Hypersomnolence and Evaluation of the Sleepy Patient

Frankie Roman MD JD
Focus Spring 2016
Nashville TN
May 7th 2016
Kleine – Levine Syndrome

- Relapsing-remitting episodes of severe hypersomnolence.
- Typical episode lasts a median 10 days (range 2.5 – 80 days).
- First episode often triggered by infection or alcohol intake.
- Further episodes recurring every 1-12 months for years.
- Patients may sleep as long as 16-20 hours per day
- Anterograde amnesia typical.
Kleine–Levin Syndrome

- When awake during episodes – patients are exhausted, apathetic, confused and slow speaking.
- Dreamlike, altered perception of environment.
- May eat ravenously (66% of cases)
- Hypersexual (53%, mostly men)
- Depressed (53% mostly women)
- Experience hallucinations and delusions (30%)
- NORMAL between episodes with regard to sleep, cognition, mood, and eating.
Kleine-Levin Syndrome

- Disease typically resolves after a median of 14 years
- Adult onset cases may be more prolonged.
- Occasionally, isolated recurrent hypersomnolence may be only symptom.
- Physical examination unremarkable except for general psychomotor slowing.
- Amnesia, transient dysphoria, or elation with insomnia may signal termination of an episode.
Kleine-Levin Syndrome – Predisposing and Precipitating Factors.

- Birth and developmental problems.
- Jewish heritage.
- Flu-like illness or upper airway infection.
- Alcohol consumption.
- Head trauma.
- Travel.
- Exposure to anesthesia.
Kleine-Levin Syndrome – Course and Complications

- Second decade usual age of onset.
- Often benign course with episode lessening in duration, severity and frequency over median course of 14 years.
- Prediction of longer disease duration – male sex, age of onset younger than 12 or older than 20, and hypersexuality.
- Complications are mainly social and occupational.
- Reduced long term working memory capacity following episodes?
Menstrual-related Kleine-Levin Syndrome

- Episodes exclusively associated with menstruation.
- Reported in only 18 women worldwide.
- Compulsive eating in 65%.
- Sexual Disinhibition in 29%.
- Depressive mood in 35%.
- Episodes last 3 to 15 days.
- Recur less than three times a year.
- Some cases have responded to contraceptive doses of estrogen and progesterone.
Kleine-Levin Syndrome – Objective findings

- MRI of Brain negative.
- Functional Brain Imaging studies during episodes demonstrate hypometabolism in thalamus, hypothalamus, mesial temporal lobe and frontal lobe.
- Autoimmune? – occasional association with HLA DQB1*02
- EEG – general slowing and bursts of bisynchronous, generalized moderate to high 5-7 Hz waves.
- PSG – difficult to interpret
- MSLT – may be normal or abnormal with short sleep latencies and SOREMPs.
- CSF levels of hypocretin-1 within normal range in patients tested.
Kleine-Levin Syndrome Diagnostic Criteria

A. Patient experiences at least 2 recurrent episodes of excessive sleepiness and sleep duration (2 days to 5 weeks).
B. Episodes recur usually more than once a year and at least once every 18 months.
C. Patient has normal alertness, cognitive function, behavior, and mood between episodes.
D. Patient must demonstrate at least one of the following during episodes:
   1. Cognitive dysfunction
   2. Altered perception
   3. Eating disorder (anorexia or hyperphagia)
   4. Disinhibited behavior (such as hypersexuality)
E. Hypersomnolence and related symptoms are not better explained by another sleep disorder, other medical, neurologic, or psychiatric disorder, (especially bipolar disorder), or use of drugs or medications.
Kleine-Levin Syndrome – Differential Diagnosis

- Tumors within the third ventricle.
- Encephalitis.
- Multiple Sclerosis.
- Head Trauma.
- Porphyria.
- Lyme Disease.
- Basilar Migraine.
- Complex partial status epilepticus.
- Bipolar Disorder.
- Depression.
- Seasonal Affective Disorder.
- Somatoform Disorder.
Long Sleeper

- Adults who sleep longer than 10 hours.
- In Children and Adolescents, sleep time is more than 2 hours longer than age specific norms.
- Sleep architecture normal.
- About 2% men and 1.5% women report sleeping at least 10 hours per night.
- Increased mortality (increase BMI, decrease glucose tolerance, increase prevalence of type 2 diabetes and CAD).
- Long sleepers over 60 – associated with male sex, low education, no physical exercise and more physical diseases.
- Sleeping long hours is REFRESHING.
Insufficient Sleep Syndrome

A. Patient has daily periods of irrepresible need to sleep or daytime lapses into sleep or, in the case of prepubertal children, there is a complaint of behavioral abnormalities attributable to sleepiness.

B. Patient’s sleep time, established by personal or collateral history, sleep logs, or actigraphy is usually shorter than expected for age.

C. Curtailed sleep pattern is present most days for at least 3 months.

D. Patient curtails sleep time by such measures as an alarm clock or being awakened by another person and generally sleeps longer where such measures are not used, such as on weekends or vacations.

E. Extension of total sleep time results in resolution of the symptoms of sleepiness.

F. Symptoms are not better explained by another untreated sleep disorder, the effects of medications or drugs, or other medical, neurologic, or mental disorder.
Hypersomnina Due to a Medical Disorder

- Hypersomnia secondary to Parkinson Disease.
- Posttraumatic hypersomnia.
- Genetic disorders associated with primary CNS somnolence.
- Hypersomnia secondary to brain tumors or infections.
- Hypersomnia secondary to endocrine disorder.
- Hypersomnia secondary to metabolic encephalopathy.
- Residual hypersomnia in patients with adequately treated OSA.
  - hypoxic injury to monoamine systems
  - obesity
  - compliance download important
Hypersomnia Due to a Medical Disorder

A. Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

B. Daytime sleepiness occurs as a consequence of a significant underlying medical or neurological condition.

C. If an MSLT is performed, the mean sleep latency is ≤ 8 minutes, and fewer than 2 sleep onset REM periods (SOREMPs) are observed.

D. Symptoms are not better explained by another untreated disorder, a mental disorder, or the effects of medications or drugs.
Hypersomnia Associated with a Psychiatric Disorder.

- Atypical Depression
- Bipolar II disorder (recurrent major depressive episodes with hypomanic episodes)
- Hypersomnia associated with a conversion disorder or somatic symptom disorder.
- Persistent hypersomnolence is associated with increased risk of recurrent depression.
- PSG – REM latency may be shortened in untreated depression. Also prolonged sleep latency and increased WASO.
- MSLT – often within normal limits despite subjective sleepiness.
Hypersomnia Associated with a Psychiatric Disorder

A. Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

B. Daytime sleepiness occurs in association with a concurrent psychiatric disorder.

C. Symptoms are not better explained by another untreated sleep disorder, a medical or a neurological disorder, or the effects of medications or drugs.
Hypersomnia Due to Medication or Substance

- Hypersomnia due to substance abuse.
- Hypersomnia due to stimulant withdrawal
  - in chronically heavy amphetamine, sleepiness most severe in first week of withdrawal and persist for up to 3 weeks.
  - significant depression
  - coffee withdrawal can produce sleepiness and inattentiveness for two to nine days.

Diagnosis confirmed if symptoms resolve after causal agent removed.
Urine Drug Screen very beneficial.


Hypersomnia Due to a Medication or Substance

- Hypersomnia due to sedating medications:
  - benzodiazepines
  - nonbenzodiazepine hypnotics
  - opioids
  - barbiturates
  - anticonvulsants
  - antipsychotics
  - anticholinergics
  - antidepressants
  - antihistamines
  - dopamine agonists
  - nsaids
  - antibiotics
  - antispasmodics
  - antiarrhythmic
  - beta blockers
Hypersomnia Due to a Medication or Substance

A. Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep.

B. Daytime sleepiness occurs as a consequence of current medication or substance use or withdrawal from a wake-promoting medication or substance.

C. Symptoms are not better explained by another untreated sleep disorder, medical or neurological disorder, or mental disorder.
Narcolepsy Type 1

A. Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

B. Presence of 1 or both of the following:

1. Cataplexy (as defined under Essential Features) and a mean sleep latency of ≤ 8 minutes and 2 or more sleep onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

2. CSF hypocretin-1 concentration, measured by immunoreactivity is either ≤ 110 pg/mL or < 1/3 of mean values obtained in normal subjects with the same standardized assay.
NARCOLEPSY TYPE 1

- Caused by deficiency of hypothalamic hypocretin (orexin) signaling.
- Relatively homogenous clinical and PSG findings.
- Cataplexy – episodes of generally brief, bilaterally symmetrical sudden loss of muscle tone with retained consciousness.
- Laughter most common trigger of cataplexy.
- Transient reversible loss of DTR during cataplectic attack is strong diagnostic finding.
- Respiratory muscles are not involved.
NARCOLEPSY TYPE 1

- Disruption of nocturnal sleep
- Hypnagogic hallucinations – vivid dreamlike experiences at transition from wake to sleep.
- Sleep paralysis – temporary inability to move voluntary muscles at sleep wake transitions.
- Obesity is a common symptom of narcolepsy.
- Panic attacks or social phobias in 20%
- Ptosis, blurred vision, diplopia.
- Narcolepsy with Cataplexy occurs in 0.02% to 0.18% in USA.
Precipitating Factors
- head trauma
- sustained sleep deprivation
- unspecified viral illness
- sudden changes in sleep wake schedule
- streptococcal infections
- vaccination against H1N1 associated influenza.
Closely associated with HLA subtypes DR2/DRB1*1501 and DQ B1*0602
Always found together in whites and Asians.
DQB1*0602 more specific in African Americans.
Almost all patients with cataplexy are positive for DQB1*0602.
12 to 38% of general population are also positive DQB1*0602.
DQB1*0301 associated with increased susceptibility to narcolepsy.
DQB1*0501 and DQB1*0601 are protective in presence of DQB1*0602.
NARCOLEPSY TYPE 2

- Cataplexy is absent.
- 10% of patients, cataplexy will develop later in the course of the disease – must change diagnosis to Narcolepsy Type 1.
- 24% of patients have low CSF hypocretin levels and positive HLA DQB1*0602 – should be classified as Narcolepsy Type 1.
- Most likely a heterogeneous disorder.
Narcolepsy Type 2

A. Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

B. A mean sleep latency of ≤ 8 minutes and 2 or more sleep onset REM periods (SOREMPs) are found on a MSLT performed according to standard techniques. A SOREMP (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

C. Cataplexy is absent.

D. Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either > 110 pg/mL or > 1/3 of mean values obtained in normal subjects with the same standardized assay.

E. Hypersomnia and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.
Multiple Sleep Latency Test

Diagram showing the Multiple Sleep Latency Test results with two groups: Control and Narcolepsy or Hypersomnia. The x-axis represents time (10 am, 12 am, 2 pm, 4 pm, 6 pm) and the y-axis represents latency. The Control group shows a steady decrease in latency, while the Narcolepsy or Hypersomnia group remains relatively constant.

References:
How good is the MSLT?

• Approximately 22% of the population has a mean sleep latency below 8 min; 5% less than 5 min
• The MSLT is narcolepsy-like (≤8 min, ≥ 2 SOREMPs) in 2-3% of the general population; with ~ ½ not complaining of excessive daytime sleepiness (Mignot et al, 2005; Singh et al., 2005).
• Test/Retest over 4 years: $\kappa\sim 0.1-0.3$ (Goldbart et al., 2014)
• Confounded by shift work, sleep deprivation, sleep apnea, delayed sleep phase

Clinical evaluation of Hypersomnia

Clinical evaluation: Evaluate cataplexy, nature and severity of sleepiness (exclude fatigue), sleep paralysis, hypnagogic hallucinations, or automatic behaviors. Rule out obstructive sleep apnea, insufficient sleep syndrome, or a circadian rhythm disorder.

Definite Cataplexy

Type 1 Narcolepsy/hypocretin deficiency
- PSG/MSLT for objective documentation, may allow for more aggressive treatment later.
- If MSLT negative, interpret with clinical context: cataplexy may be sufficient to diagnose narcolepsy. Consider repeat MSLT.
- Consider measuring Hypocretin-1 if:
  1. Psychotropic medications
  2. Associated sleep disorders
  3. Confounding neurological or psychiatric disorders
  4. Very young child

No Cataplexy or Atypical Cataplexy

No cataplexy, many SOREMPs consider CSF hypocretin

Other Hypersomnia
- Preceded by PSG to rule out other sleep disorders document adequate nocturnal sleep. No shift work
- If other sleep disorder (e.g. OSA), then treat before MSLT.
- Positive MSLT MSL ≤8 minutes and ≥ 2 SOREMPs: Narcolepsy without cataplexy

Conclusion

- Clinical history still extremely important.
- Sleep logs still very important and can shed light on lifestyle habits, work hours, medications, supplements and other factors which could potentially contribute to sleepiness.
- Actigraphy – use patient’s own wearable device (Fit Bit, Jaw Bone, Nike Fuel) to get better sense of sleep wake schedule.
- Genetic testing may play a role.
- Treatment must be multidimensional.
- Behavioral modification – sleep hygiene, diet, scheduled napping.
- Supportive environment – education, support groups.
Conclusion

The End.
Treatment must be multidimensional

- Pharmacological treatment
- Behavioral (scheduled napping, food regimen, sleep hygiene)
- Supportive (work environment, driving, support groups, narcolepsy association)