Sleep and wake disorders

5th scholar year

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Examination in sleep disorders

- Medical history (including „objective“ – third party - anamnesis)
- Questionnaires, scales
- Laboratory tests

Medical history

Family history

- Biological hereditability – e.g. in case of restless leg syndrome
- Psychosocial value of disease in a family (secondary benefits) – e.g. insomnia
- Psychiatric and neurological disorders, addictions!

Social history

- Regularity of life regimen
  Shift work schedule/night shifts

- Common bedroom/shared bed (= objective information about behavior during sleep)

Medications (including addictions and withdrawal)

Special attention to:

- hypnotics
- sedative medication, antipsychotics, antidepressants
- psychostimulants
- thyroid hormones, thyroid suppressants (insomnia/sleepiness)
- beta blockers (insomnia)
- statins (insomnia)
- L-DOPA and dopamine agonists (sleepiness, delirium)
- antiallergic medication (sleepiness)

Sleep/wake anamnesis

- Evening: going to bed/falling asleep (time, circumstances)
- Night: continuity of sleep, snoring, abnormal movements / behaviour etc.
- Morning: awakening/getting up (time, circumstances, feeling of being refreshed)
- Daytime: quality of wakefulness, planned naps, unwanted sleep

THE EPWORTH SLEEPINESS SCALE*

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

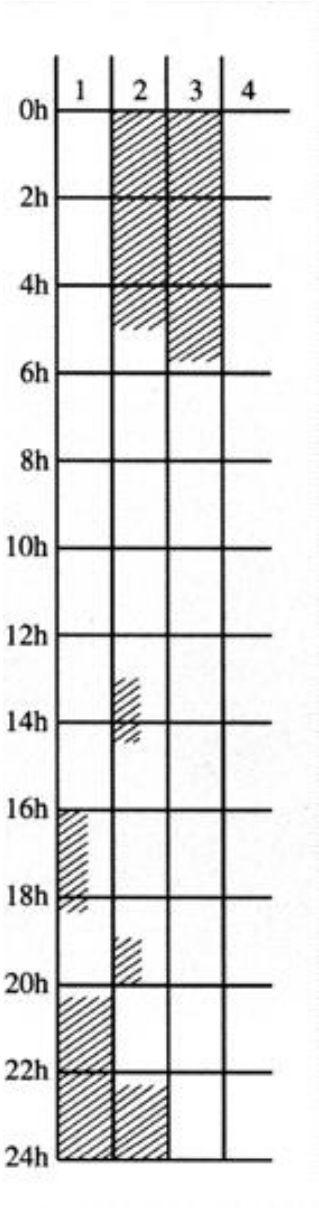
SITUATION	CHANCE OF DOZING
Sitting and reading	_____
Watching TV	_____
Sitting, inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____

TOTAL = _____

<10 normal vigilance
≥10 excessive daytime sleepiness

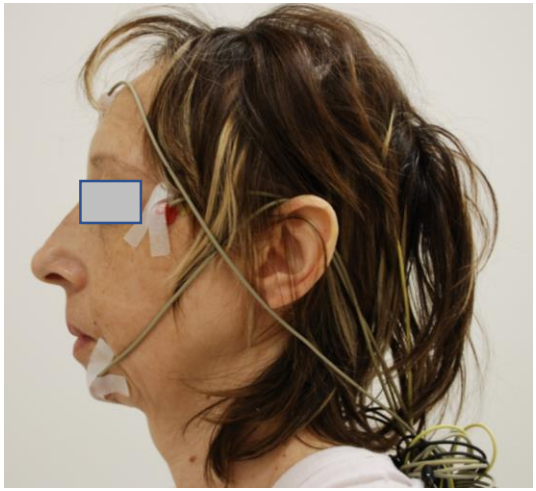
Sleep diary /sleep log

(different layouts)
Usually period of 2-4 weeks



- Quick information about long-term period
- Tool of the cognitive behavioral therapy (CBT) of insomnia

Night sleep - polysomnography

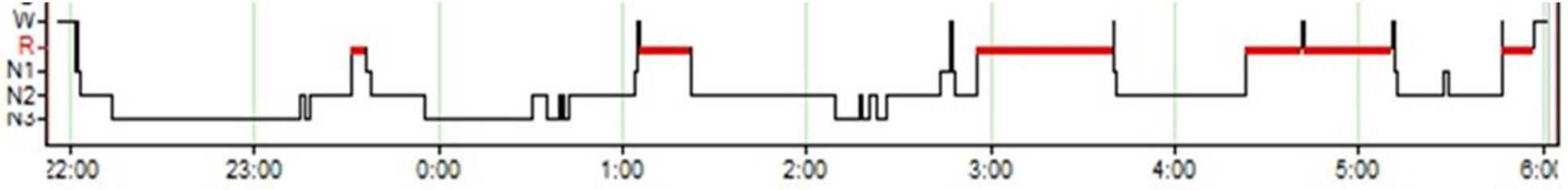


Basic parameters:

- **electroencephalography (EEG)**
- **eye movements (EOG)**
- **chin muscle aktivity (EMG)**

Other parameters:
respiration (air flow + respiratory movements), O_2 saturation (puls oxymetry), ECG, body position, leg movements ….
Video

Hypnogram



- sleep cycles (NREM/REM cycles)
- un-/interrupted course (awakening >15 s, arousal <15 s)
- sleep onset latency
- REM sleep latency
- duration of individual sleep stages and of wake after sleep onset

Sleep efficiency:
sleep duration/time in bed x 100 (%)

Daytime: Multiple Sleep Latency Test - MSLT

- Dark, calm room
- 20-minute opportunity to fall asleep for 15 minutes
- 5x in 2-hour intervals (first 9.00 a.m.)
- *Instructions: Close your eyes and do not resist sleep.*

Results:

- Mean sleep latency (measure of daytime sleepiness)
  < 8 minutes – excessive daytime sleepiness
- Eventually presence of REM sleep (sign of narcolepsy)

Sleep and wake disorders

- Insomnia
- Sleep related breathing disorders
- Central hypersomnias
- Circadian rhythm disorders
- Parasomnias
- Sleep-related movement disorders

- Sleep disorders in other medical conditions

Insomnia

insomnia disorder x insomnia symptom

Insomnia generally - (subjectiv) difficulty
- initiating sleep
- maintaining sleep (sleep continuity)
- waking up earlier than desired

Insomnia Disorder
- dysfunctional features during wakefulness!
- adequate opportunity and condition to sleep
- not better explained by another sleep disorder (e.g. RLS)
- not caused solely by another disease

=comorbidity does not explain sufficiently insomnia
(comorbidity prevalence - 70-90%)

Chronic and Short-Term Insomnia Disorder (cut-off duration: 3 months)

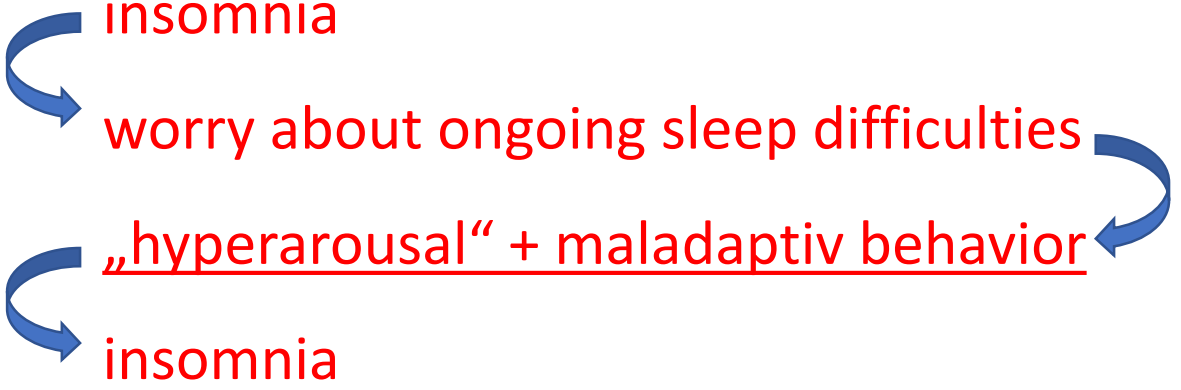
Lifelong prevalence: Chronic 5-10%, Short-Term 30- 50%

Insomnia Disorder
„dysfunctional features during wakefulness“ - condition sine qua non!

- Fatigue/malaise.
- Attention, concentration, or memory impairment.
- Impaired social, family, vocational, or academic performance.
- Mood disturbance/irritability.
- Daytime sleepiness.
- Behavioral problems (e.g., hyperactivity, impulsivity, aggression).
- Reduced motivation/energy/initiative.
- Proneness for errors/accidents.
- **Concerns about or dissatisfaction with sleep.**

Excessive focus on and worry about ongoing sleep difficulties and their associated daytime consequences. Thoughts about ongoing sleep difficulties are amplified as bedtime approaches.
Anxiety about sleep is common.
Although many patients with insomnia may appear anxious and worry-prone, their anxiety and worry are often focused mainly on their sleep difficulties.

Pathophysiology – circulus vitiosus



Nonpharmacological treatment

Cognitive behavioral treatment - CBT

Pharmacological treatment

Short-term insomnia disorder or insomnia symptom → prevent chronification

chronic insomnia disorder – psychotherapy is not available/effective, the patient prefers pharmacotherapy

- benzodiazepine receptors agonists
  - nonbenzodiazepine hypnotics, Z hypnotics
  - benzodiazepines

Short-term medication (max.4 weeks)

Intermitent medication

Side effects:
- Addiction
- Tolerance
- Insomnia rebound

- Sedating antidepressants (e.g. trazodone)
- Melatonin (elderly)
- Antipsychotics (atypic) – ultimum refugium

Insomnia symptom

- Wrong lifestyle regimen
- Stimulant substances
- Irregular (e.g. shift work) regimen
- Addictions
- Psychiatric conditions (anxiety, depression, schizophrenia)
- Medications
- Other sleep disorders (restless legs syndrome, sleep apnea, circadian disturbances)
- Neurological diseases (Parkinson s disease, stroke, brain injury ....)
- Other somatic diseases: arrhythmias, heart insufficiency, asthma, bronchitis, gastroduodenal reflux, pollakiuria
- PAIN

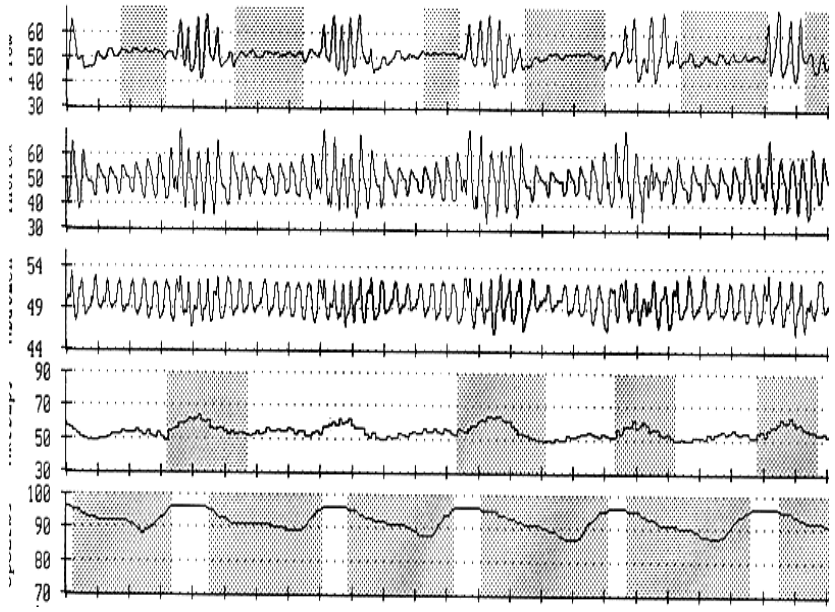
Sleep related breathing disorders

- **Obstructive sleep apnea**
- **Central sleep apnea**
- **Hypoventilation**
  - related to obesity
  - related to lung diseases
  - related to neuromuscular diseases

Sleep apnea

Obstructive - OSA

more common -prevalence 2-10% !



flow

thorax

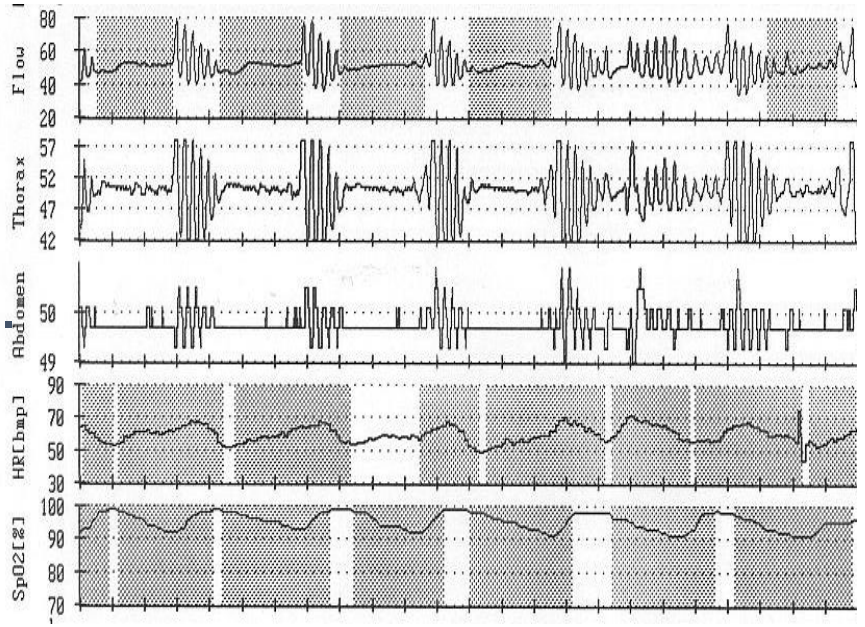
abdom.

HR.

O_2

4 min

Central - CSA



4 min

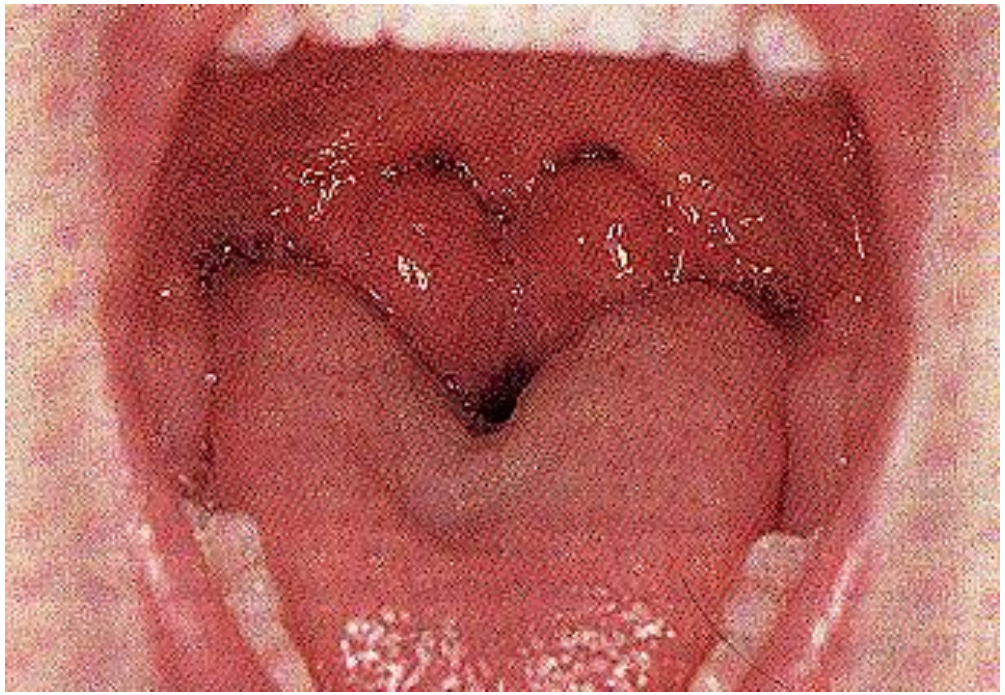
Etiopathogenesis

Anatomic narrowing of upper airway

CSA in heart failure:

- slower blood flow
- longer time between lungs and chemoreceptors.
- hyperregulation – Cheyne-Stokes breathing

Obstructive sleep apnea:
Enlarged tonsils block pharyngeal gate (a child)



healthy

Sagittal section – middle line

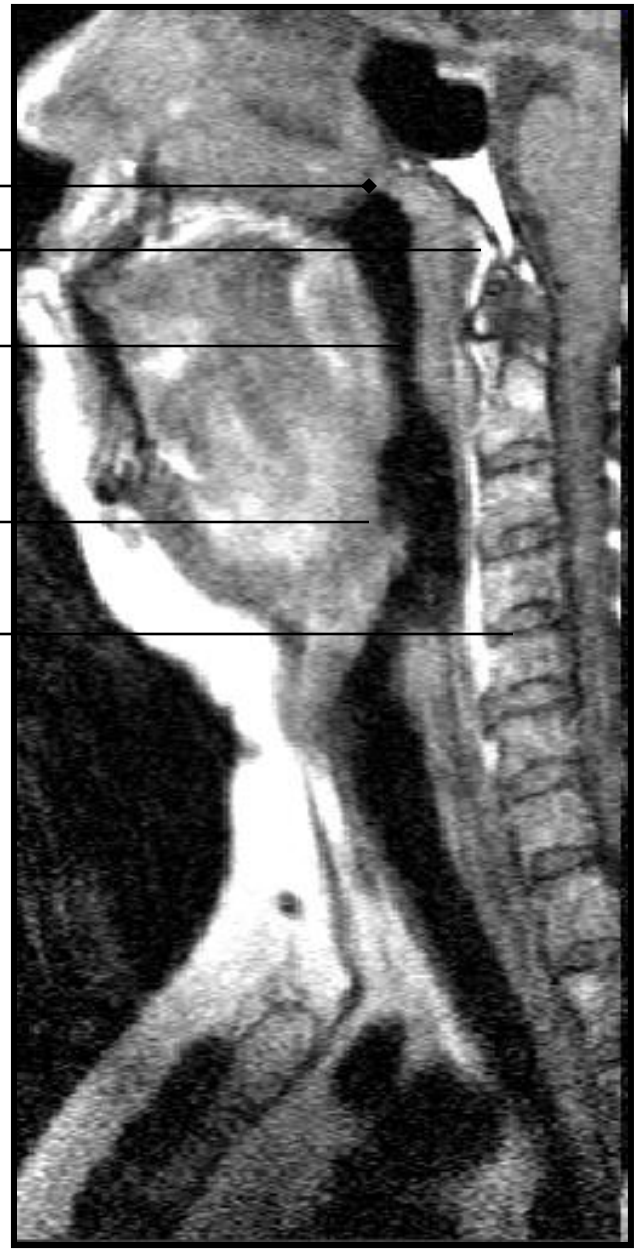
apneic

nasopharynx

velopharynx

retrobasilingual space

Hyoid level



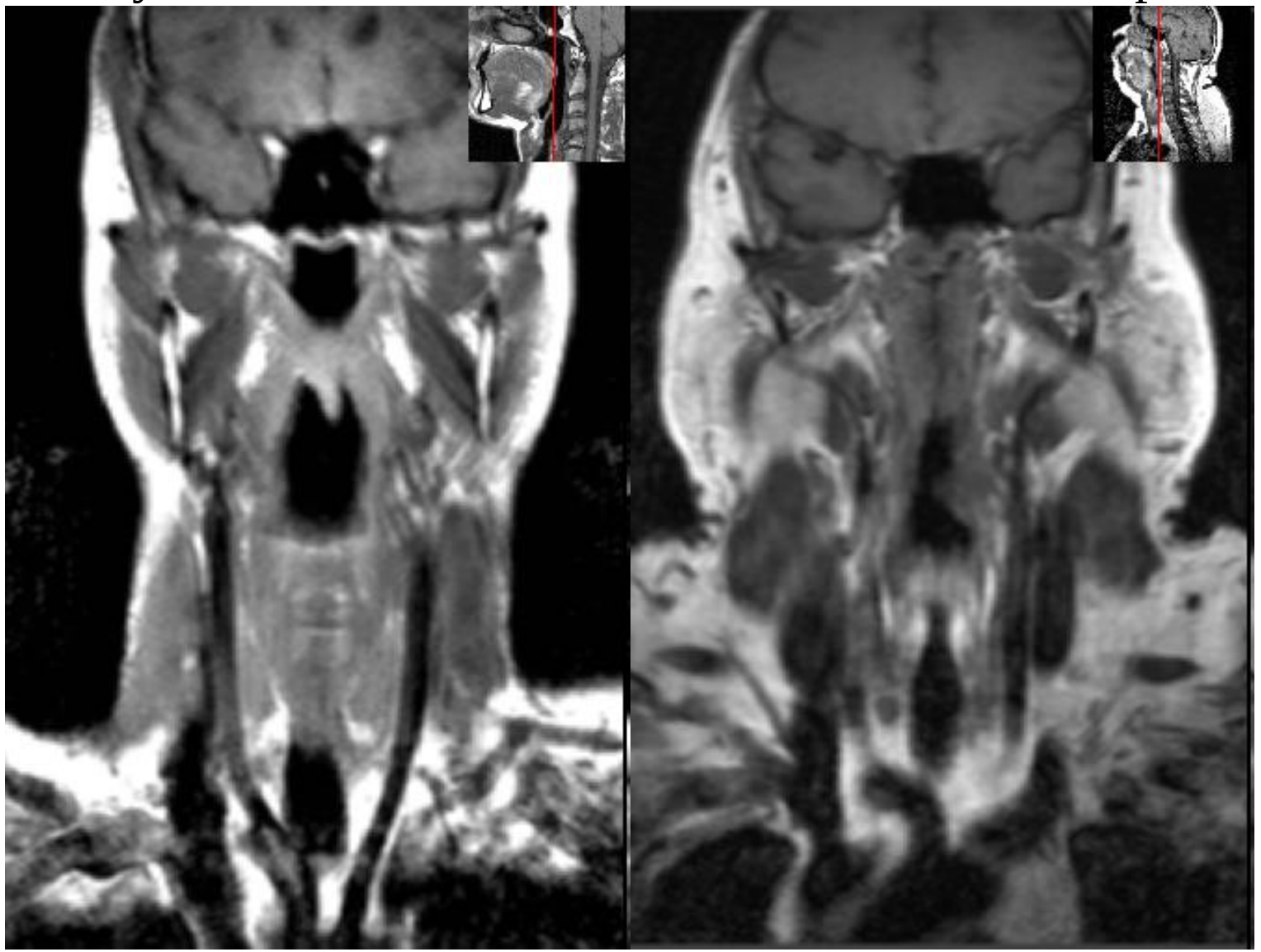
healthy

apneic

Coronary sections

healthy

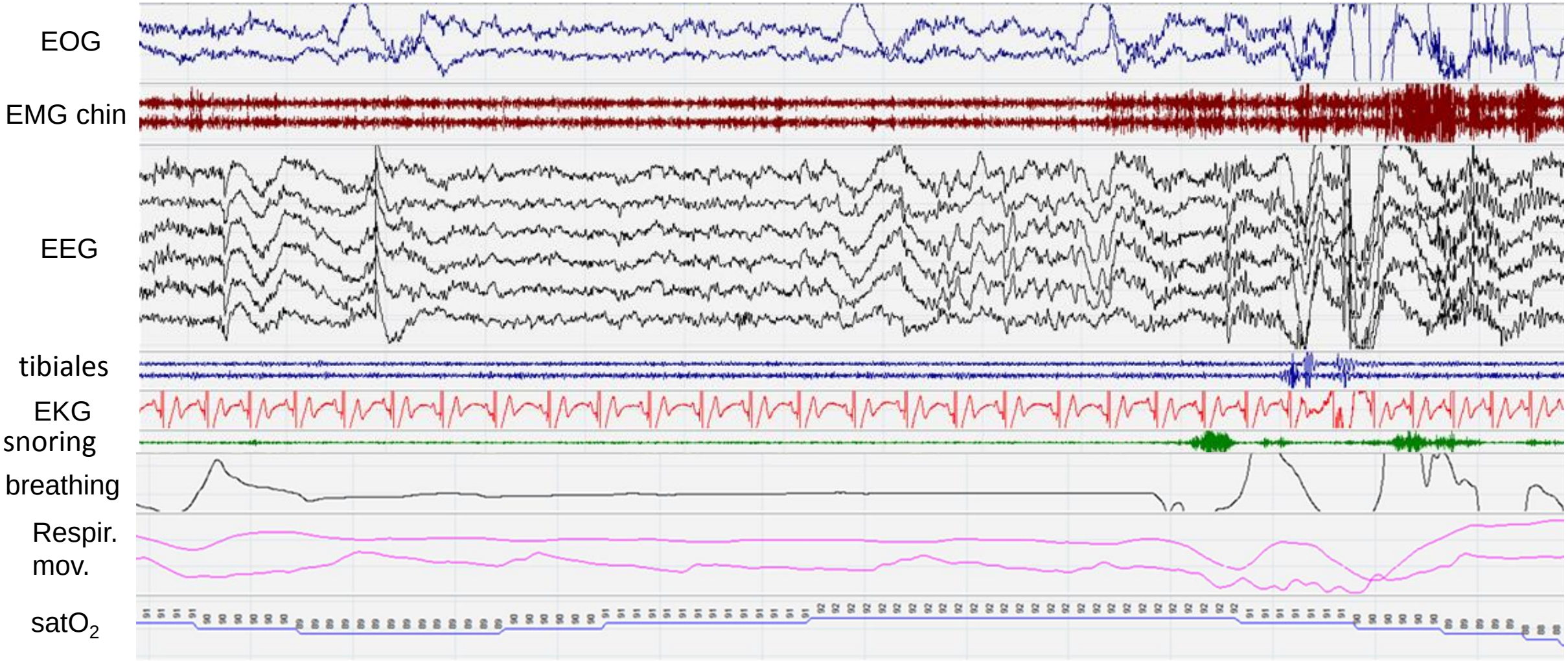
apneic



healthy

apneic

Apnea termination – arousal with sympathetic activation (tachycardia,rise of blood pressure, increased muscle tone etc.)



Obstructive sleep apnea – main quantitative parameter

AHI – apnoe/hypopnoe index

= number of apneas and hypopneas per 1hour

cut-off: AHI > 5

ODI – oxygen desaturation index

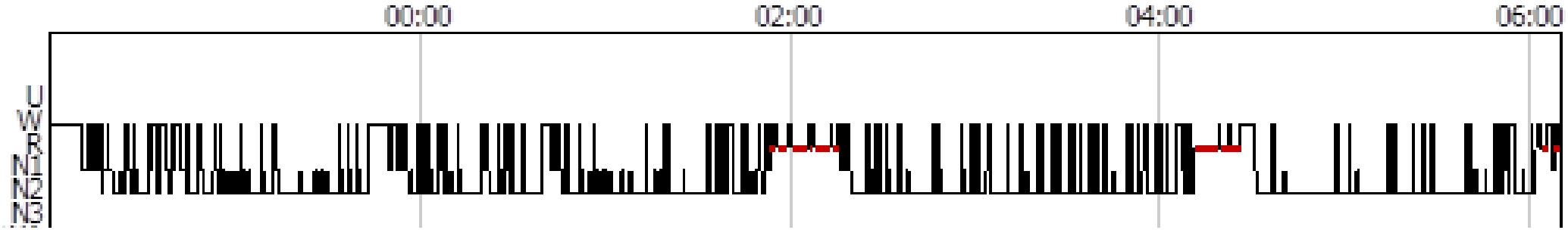
number of saturation dips per 1hour

Consequences of obstructive sleep apnea (OSA)

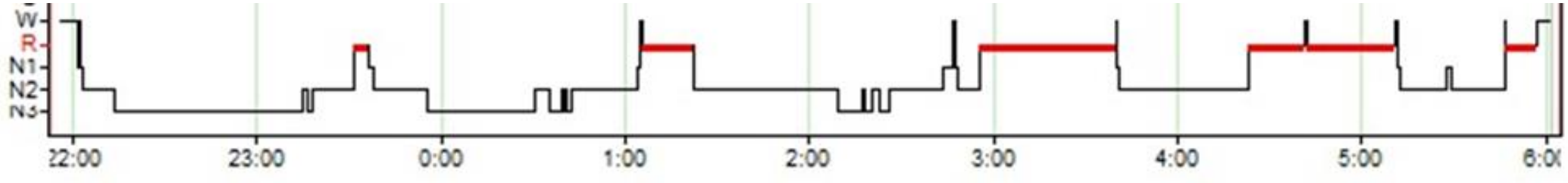
OSA: sleep fragmentation

127 awakenings,
N3 sleep absent ,
reduced REM sleep

OSA

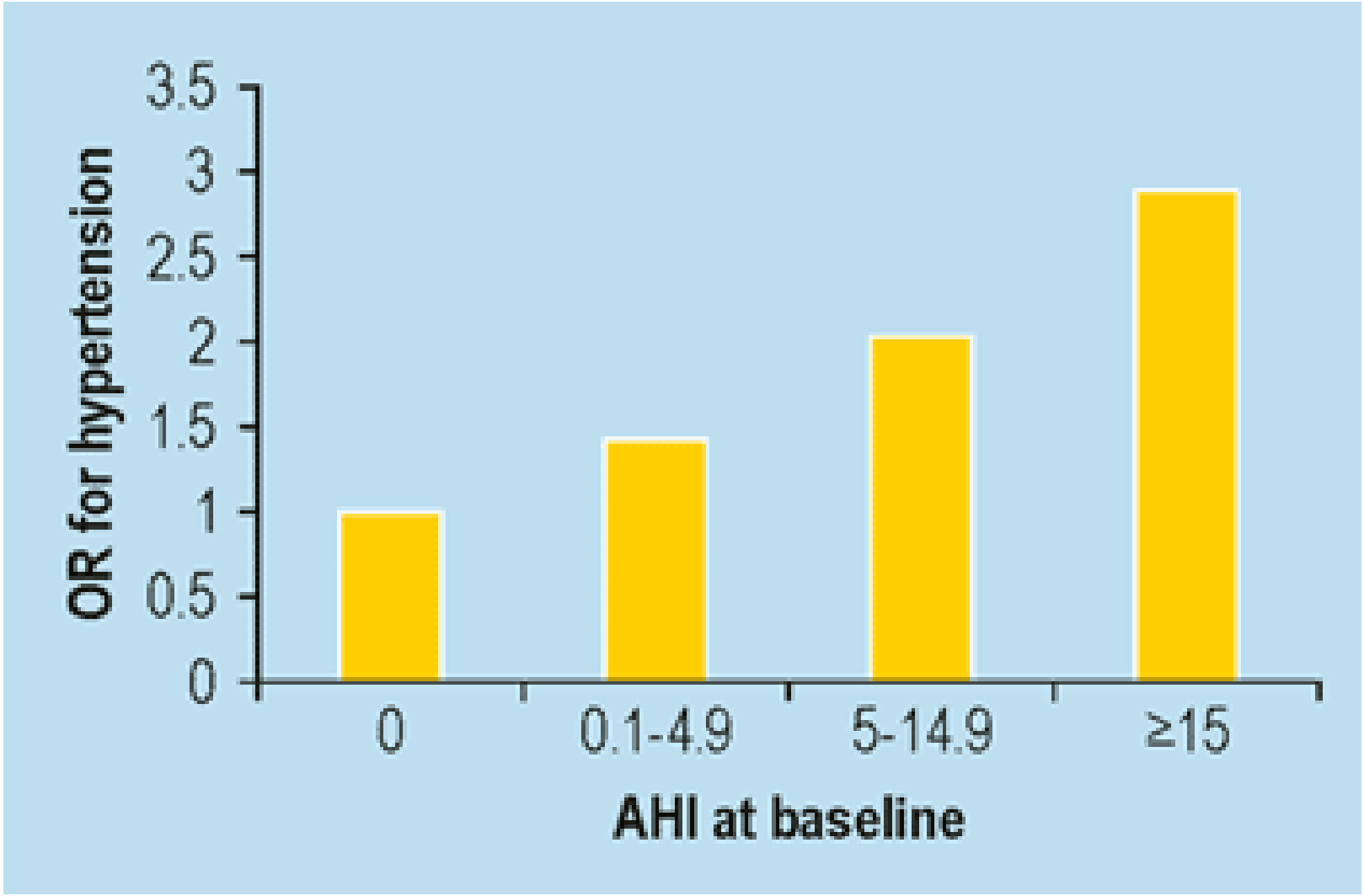


NORM



Consequence:
Excessive daytime sleepiness

OSA and hypertension

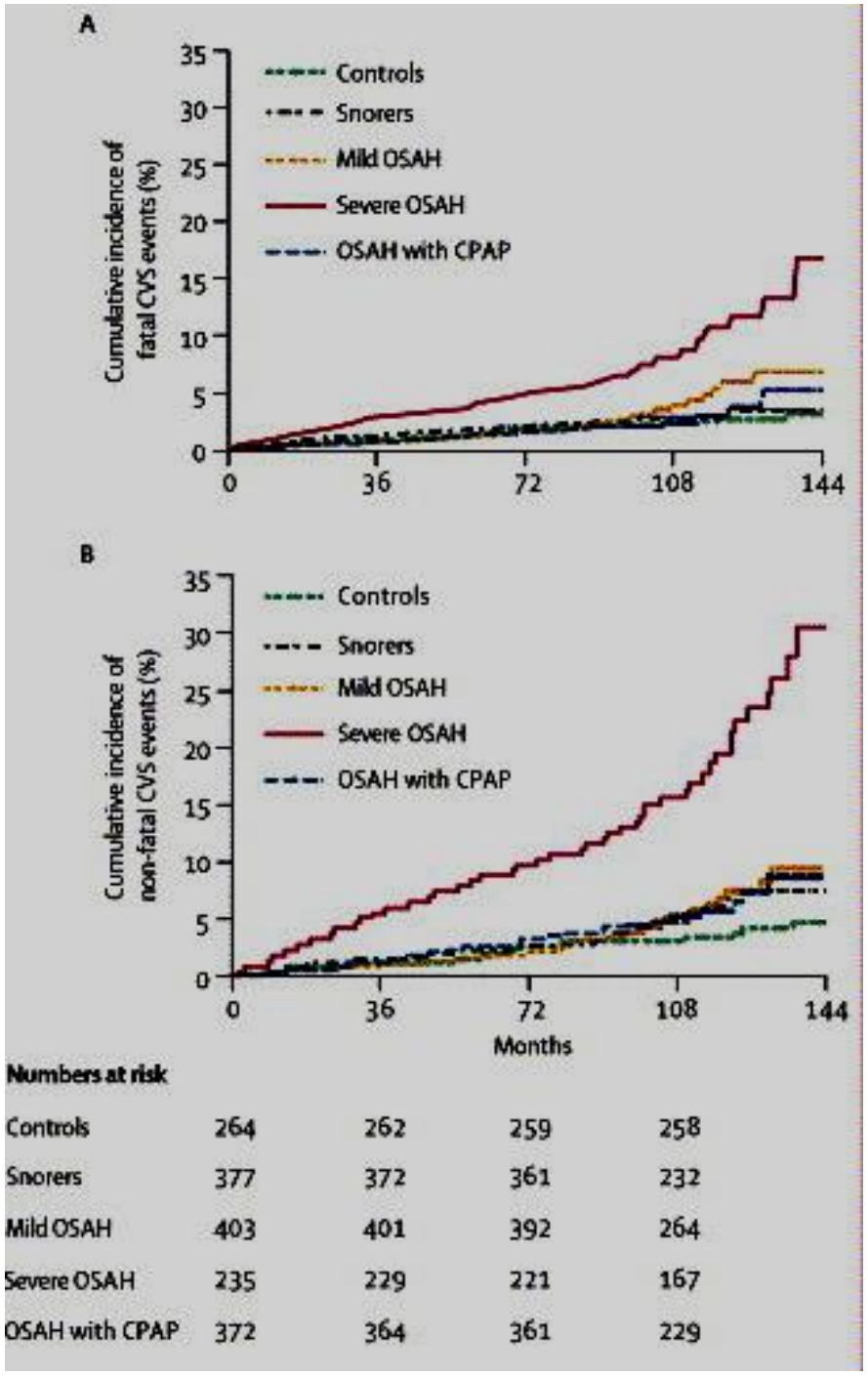


Wisconsin Sleep Cohort Study

Fatal cardiovascular events

Non-fatal cardiovascular events

>10 years



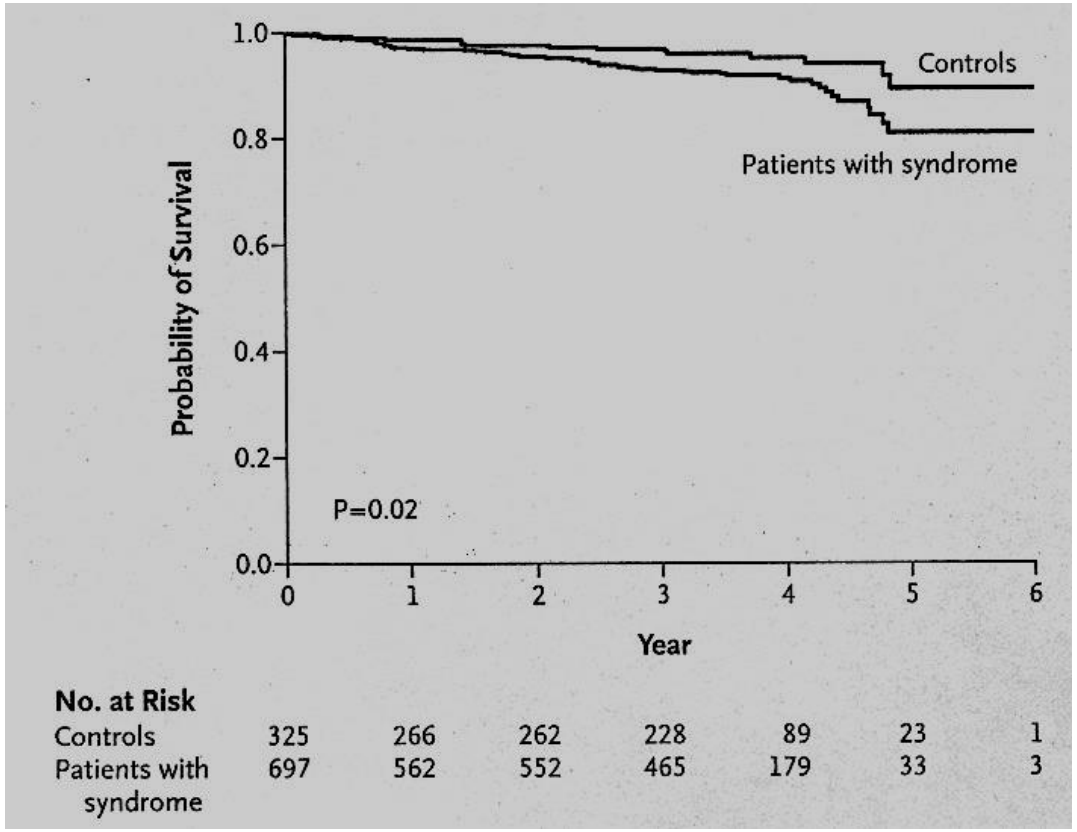
Marin et al, Lancet 2005

Yaggi et al, NEJM 2005:

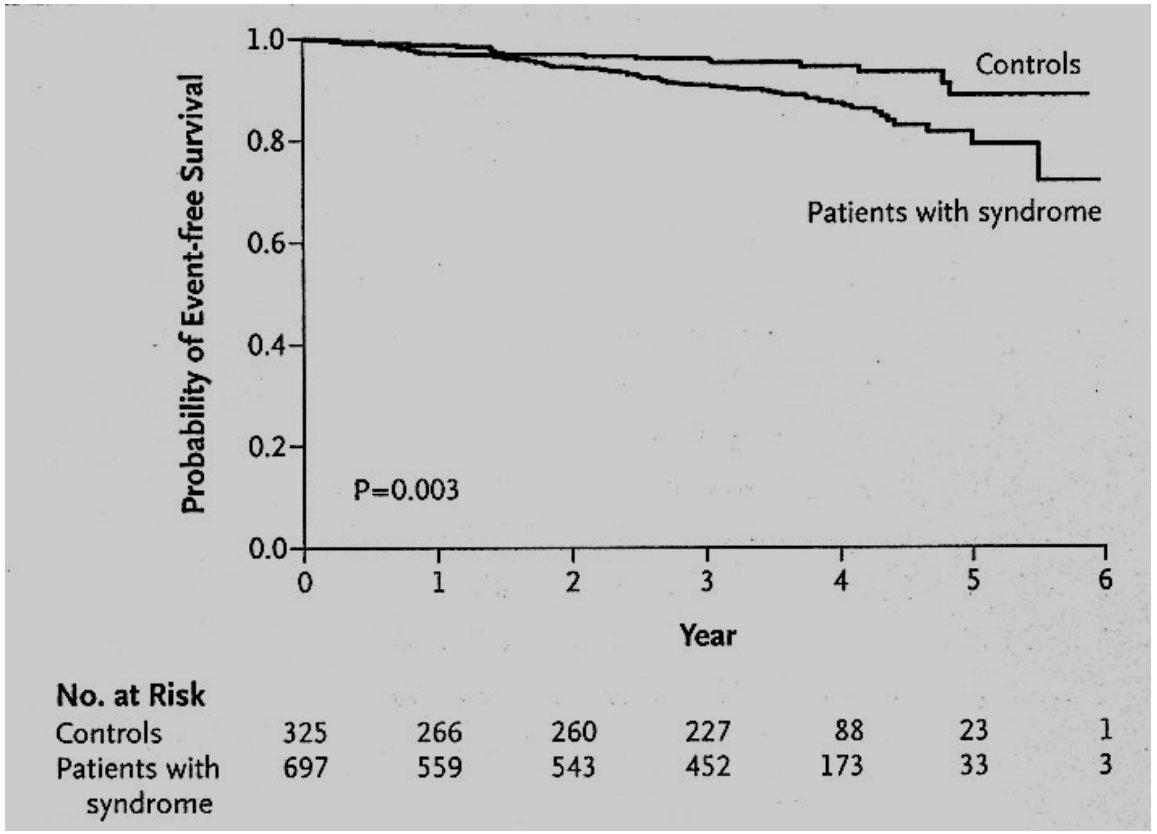
1022 subjects: 697 OSA (AHI≥5); 325 controls

OSA: adjusted likelihood of stroke or death 1.97 (95% interval 1.12-3.48, P=0.01)

death



stroke



Consequences of sleep apnea – *to remember!*

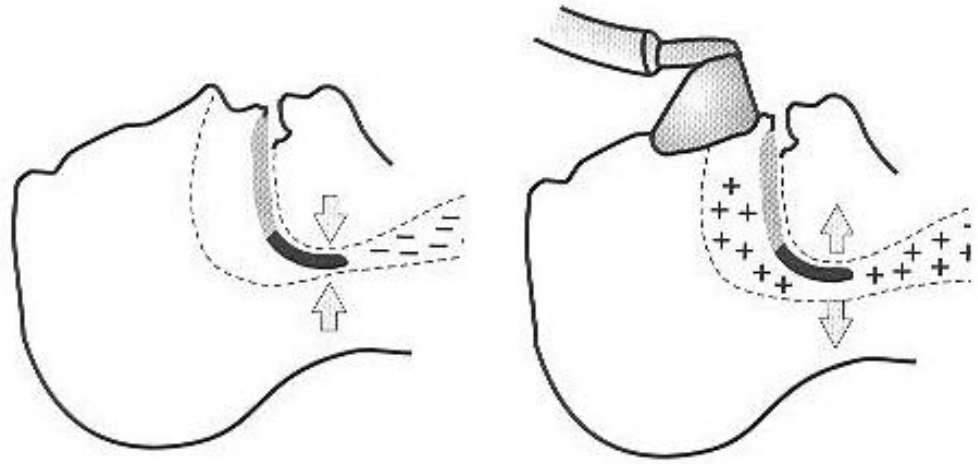
- Fragmented sleep and excessive daytime sleepiness
- Increased mortality
- Higher incidence of hypertension, coronary artery disease and stroke
- Higher incidence of metabolic diseases (diabetes typ 2 and atherosclerosis)

Treatment of obstructive sleep apnea

- Weight loss
- Sleeping on a side
- Regular regimen and sufficient sleep duration
- Orthodontic mandibular protraction

Surgery (anatomical abnormalities, othewise healthy patients
- Uvulopalatopharyngoplasty
- Tonsillectomy – children
- Maxillary mandibular advancement
- Septoplasty

CPAP – Continuous Positive Airway Pressure during sleep



Sleep-related hypoventilation/hypoxia in neuromuscular diseases and obesity

Insufficient function of „respiratory pump“

(comorbid obstructive sleep apnea)

Treatment:

underlying disease – if possible,

non-invasive/invasive ventilation

Obesity hypoventilation syndrome
(„Pickwickian syndrome“)

Central hypersomnias

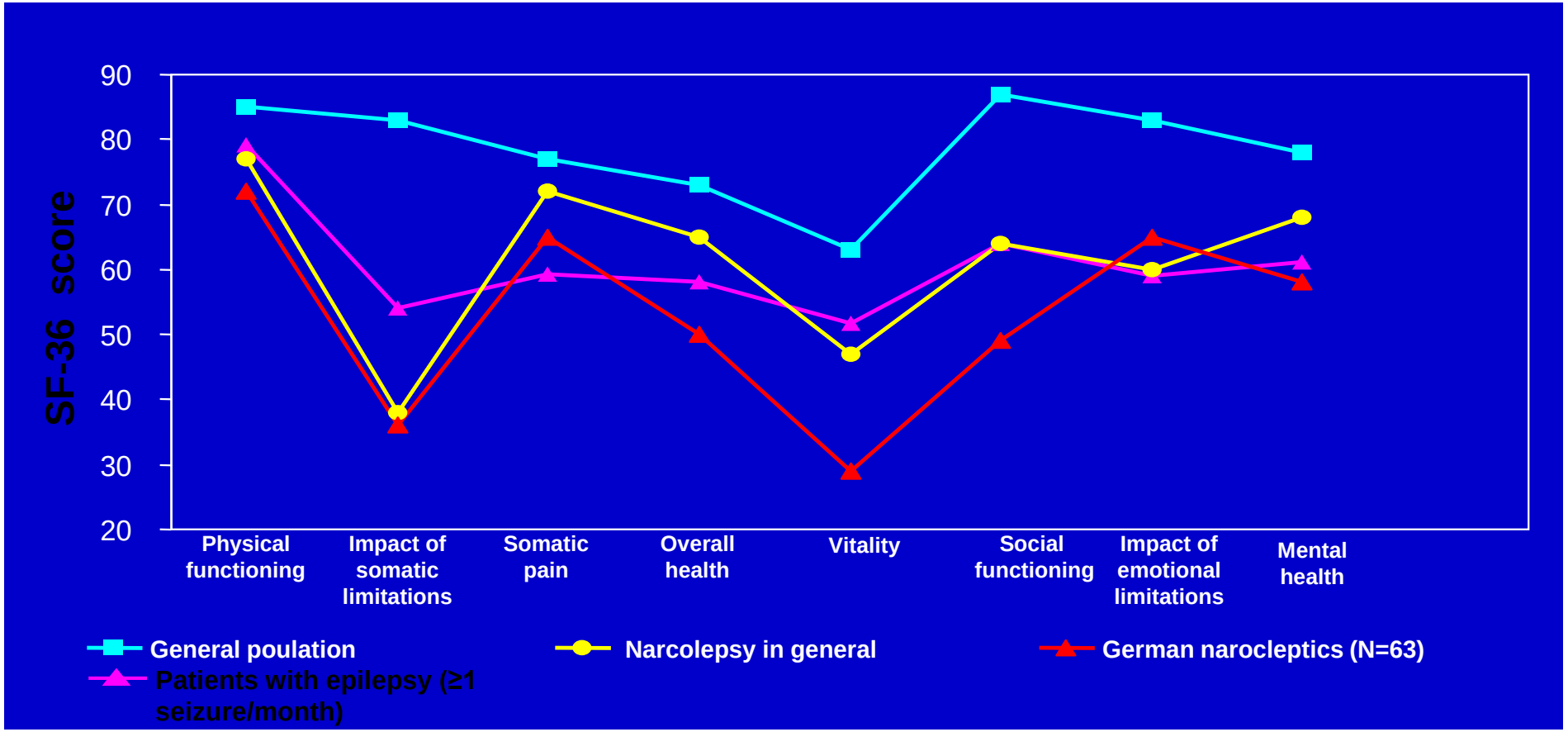
- Narcolepsy with cataplexy **(narcolepsy type 1)**
- Narcolepsy without cataplexy **(narcolepsy type 2)**
- Idiopathic hypersomnia
- Reccurent hypersomnia (Kleine-Levin syndrome)

Narcolepsy

Prevalence 0,02-0,05%

Late diagnosis!

Narcolepsy - reduced quality of life!



SF-36 - questionnaire used to assess and compare quality of life between different diseases

Data from general population and narcolepsy in general: Ware et al. 1993; German narcoleptics with courtesy of G Mayer. Data from patients with epilepsy: Baker et al. *Epilepsia* 1997;38:353-362.

Narcolepsy – clinical symptoms

Both types of narcolepsy

- Excessive daytime sleepiness

Narkolepsie with cataplexy (typ 1) – symptoms of dissociated REM sleep

- Cataplexy
- Hypnagogic hallucinations
- Sleep paralysis

Fragmented night sleep (mostly typ I)

Narcolepsy – excessive daytime sleepiness

Falling asleep, sometimes without preceding sleepiness, sometimes imperative. Duration – up to 30 minutes. Several naps per day. Refreshing sleep

Episodes of sleepiness

Automatic behavior (after falling asleep during certain activity)

Cataplexy

Sudden, fast progressing (and fluctuating) more or less complete **symmetrical loss of muscle tone after emotional response** (laughter, excitement, surprise…):

Feeling of weakness – loss of facial expression – lost capability of word pronouncing - incapability of holding objects in own hands – drooping of the knees – incapability of standing – fall.

Breathing, swallowing and eye movements preserved.

Consciousness and wakefulness not altered.

Duration – mostly <2 min

Frequency of occurence varies (up to several times per day)

Pathognomonic symptom of narcolepsy with cataplexy

Sleep paralysis

- „Paralysis“ like REM-sleep associated atonia
- After awakening or before falling asleep (incl. daytime sleep)
- Respiration not constricted
- Consciousness and eye movements not altered
- Very unpleasant experience
- Termination – spontaneously
- Frequently accompanied by hypnagogic hallucination
- Occurence – infrequent or several times per week (more common in younger patients), ceases to occur after years of disease duration

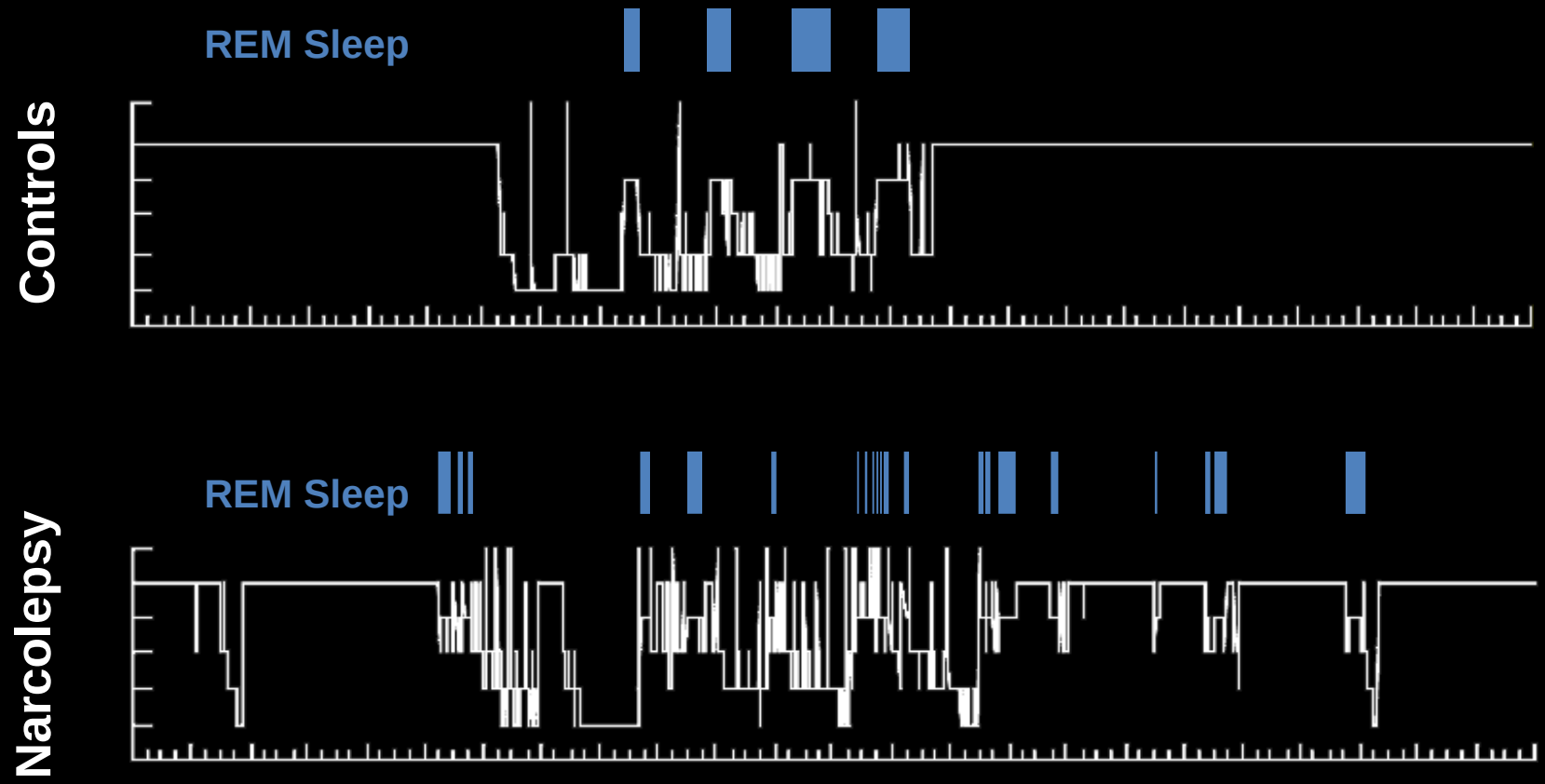
(May occur sporadically in healthy young people)

Hypnagogic (hypnopompic) hallucinations/pseudohallucinations

- Hallucinations before falling asleep or after awakening (even during daytime)
- Visual, tactile, auditory
- Often complex, terrifying (thieves, fire, corpses, torture, monsters...)
- Frequency of occurence varies (more common in younger patients)

(may occur sporadically in healthy people, especially in youth, but usually lack complex character)

Narcolepsy during night: Poor-quality sleep
Sleep onset REM (SOREM)
Dreams (often dramatic and nightmarish)
REM sleep behaviour disorder



Etiopathogenesis of narcolepsy with cataplexy (type 1):

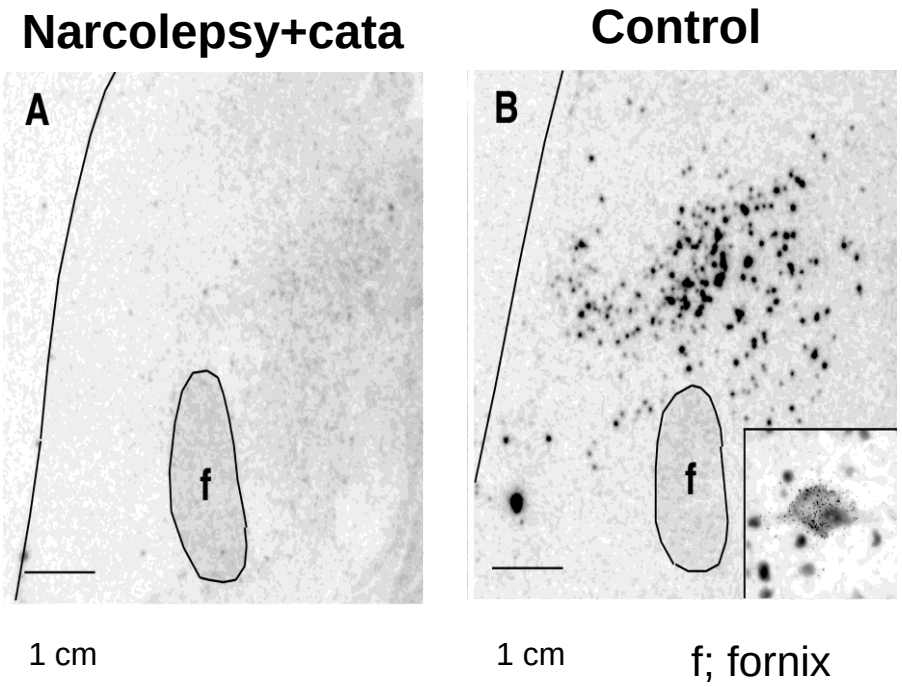
Disappearance of hypocretin neurons in lateral hypothalamus and hypocretin deficiency

Genetic disposition:
HLA DQB1*0602 +

External trigger: stress, infection
(H1N1, streptococcal)

Autoimmune event against hypocretin neurons in hypothalamus

Lateral hypothalamus
(necropsy)



Adapted with permission of: Nishino et al. *Ann Neurol.* 2001;50:381; Peyron et al. *Nat Med*. 2000;6:991.

Etiopatogenesis of narcolepsy without cataplexy (typ 2)

?

Narcolepsy work-up (diagnostic procedure)

- Excessive daytime sleepiness
- Night polysomnography
- Multiple sleep latency test(MSLT): mean sleep latecy <8 min
  REM sleep in 2 or more tests

<u>Narcolepsy with cataplexy (typ 1)</u>

- Evident cataplexy
- low hypocretin in CSF
- HLA DQB1*0602 + (support)

<u>Narcolepsy without cataplexy (typ 2)</u>

- No cataplexy
- Normal hypocretin in CSF

Narcolepsy – treatment (only symptomatic)

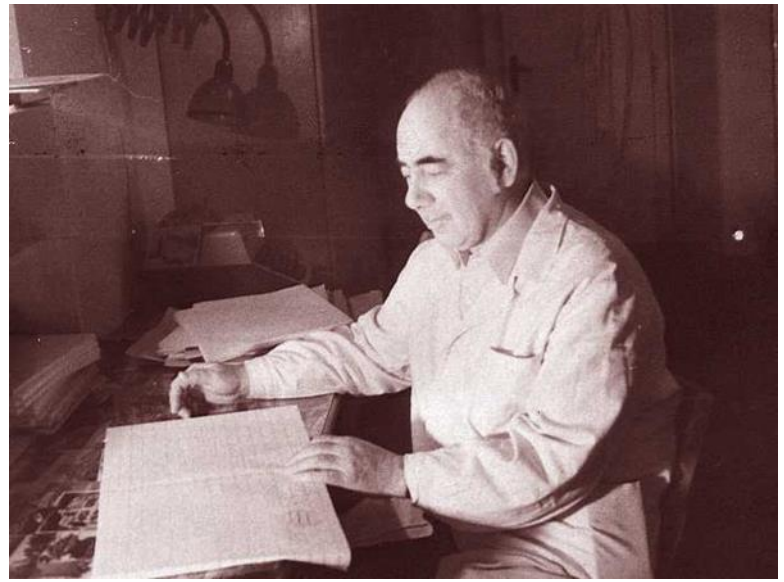
Excessive daytime sleepiness

- Planned short naps
- Stimulants:
  modafinil (Vigil),
  methylfenidate (Ritalin)
- Oxybat - gammahydroxybutyrat (Xyrem)
- Pitolisant (Wakix)

Cataplexy (+ sleep paralysis, hypnagogic hallucinations)

- Antidepresants:
  tricyklic: clomipramin
  SNRI: venlafaxin
  SSRI: (es)citalopram, fluoxetin
- Oxybat - gammahydroxybutyrat (Xyrem)
- (avoiding situations trigerring cataplexy)

Idiopathic hypersomnia



Bedřich Roth 1919 - 1989

- Less frequent than narcolepsy
  adult age
  unknown etiology

- Symptoms:
  Excessive daytime sleepiness
  Difficult awakening – sleep drunkenness
  Daytime sleepiness can be controlled
  Daytime sleep is long and not refreshing (that´s why patients with IH try not to sleep during the day)

- Treatment:
  Stimulants: modafinil, methylphenidate

Circadian rhythm sleep disorders

- Delayed sleep phase syndrome (=sleep delay)
- Advanced sleep phase syndrome
- Intolerance of shift work regimen
- Free-running circadian rhythms (e.g. blind people)

Parasomnias

Undesirable conditions or experience occuring at the beginning of sleep or in the course of sleep and during awakenings and arousals.

CNS activation + motor activity + autonomic activation + mental experience/dream.

Sleep-related abnormal: movements, behaviour, emotions, perception, dreaming and activity of autonomic nervous system.

Parasomnias are considered as diseases because they lead to injuries and sleep fragmentation and have adverse medical and psychosocial consequences.

Parasomnias - overview

NREM parasomnias - disorders of arousal from NREM sleep:
confusional arousal,
sleepwalking,
night terrors

Parasomnias associated with REM sleep:

REM sleep behaviour disorder (RBD),
sleep paralysis,
nightmare disorder

Other parasomnias:

enuresis nocturna,
exploding head syndrome

Parasomnias caused by abnormal arousal mechanisms (confusional arousal, sleepwalking, night terrors)

Common pathophysiology - incomplete awakening from NREM sleep

= manifestations of NREM sleep and wake at the same time (behavior/emotions and EEG).

Awakening induced or spontaneous

Behaviors, thoughts and emotions that are more or less imperfect and inappropriate

Hereditary disposition

Treatment: regimen (sleep hygiene, stress avoiding), psychoterapy, clonazepam

Technical measures against injuries!

Sleep drunkenness
(sleep inertia, confusional awakening)

Symptoms of various severity:

discrete indisposition after awakening, characteristic „drunkenness“ symptoms, incapability of being oriented after awakening, erroneous or even dangerous behavior with confusion, sometimes escapee or defensive activity, etc.

Children are totally confused, do not recognize parents.

Duration: several seconds to tens of minutes

Sleepwalking

- Complex automatic behavior (sitting up, walking, complex activities)
- Morning amnesia
- Duration: minutes to tens of minutes
- Risk of injury although behavior is seemingly rational and patient overcomes obstacles in a seemingly correct way

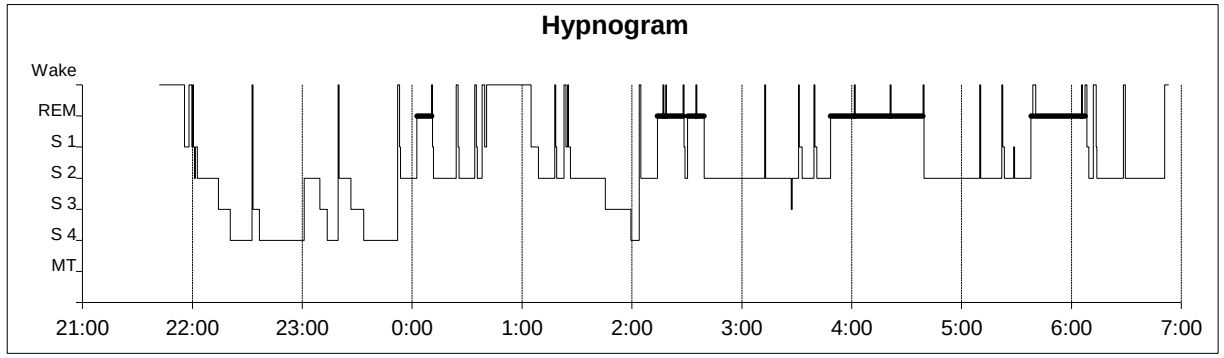
- Onset between 4th – 8th year of age, vanishes mostly in adolescence, repetitive episodes in 1- 5 % children
- Genetic predisposition
- May start in young adulthood

girl, 12 y.

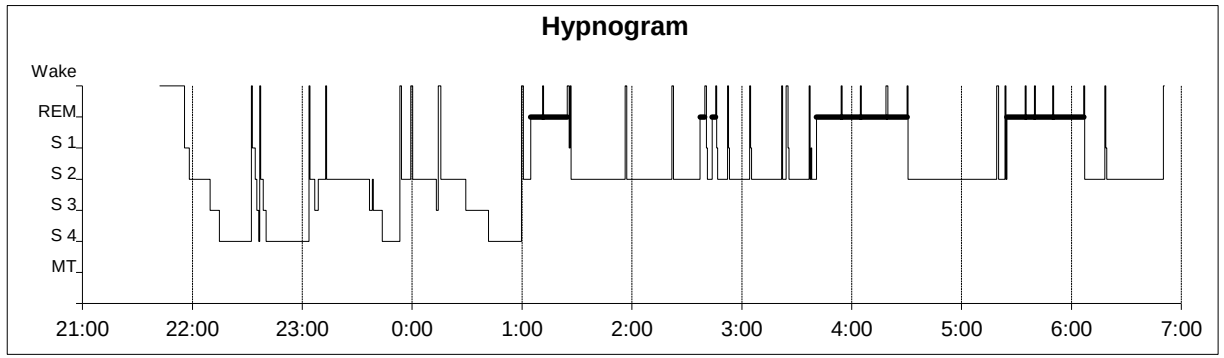
Sleepwalking onset at 12 y.

Sporadic quit walks inside the flat.

She fall out of the window in the 2nd floor. Multiple fractures of lower limbs including pelvis. Amnesia.



5 unprovoked arousals from deep NREM sleep



4 unprovoked arousals from deep NREM sleep

Night terrors (pavor nocturnus)

Children

- Sudden awakening with crying, shouting, intensive fear and autonomic activation (tachycardia, tachypnea)
- disorientation, difficult to be awaken, morning amnesia
- prevalence at years 4 - 6: 3-6%

Adults

- escapes from danger (→injury)
- partial memory

- Provoked especially by fever and sleep deprivation

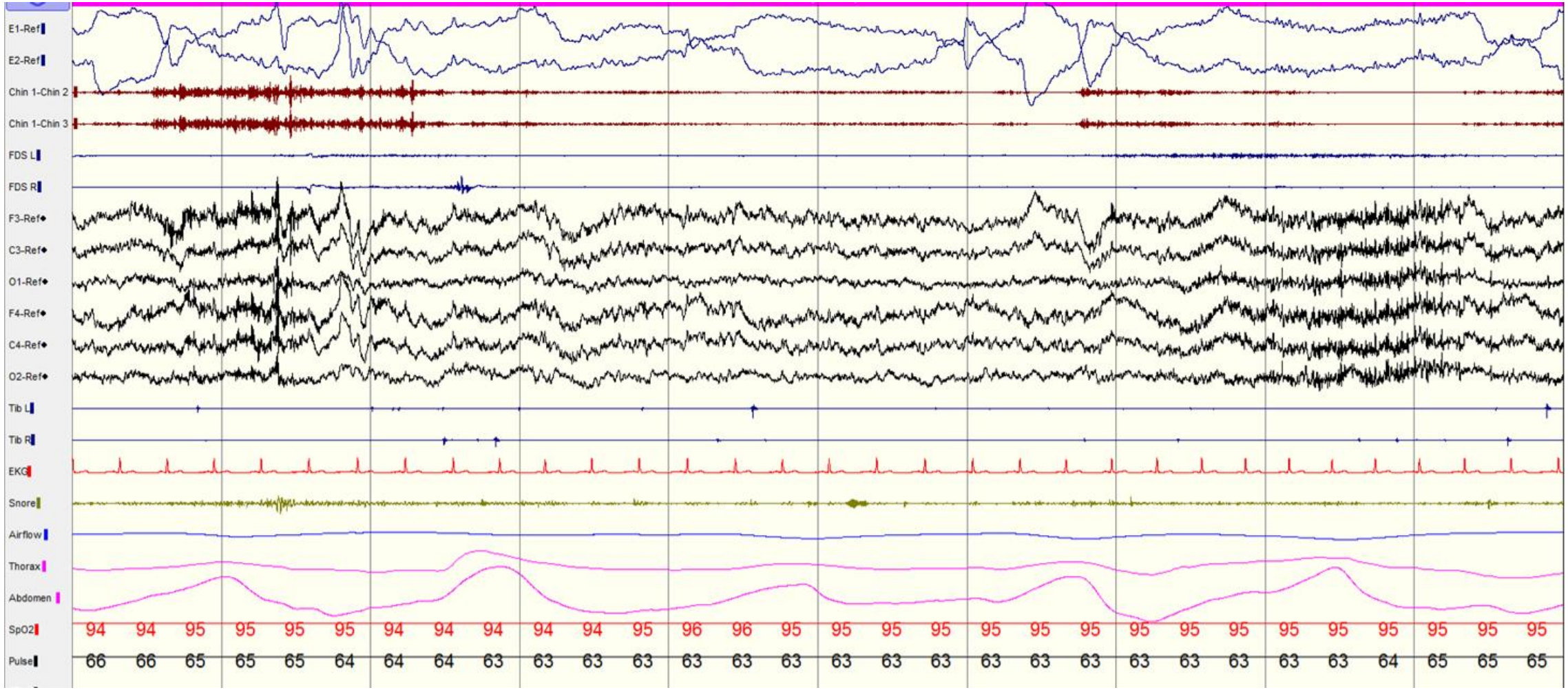
REM sleep behavior disorder - RBD

Dream enactment in REM sleep (abnormal behavior and vocalisations).

Insufficient muscular atonia in REM sleep.

Insuficient REM sleep atonia, polysomnography

line 3 and 4 – EMG, mentalis muscles



30 s

RBD symptoms

Vocalisations and/or **complex behavior**.

- laughter, small movements
- dreams usually unpleasant – the patients is threatened or attacked by hostile people or animals.
- Patients awakened at the end of their dreams report dream contents as a coherent story which is relates to previous behavior.
- Falls out of bed.
- Emotional character. Aggressiveness, defensive behavior, anxiety.
- Eyes are closed – a patient is oriented in a dream context – not according to real actual environment.
- Frequent injuries (also the bedpartner)

Idiopathic RBD

Absence of the disease with which RBD usually occurs

age >50 y.

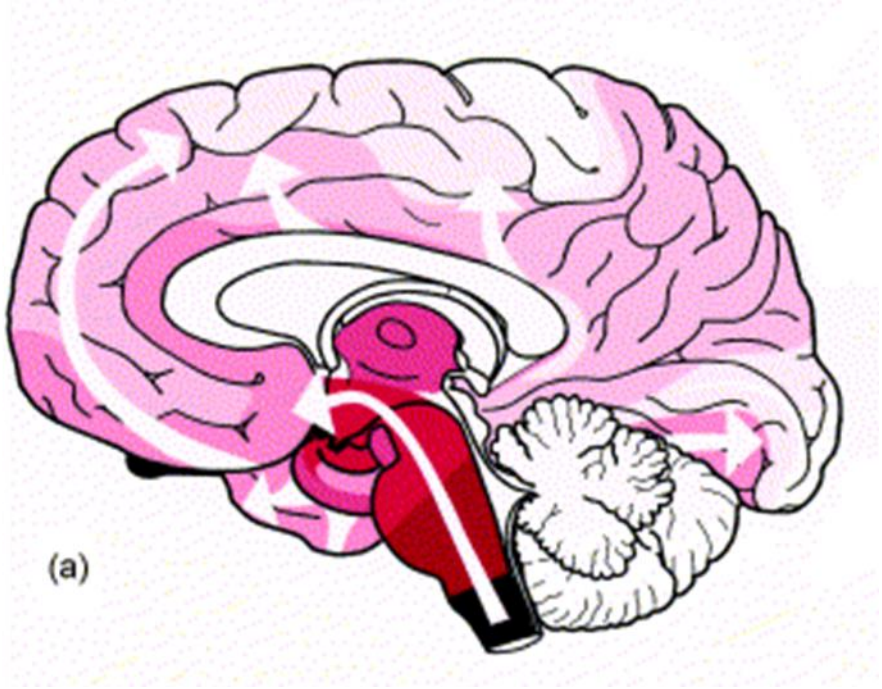
Prevalence 1-2% in people >60y

Etiology – **prodromal stage of synucleionpathies**

Secondary RBD

synukleinopaties (Parkinson´s disease, Lewy body disease, multisystem atrophy).

narcolepsy



Pathological storage of synuclein in the brain in Parkinson's disease begins caudally and proceeds rostrally.
REM sleep muscle atonia and smell are affected earlier than movement and cognition.

Treatment (symptomatic) – **Clonazepam**, melatonin at bedtime

Sleep-related movement disorders

- Restless leg syndrome (RLS)
- Periodic limb movement in sleep (PLMS)
- Limb cramps during sleep
- Bruxism
- Sleep related rhythmic movement disorder

Restless Leg Syndrome (RLS)

- Urge to move limbs, especially lower limbs.
  Mostly associated with paresthesias.
- Pronounced while resting or performing no activity.
- Partial or complete relief by moving (at least during the movements)
- Nocturnal and evening maximum.

Supportive for dg:

Periodic limb movements - PLM (during both wakefulness and sleep).

Positive family history concerning RLS.

Responsiveness to dopaminergic therapy.

Etiology of RLS

Idiopathic

- Altered dopaminergic neurotransmisson
- Lack of neuronal iron levels in conditions wíth normal extracerebral iron level
- Genetic basis

Secondary

- Iron deficiency
- Renal insufficiency
- Pregnancy
- Medications (mirtazapine, SSRI)
- CNS lesions (MS, PD, HIV, spinal cord lesions)
- Altered dopaminergic neurotransmisson

Treatment of RLS

Administration of medication mostly in the evening / event. during the night or afternoon hours. 24-hour level is rarely needed
A portion of patients: ad hoc application.

Some patients: progression of symptoms in consequence of the therapy – augmentation. Change the drug is needed.

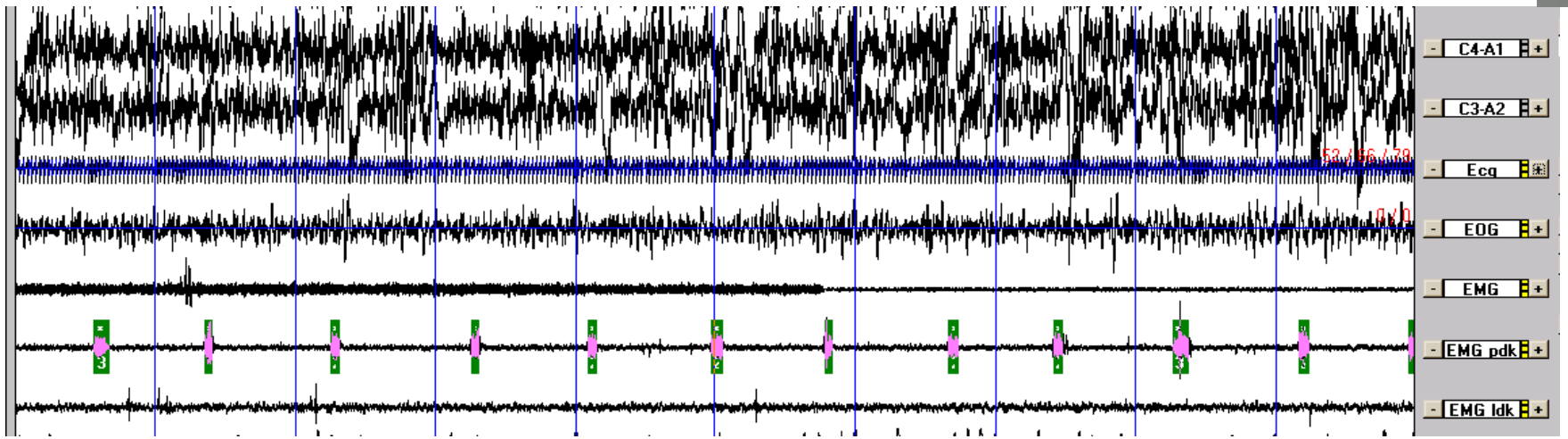
- Dopaminergic th. (small doses!!)
  dopamine agonists – pramipexol, ropinirol, rotigotine
  (ad hoc L-DOPA)
- Opiates oxycodone, tramadol
- Anticovulsants gabapentin, pregabaline
- Iron per os (in all forms if ferritin <75ug/l)
- Regimen measures reduced caffeine, regular physical load

Periodic limb movements in sleep – PLMS

Episode/s of stereotypical repetitive limb (usually leg) movements occuring during sleep / nighttime rest period

- typical: dorsiflexion of hallux (similar to Babinski)
  + flexion in ancle, knees and hips
- duration 0.5 – 10 s
- interval 5 – 90 s

Sleep fragmentation in some patients



5 min

Sleep and wake disorders – reminder

- Quality of life impairment
- Cognitive consequences
- Important comorbidity including mood impairment
- Risk of injuries
- Social consequences
- Symptom (in some cases the first one) of other diseases