleep with muscle atonia – diaphragm remains the only muscle working for ventilation)  $\rightarrow$  **SLEEP HYPOVENTILATION** (H: nocturnal oxygen, sleep in semi-sitting position).

• precipitating factors:

1. CNS depressants – alcohol, hypnotics, etc
2. Sleeping supine
3. Sleep deprivation

In severe cases, apneas occur continuously throughout night and in all body positions!



**CLINICAL FEATURES**

Some patients have no complaints!

1. **Loud snoring** (sometimes > 90 dB) begins years before onset of sleep apnea.
  - Snoring will not occur even with very narrow pharynx if floppy tissue is absent!
2. **Nocturnal restlessness** – frequent brief *awakenings* (gasping for breath), *changes in body position* (attempts to find sleeping position compatible with airway patency - patients may sleep in chair, sitting up on side of bed, leaning against wall).
  - Despite restlessness, patients usually have impression that sleep has been continuous.

3. Frequent nocturnal urination (enuresis in children), sense that sleep is not restful.
4. Morning headaches, decreased libido.
5. **Excessive daytime sleepiness!!!** → impaired memory and concentration, etc

Major complaint is *hypersomnia*, not *insomnia*!

- apnea may worsen with age (may be due to weight gain).

### DIAGNOSIS

**Overnight polysomnography (sleep study)** – gold standard for diagnosis – respiratory muscle contractions, but no airflow →  $P_{O_2} \downarrow$

- reduced amounts of REM and stage 3-4 sleep.
- **apnea-hypopnea index (AHI)** – number of apneas / hypopneas per hour of sleep.  
 $AHI > 5$  is diagnostic of OSA

**MSLT** - excessive sleepiness.

**Airway anatomy assessments** (fiberoptic endoscopy) - limited value in determining site of obstruction because airway dynamics differ in sleep and wakefulness.

### COMPLICATIONS

- *life threatening!*:

1. Sequelae of excessive daytime sleepiness (motor vehicle accidents, etc)
2. Cardiac arrhythmias, arterial hypertension, pulmonary hypertension, MI, heart failure, stroke.

### TREATMENT

N.B. if *hypnotic* is administered because of incorrect diagnosis, restlessness and wandering in confused state may occur at night!

Whatever treatment is used, *outcome should be assessed with SLEEP STUDY* - many patients experience more subjective than objective improvement.

1. Avoid precipitating factors; do not sleep supine; pakelti lovos galvūgalį.
2. **Body weight** ↓
3. Removal of enlarged tonsils and adenoids
4. **Continuous positive airway pressure (CPAP)** by nasal mask - revolutionized management!
  - functions as air splint (use trial with polysomnography to determine pressure required).
  - effective in 80-90% patients.
  - can be used by children.
  - if nasal obstruction prevents use, treatment with decongestants, steroid inhalers, septoplasty, or other nasal surgery may be required.
  - more expensive **bilevel positive airway pressure (BPAP)** devices provide different pressures during inspiration and expiration; sometimes better tolerated (esp. by claustrophobic patients).
5. Special **orthodontic appliances** (pakelia soft palate, patraukia liežuvį ir mandible į priekį).
6. **ARMODAFINIL** – FDA approved to improve wakefulness during daytime.
7. Surgery (last resort):
  - a) **uvulopalatopharyngoplasty (UPPP)** - removal of *uvula*, portions of *soft palate*, and redundant *pharyngeal tissue* - eliminates snoring in > 80%, produces improvement in 50% patients. N.B. complete resolution of sleep apnea is uncommon!
  - b) **laser-assisted UPP** - staged outpatient procedure; less effective than standard UPP.
  - c) **maxillofacial surgery** (advancement of mandible, maxilla) - for selected patients.
  - d) tracheostomy



## UPPER AIRWAY RESISTANCE SYNDROME

- pharyngeal narrowing with high resistance to airflow associated with *compensatory increased respiratory effort* → no hypoxemia, but still leads to arousals (sleep fragmentation).
- differences from obstructive sleep apnea:
  - body weight tends to be normal or near-normal.
  - higher proportion of women and children.
  - no hypoxemia-related complications!
- during diagnostic polysomnography add *intraesophageal pressure measurement*.

## CENTRAL SLEEP APNEA

- nutrūkstanti respiratory center veikla.
- < 10% sleep apnea cases.
- kartais aptinkama *decreased chemoreceptor sensitivity* to  $P_{O_2}$ ,  $P_{CO_2}$ .
- sunkiausia forma – **ONDINE curse**.
- etiology:
  - 1) idiopathic
  - 2) congestive heart failure
  - 3) caudal brain stem pathology (poliomyelitis was classic disorder).
 N.B. normoje miego metu jau trumkas  $P_{CO_2}$  nedaug ↓
- galima SIDS (sudden infant death syndrome) priežastis.
- **polysomnography** – no respiratory muscle contractions, no airflow →  $P_{O_2}$  ↓.
- treatment:
  - a) respiratory stimulants
  - b) bilevel positive airway pressure (BIPAP) ventilation
  - c) implantable phrenic nerve stimulator (diaphragmatic pacing).

## PERIODIC LIMB MOVEMENT DISORDER (PLMD), RESTLESS LEGS SYNDROME (RLS)

**PLMD (s. NOCTURNAL MYOCLONUS)** - stereotyped periodic **LEG MOVEMENTS DURING SLEEP**.

- movements typically last for  $\approx 0,5-5,0$  second and occur periodically at 20-40 second intervals for minutes ÷ hours during sleep.
- consist of **great toe** extension (as in Babinski) + triple flexion (i.e. **ankle** dorsiflexion + **knee** flexion + **hip** flexion).
- although originally described as "myoclonic" (Sir Charles Symonds in 1953), these movements are not as jerky and do not occur in isolated muscles.
- movements occur primarily in light NREM sleep and disappear with REM atonia; *movements cause arousals*.

**Sleep-maintenance insomnia** or **excessive daytime sleepiness**

(disorder may be **asymptomatic** - as incidental finding on polysomnogram or because spouse is unable to sleep owing to leg kicks).

- PATHOPHYSIOLOGY unknown;
  - disinhibition of CNS pacemaker that affects reticular excitability?

- similarity to Babinski sign or triple flexion response suggests pyramidal / dorsal reticulospinal tract dysfunction.
- PREVALENCE 5% in age 30-50 years and 30-45% in > 65 years.
- NEUROLOGIC EXAMINATION normal!
- DIAGNOSIS – *polysomnography* with bilateral anterior tibialis EMG.
- DIFFERENTIAL DIAGNOSIS – **hypnic jerks (s. sleep starts)** - do not recur periodically.  
N.B. most **movement disorders** are inhibited by sleep!

**RLS** - **UNPLEASANT SENSATIONS IN LEGS** (vs. PLMD – no such sensations); all 4 diagnostic criteria must be fulfilled:

- 1) **urge to move**; usually accompanied / caused by uncomfortable and unpleasant sensations in legs (sometimes urge to move is present without uncomfortable sensations and sometimes arms or other body parts are involved in addition to legs).
  - 2) urge to move / unpleasant sensations **begin / worsen at rest** (such as lying or sitting).
  - 3) partially or totally **relieved by movement** (walking or stretching).
  - 4) worse in evening-night than daytime
- gradual buildup of deep crawling (“ants crawling under skin”), pulling, itching, aching, “pins-and-needles” in muscles or bones of calves and thighs.
  - as sensation builds, associated **urge to move** gradually becomes irresistible and *movement / walking / rubbing provides temporary relief*.
  - worse at rest, in evening and at night → *difficulty getting to sleep ± frequent awakenings* (flex and extend legs, repeatedly turn over in bed, get out of bed and walk, etc).
- Sleep-onset insomnia** is rule!
- 80-90% RLS patients have PLMD (contributes to awakenings), but reverse is not case.
  - symptoms *disappear by early morning* (patient then can obtain more refreshing sleep).
  - actual CAUSE not known (thought to result from abnormalities in dopamine neurotransmission possibly triggered by CNS iron dysregulation).
    - may be induced / aggravated by *iron deficiency anemia!!!, chronic renal failure, pregnancy* (10-20% pregnant women; usually resolves postpartum), *withdrawal from hypnotics*.
  - PREVALENCE ≈ 7% for adult population (increases with age).
    - 30-50% patients have affected family members.
    - women : men = 2 : 1.
  - symptoms begin after age 40.
  - NEUROLOGIC EXAMINATION usually normal, except of *waking dyskinesias* (during attempts to remain still, many patients fidget, swing legs, have movements similar to extensor movements during sleep); vs. PLMD – no waking dyskinesias.
    - **forced immobilization test** may provoke dyskinesias.
    - *peripheral neuropathy* may be factor in some cases, although peripheral nerve function is clinically normal.
  - variable course - some have long periods of stability, whereas others worsen with age; permanent remissions are rare.
  - DIAGNOSIS is based on *history*.  
Most important question "Do your legs keep you from falling asleep?"
  - DIFFERENTIAL DIAGNOSIS:
    - 1) **akathisia** - body restlessness and compulsion to move, but sensory component is less than with RLS and not exacerbated at night.
    - 2) **peripheral neuropathy** - dysesthesias are more distal, felt more on surface, ± not relieved by movement.
    - 3) **claudication** - relieved by rest.
    - 4) **leg cramps** - palpable tightness of muscles.

- 5) positional discomfort, arthritic disorders
- 6) anxiety disorders

**TREATMENT**

**DOPAMINERGIC AGONISTS** - bedtime dose:

- a) **LEVODOPA** + (**CARBIDOPA** or **BENSERAZIDE**)
  - b) **ROPINIROLE** (potent D<sub>2</sub>-agonist) – FDA approved for RLS.
  - c) **ROTIGOTINE** transdermal low-dose patch
- some patients require additional doses during night (or controlled-release formulations).
  - some patients develop tolerance, increased daytime symptoms of restless legs.  
H: temporary withdrawal and reinstatement or levodopa-carbidopa around clock.

**BENZODIAZEPINES** (particularly **CLONAZEPAM!!!**) - prevent awakening but not nocturnal movements.

**OPIATES** (**PROPOXYPHENE**, **CODEINE**, **HYDROCODONE**) reduce unpleasant sensations in severe cases.

**OTHER DRUGS** (**CLONIDINE**, **BACLOFEN**, **CARBAMAZEPINE**, **GABAPENTIN\***) are sometimes helpful.

\*FDA approved extended-release tablets!!!

BIBLIOGRAPHY see p. S40 >>