CENTRAL HYPERSOMNIA

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WHO, WHAT, WHERE

A spectrum of sleep disorders characterised by Excessive Daytime Sleepiness in the absence of uninterrupted nocturnal sleep or circadian rhythm disorders

Narcolepsy was first described by Jean Baptiste Gélineau of a 38 y/o wine merchant >200 sleep attacks per day

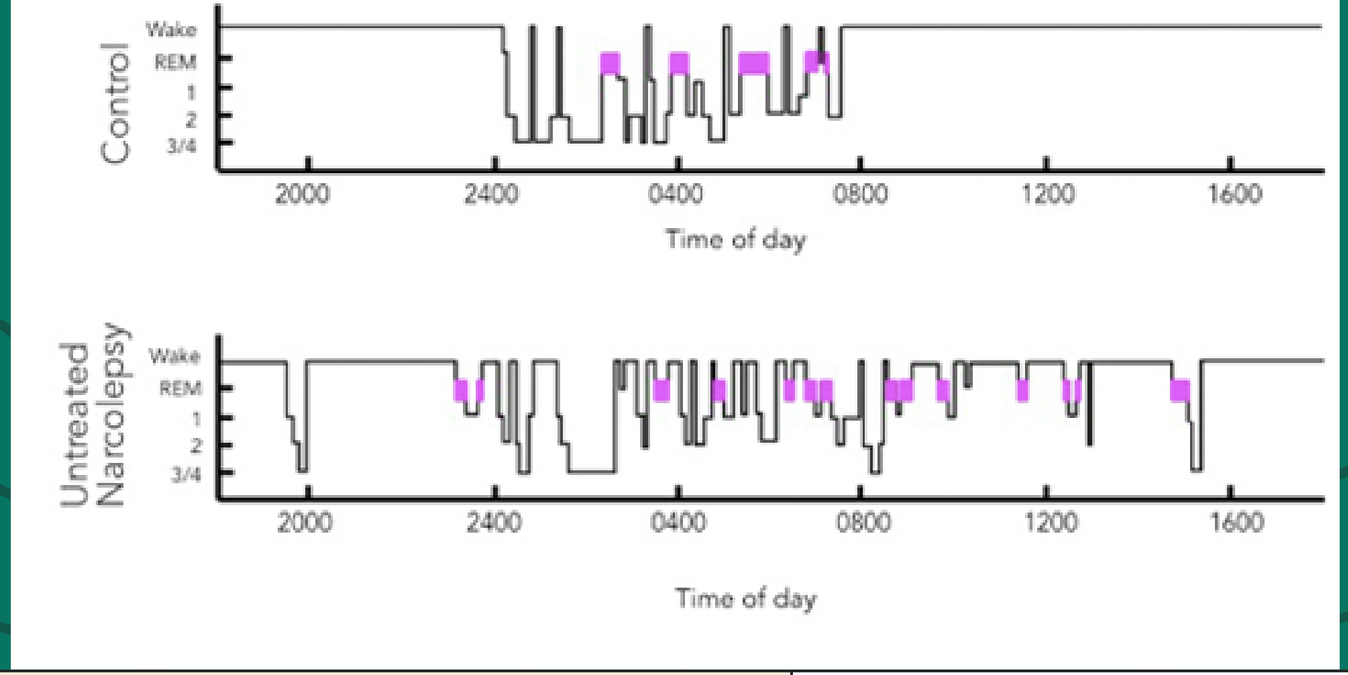
Idiopathic Hypersomnia was detailed by Bedrich Roth in a series of 642 patients seen over 30 days.

International Classification of Sleep Disorders-3

- Narcolepsy Type I
- Narcolepsy Type II
- Idiopathic Hypersomnia
- Keline Levin syndrome
- Hypersomnolence due to medical disorder
- Hypersomnolence due to medication/substance use
- Hypersomnolence associated with psychiatric disease
- Insufficient Sleep Syndrome

NARCOLEPSY Type 1

DEFINITION	This condition involves unstable sleep/wake regulation, extreme sleepiness, fragmented nocturnal sleep, and potential intrusion of REM sleep into wakefulness, including cataplexy, hallucinations, and sleep paralysis. Nocturnal symptoms include short sleep onset latency, reduced sleep efficiency and quality, and increased state transitions.
DIAGNOSTIC CRITERIA	• Daily periods of irrepressible need to sleep OR daytime lapses into sleep, occurring for at least 3 months, AND • One or both of: 1. Cataplexy AND MSL </= 8 min AND 2 + SOREMs (or nocturnal 15 min SOREM and 1+ MSLT SOREM) 2. Low CSF Orexin concentration (</= 110 pg/ml OR <⅓ of control values
PREVALENCE	1 in 2000 Family members have increased risk of hypersomnolence 25-31 % concordance in monozygotic twins



CORE FEATURES	**TETRAD:** • EDS - 100% • Cataplexy- most • Sleep paralysis • Hypnagogic/Hypnapompic hallucinations- 63%
OTHER FEATURES	• Sleep fragmentation • REM sleep behaviour disorder

NARCOLEPSY Type 11

- **DIAGNOSTIC CRITERIA**

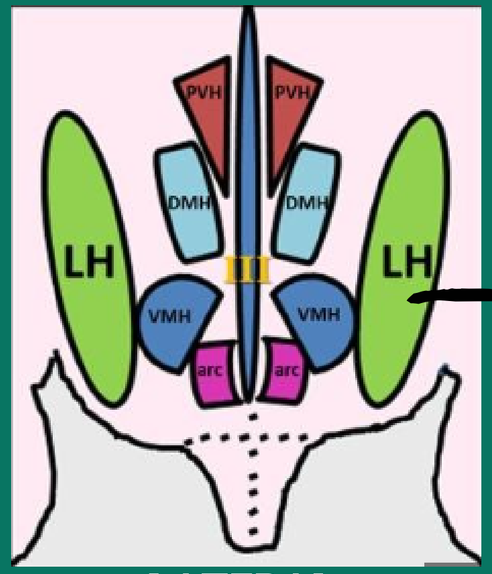
- Daily periods of irrepressible need to sleep OR daytime lapses into sleep, occurring for at least 3 months, AND
- MSL < 8 min AND 2 + SOREMs (or nocturnal 15 min SOREM and 1+ MSLT SOREM) AND
- NO Cataplexy, AND
- Hypocretin is >110 (or > ⅓ controls) or unmeasured, AND
- Not better explained by any other cause of hypersomnolence

Prevalence-

- Medical claims database of 8.4 million people of which 0.065% are type 2 narcoleptic
- According to the Wisconsin sleep cohort 0.20 % are type 2 narcoleptic.

Family members have increased risk of hypersomnolence

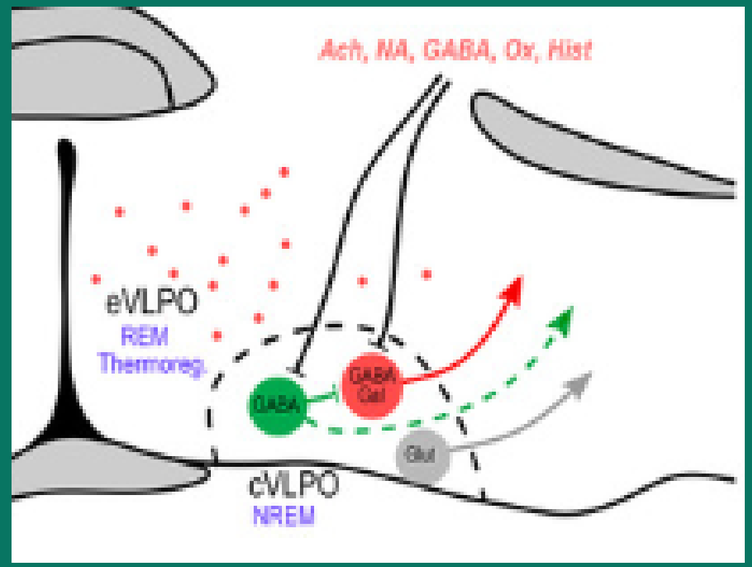
PATHOPHYSIOLOGY OF NARCOLEPSY I & II



LATERAL HYPOTHALAMUS

Orexinergic neurons

RETICULAR ACTIVATING SYSTEM



VENTROLATERAL PREOPTIC NUCLEUS of Anterior Hypothalamus

NORMAL SLEEP-WAKE MECHANISM

Orexinergic neurons from lateral hypothalamus increse the activity of the nulei of RAS

RETICULAR ACTIVATING SYSTEM(RAS)

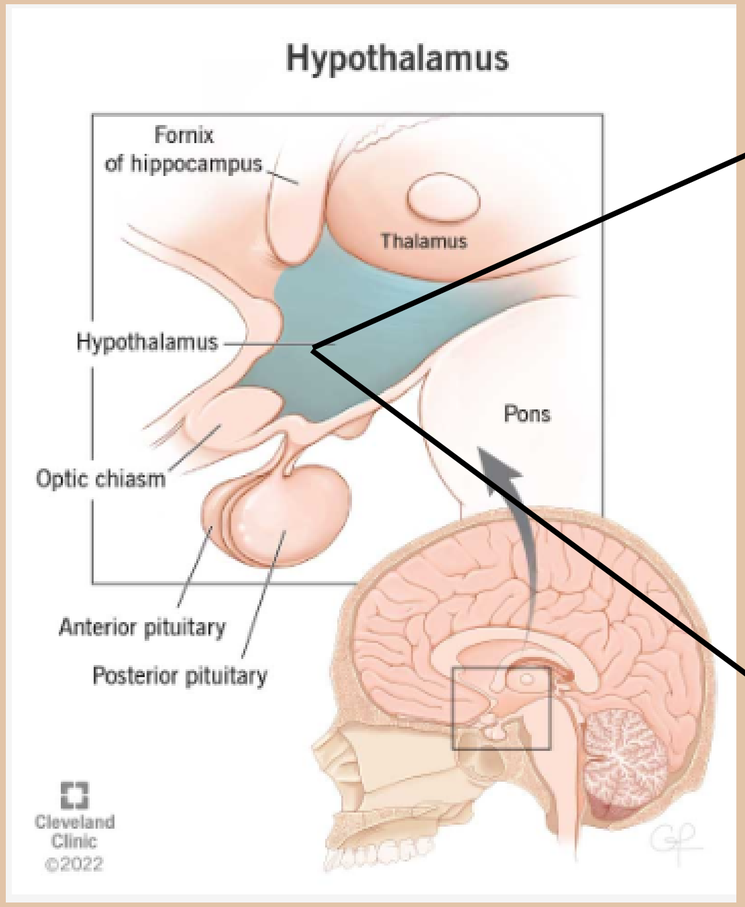
RAS increases wake promoting neurotransmitters in the cortex

Dopamine, Nor-epinehrine, Serotonin, Histamine inhibit REM

RAS also inhibits the sleep promoting Ventrolateral Preoptic Nuclues (VLPO) in the anterior hypothalamus, suppressing GABA thus increasing the motor activity

The VLPO also inhibits RAS , thus both the wake promoting and sleep promoting systems inhibit each other mutually

- During normal REM sleep, orexin decreases, thus decreasing RAS activity and promotes atonia.
- In narcolepsy type 1, the mechanism that separates wake from sleep becomes unstable without sufficient levels of orexin.
- The RAS no longer consistently causes the release of wake-promoting neurotransmitters to the cortex and inconsistently inhibits the VLPO.
- This results in rapid transitions between sleep and wake and allows the intrusion of REM-related phenomena (cataplexy, hypnagogic and hypnopompic hallucinations and sleep paralysis) into wakefulness.
- The pathophysiology of narcolepsy type 2 is not well understood.
- It has been hypothesised to be due to partial/less severe loss of orexin in the hypothalamus


Hypothalamus
Fornix
of hippocampus
Thalamus
Hypothalamus
Pons
Optic chiasm
Anterior pituitary
Posterior pituitary
Cleveland
Clinic
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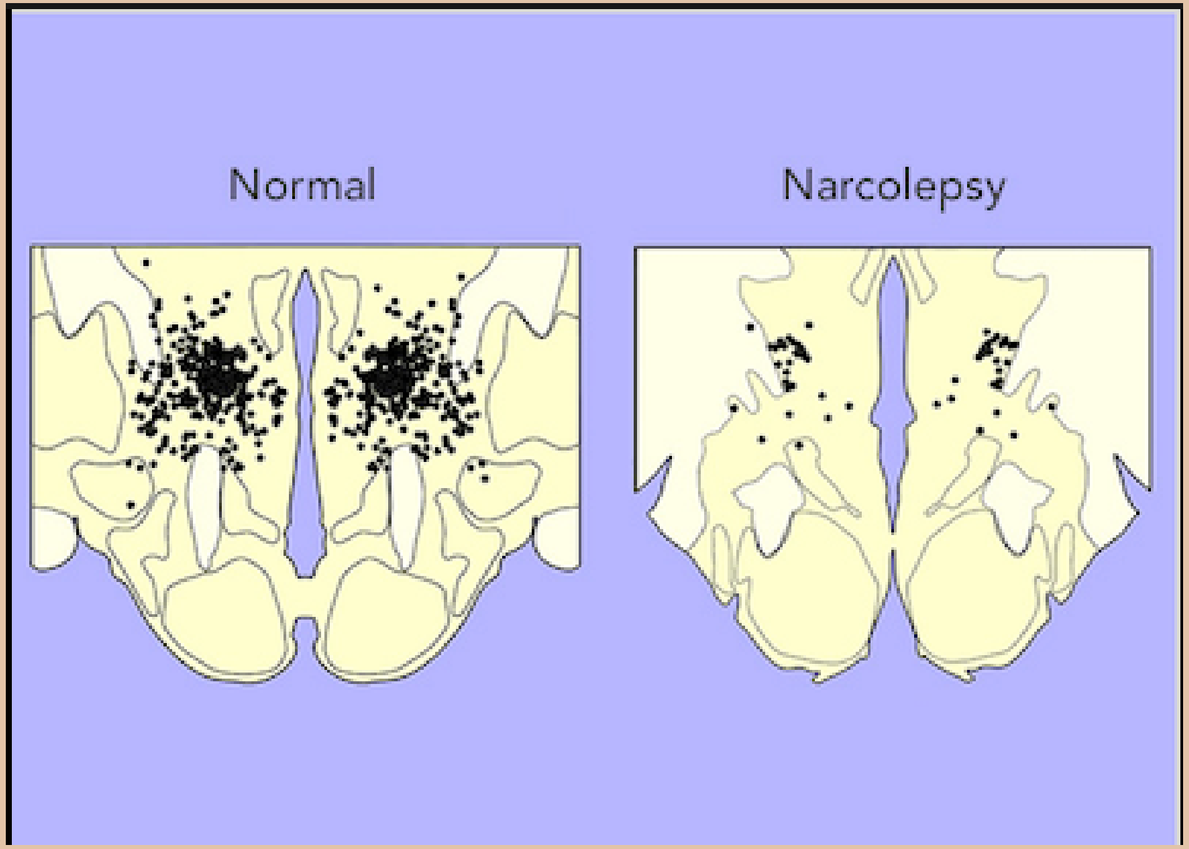
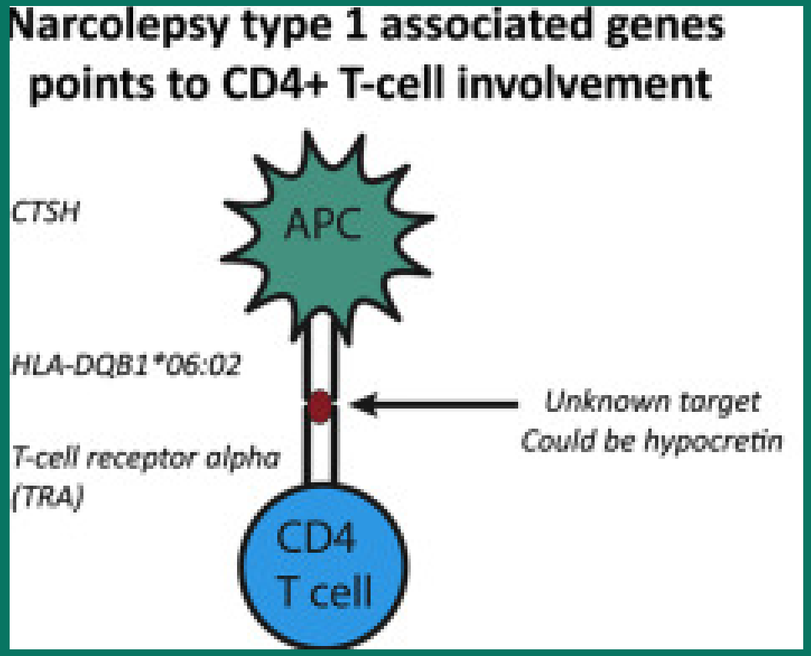
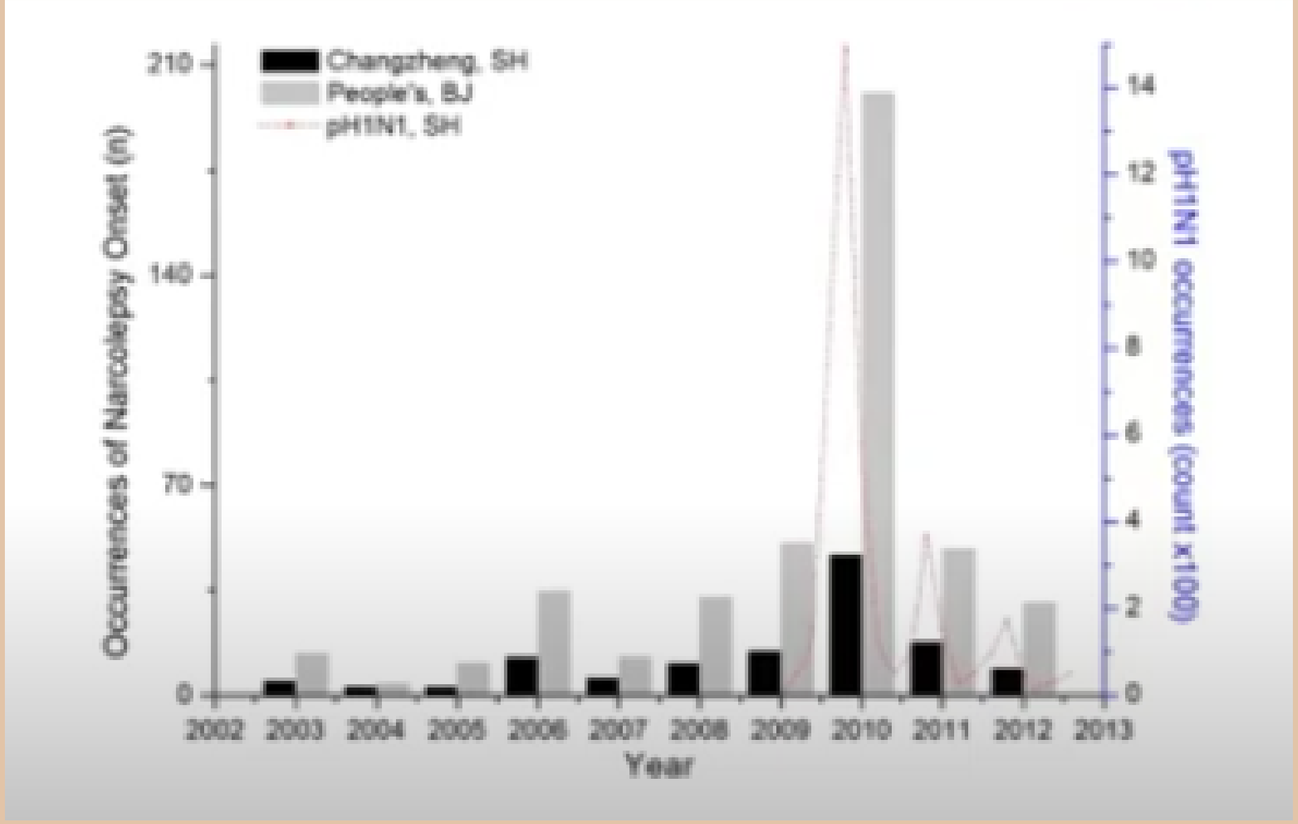

Normal
Narcolepsy

Other Possible Mechanism

- The autoimmune hypothesis- HLA-DQB1*0602 , seen to be positive in 85% patients with **Narcolepsy Type 1.**
- They have more hypocretin/orexin reactive CD4+ and CD8+ T-cells



Clue to pathogenesis than as a diagnostic test



H1N1 vaccine - Pandemrix in 2010

H1N1 infection in 2009

IDIOPATHIC HYPERSOMNIA

DIAGNOSTIC CRITERIA

- Excessive daytime sleepiness lasting at least 3 months
- No cataplexy
- No more than 1 SOREM between PSG and MSLT
- Not better explained by any other causes

EPIDEMIOLOGY

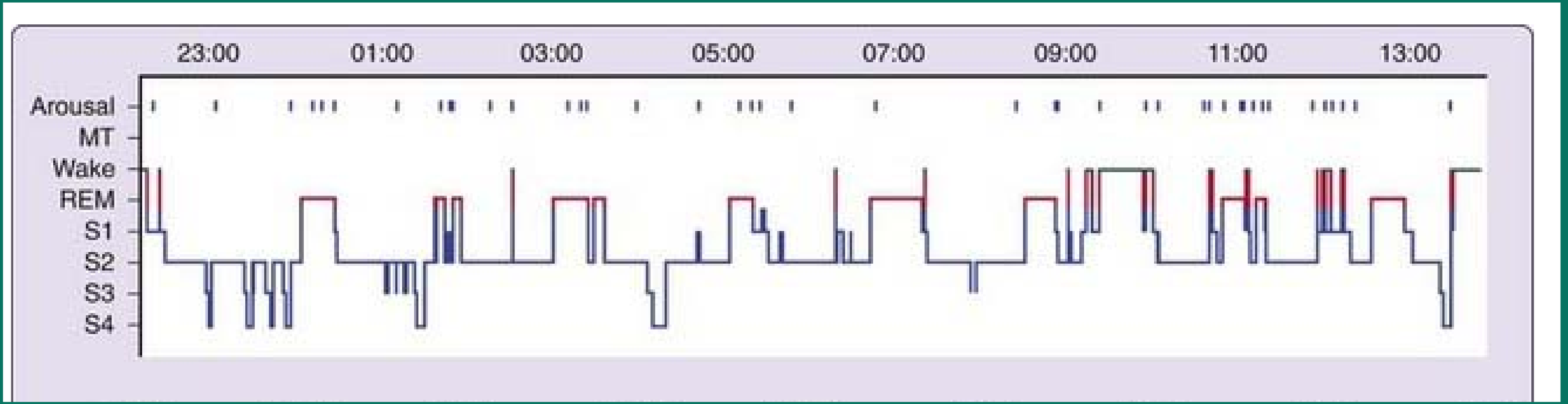
- “RARE’ - 0.5 %
- onset- late adoloscence/early adulthood
- Female predominance

- Severe/prolonged sleep inertia
- Unrefreshing naps > 1 hour
- PSG sleep efficiency >/= 90%

PATHOPHYSIOLOGY

POSSIBLE THEORIES

- Abnormal activation of GABA-A receptors.
- Loss of Histamine in the CNS
- Autonomic dysfunction- heart rate variability during sleep, orthostasis
- Circadian dysfunction- may be seen



3 different options for objective diagnosis(need to meet at least one):

- MSLT - MSL </= 8 mins
- 24 hr PSG >/= 660 (11 hours) mins of sleep duration
- 7 day actigraphy- total estimated sleep time- >/= 660 minutes (11 hours)

KLEINE-LEVIN SYNDROME

Kleine-Levin syndrome (KLS) is a rare relapsing-remitting sleep disorder distinguished by recurrent periods of severe hypersomnia
accompanied by cognitive, mood, and behavioral changes.

EPIDEMIOLOGY

- 1 in 5 million,
- Age of onset- 12-20,
- 2/3rd-boys,
- ~5% have family history

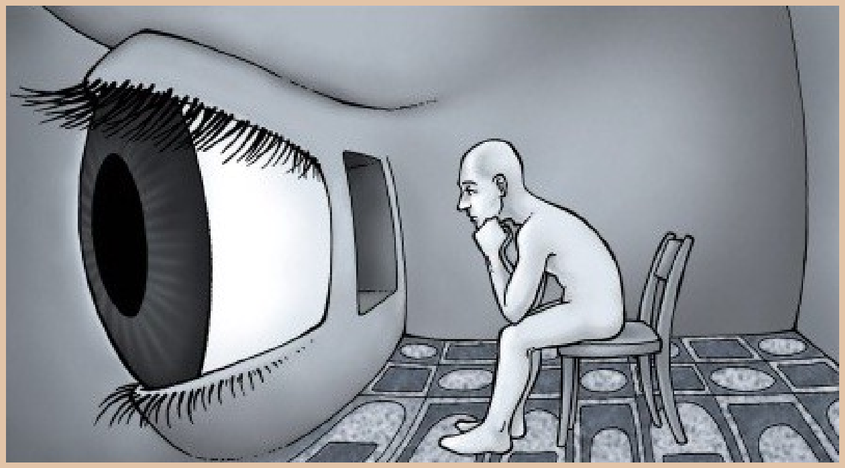
DIAGNOSTIC CRITERIA

At least 2 episodes of excessive sleepiness(for atleast 15-22 hours) for 2 days to 5 weeks
(median duration-13 days, median frequency- 3-6 months without cataplexy.
median duration - 15 years, can outgrow)
In addition to excessive sleepiness, bouts must demonstrate at least one of:

- Cognitive dysfunction
- Altered perception (derealisation, depersonalisation)
- Eating disorder(anorexia or hyperphagia)
- Disinhibited behaviour

Normal alertness, cognition, behaviour and mood between bouts
MSLT mean sleep latency, no of SOREM, 24hr measured sleep time are not required for diagnosis.

Typical symptoms during bouts



- Hypersomnia
- Altered cognition
- Derealisation>90%
- Apathy~100%
- Irritabilty

Atypical symtoms include

- Hypersexuality- Boys(58%)>girls(38%)
- hyperphagia-66%
- Meningitis like- headache, photophobia, neck stiffness
- painful hyperacusis
- hallucinations, anxiety, depressed mood/flat affect

POSSIBLE PATHOGENESIS

- Genetic links were reported in some patients with KLS, like variation in TRANK1 in addition to several uncommon variations in the LMOD3 gene
- Functional neuroimaging studies such as fMRI-BOLD, Positron Emission Tomography (PET) or SPECT were done to study the mechanism.
- Hyper insomnia, the main feature of this disease during the symptomatic periods, was associated with decreased thalamic activity
- Hyperactivity of the thalamus and hypothalamus were the main features shown during the asymptomatic period.

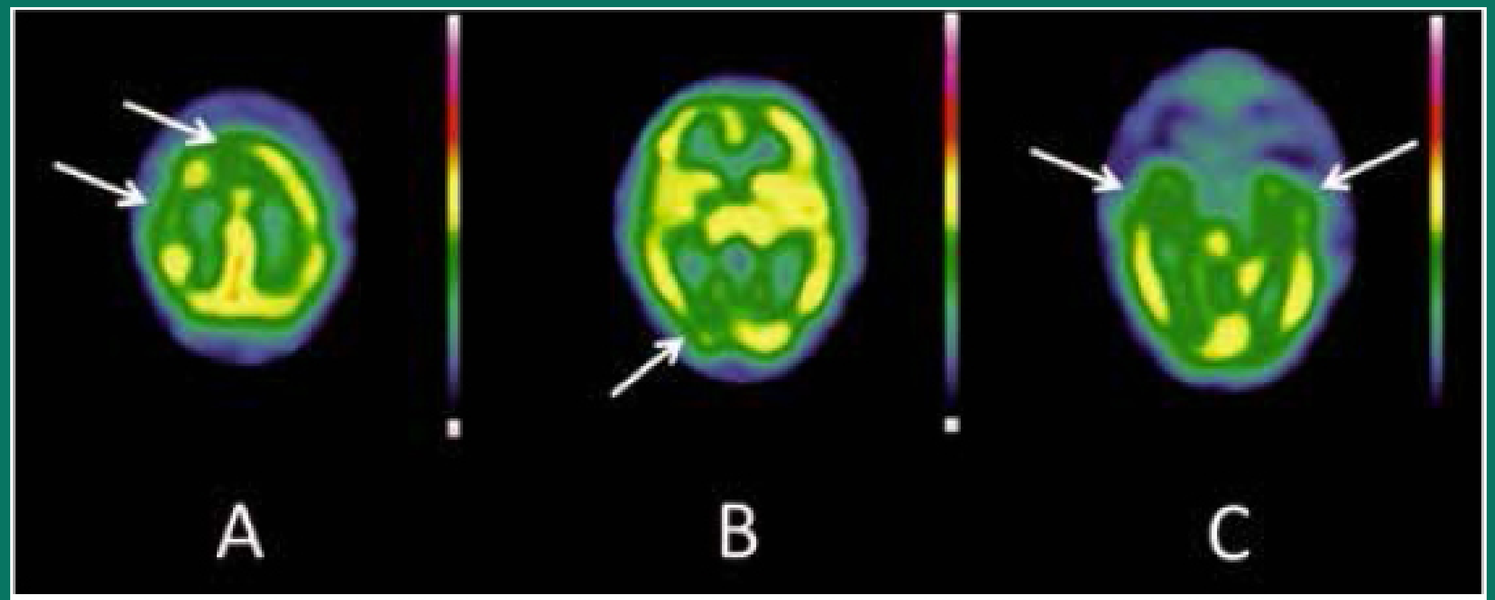
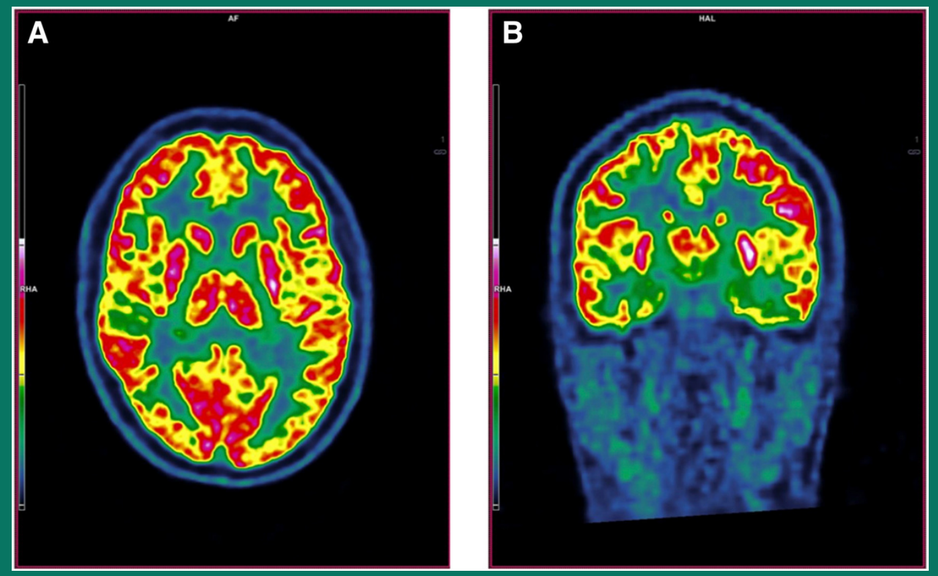


Fig. 1. SPECT brain Tc99m (March 2013): A = reduced right frontal and paracingular cortex; B = reduced posterior parietal and right parieto-occipital cortex; C = reduced perfusion bilateral temporal poles.



Functional brain imaging (using 18-fluorodeoxyglucose positron emission tomography) during an asymptomatic period in the patient with KLS. (A) **Axial slice showing mild bilateral hypometabolism in the posterior associative temporo-occipital cortex.** (B) **Frontal slice showing bilateral hippocampal hypometabolism. KLS = Kleine-Levin syndrome.**

HYPERSOMNOLENCE DUE TO A MEDICAL DISORDER

DIAGNOSTIC CRITERIA

- Daily sleepiness for 3 months
- Not due to other sleep disorder, psychiatric condition, or medication
- If MSLT done, MSL “usually” <8 minwith 0-1 SOREM- distinguishes narcolepsy due to a medical disorder

MEDICAL	NEUROLOGIC
Encephalopathies- Metabolic and Hepatic	Parkinsonism
Systemic Inflammation- Rheumatoid arthritis, Cancer, Chronic infection	Myotonic dystrophy
Genetic Syndromes- Niemann Pick type C, Prader-Willi, Fragile X	Traumatic Brain Injury
Endocrine disease- Hypothyroidism	Injury/Insult to Hypothalamus, B/L thalamus and Midbrain- Stroke, Tumor, Sarcoid.

HYPERSOMNIA DUE TO DRUG/SUBSTANCE

- Daily sleepiness , duration not included
- Caused by either initiation of sedating medication or withdrawal of alerting medication

Medications

- Sedatives and hypnotics
- Anti epileptics
- Dopamine agonsits
- Psychiatric - antidepressants, antipsychotics(dopamine antagonists), BZDs, Barbiturates
- Anticholinergics- Quitiapine, Trihexyphenidyl, Olanzapine
- Antihistamines- Diphenhydramine, Promethazine, Dimenhydrinate
- Muscle relaxants, pain meds-
- Anti-arrhythmics- class IV (Beta-blockers)
- Beta-blockers- Atenolol, Metoprolol
- Discontinuation of wake promoting agents (modafinil, amphetamines)
- Substance abuse- marijuana, opiates, cannabis

HYPERSOMNIA COMORBID TO A PSYCHIATRIC CONDITION

- Daily sleepiness for 3 months
- Comorbid psychiatric disorder
- Not better explained by other causes of central hypersomnolence

- Conditions-
- Most common- Mood disorders- atypical depression, SAD, Bipolar type 2, Anxiety Disorders,Somatoform disorders
- Least common- Thought disorders, Adjustment Disorders and Personality disorders.

INSUFFICIENT SLEEP SYNDROME

- Arguably not central
- Behaviourally Induced lack of sleep resulting in sleepiness
- Huge piece of DD for other central hypersomnias
- Diagnostic criteria-
- Daily sleepiness (in prepubertal children-behavioural problems),
- Sleep shorter than expected for age
- Sleep pattern must be present for most days x at least 3 months
- Use measures to shorten sleep
- Sleep longer without these measures
- Symptoms resolve with sleep extension.

TREATMENT

NON-PHARMACOLOGIC STRATEGIES

NARCOLEPSY TYPE-1

Regular nocturnal sleep times AND short scheduled naps(in those with severe residual EDS)

School/work accommodations

Counselling/support
Safety
Medication side effects
Support groups- wake up narcolepsy, narcolepsynetwork.com

IDIOPATHIC HYPERSOMNIA

Naps are not typically helpful

School/work accommodations- late start time

Counselling/support
Safety
Medication side effects
Support groups

	Narcolepsy Type I & II	Idiopathic Hypersomnia	Kleine Levin syndrome	Hypersomnia 2o to α-synucleinopathies	Post traumatic hypersomnia	Genetic disorders
MODAFINIL	+++	+++		conditional	conditional	conditional
PITOLOSANT	+++	conditional				
SOLRIAMFETOL	+++					
SODIUM OXYBATE	+++	conditional		conditional		
ARMODAFINIL	conditional			conditional	conditional	
METHYL PHENIDATE	conditional	conditional				
LITHIUM			conditional			
DEXTRO AMPHETAMINE	conditional					

MODAFINIL/ARMODAFINIL-
nervousness/irritability
palpitations/tachycardia
Headache
Nausea
rhinitis/pharyngitis
SJS
mania/psychosis/hallucinations/suicidal ideation
Angioedema

MUST USE BIRTH CONTROL OTHER THAN/IN ADDITION TO OCPs

AMPHETAMINES/METHYLPHENIDATE

irritability/anxiety
Palpitations, elevated HR/BP
Drug dependence (methylphenidate) and high abuse potential(dextroamphetamine) - **black box warnings**

PITOLISANT

H3 antagonist/inverse agonist
Used for EDS with Narcolepsy (type 1 or 2)
Decreased cataplexy by 75 %

S/E- headache, insomnia, GI distress and discomfort,

MUST USE OTHER CONTRACEPTIVE ALTERNATIVES OTHER THAN OCPs.

SOLRIAMFETOL

Dopamine and norepinephrine reuptake inhibitor
Used for sleepiness associated with Narcolepsy(type 1 or type 2), OSA
Available since 2019
Schedule IV
S/E- headache, nausea, decreased appetite, nasopharyngitis, dry mouth, anxiety, small increase in HR and BP

SODIUM OXYBATE

Sodium salt of GHB, thus restricted distribution and drug diversion/misuse
Dosed at bedtime and 2.5-4 hrs later, short t ½
Bed wetting, nausea, sleepwalking, mood changes/thought changes
Black box warning - high abuse potential, CNS depression -> respiratory depression, seizures, coma and death

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Thank You