Primary Hypersomnias of Central Origin

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Hypersomnia
: increased sleep amounts
: primary, centrally mediated excessive day time sleepiness

Billiard 1996, Roth 1976, Bassetti 1997, Dauvilliers 2006, Black 2004

Excessive daytime sleepiness
: inability to maintain an alert state during the major waking episodes of the day, resulting in unintended lapses into drowsiness or sleep

ICSD – 2

낮에 졸리다 .. 피곤하다, 기력이 없다, 몸이 처진다.

International Classification of Sleep Disorders, 2nd Edition
Diagnostic Criteria for Hypersomnia

- **Narcolepsy With Cataplexy**
- **Narcolepsy Without Cataplexy**
  - Narcolepsy due to medical condition
  - Narcolepsy, unspecific
- **Recurrent Hypersomnia**
  - Kleine-Levin syndrome
  - Menstrual-related hypersomnia
- **Idiopathic Hypersomnia With Long Sleep Time**
- **Idiopathic Hypersomnia Without Long Sleep Time**
  - Behaviorally induced insufficient sleep syndrome
  - Hypersomnia due to medical condition
  - Hypersomnia due to drug or substance
  - Hypersomnia not due to substance or known physiologic condition (nonorganic hypersomnia)
  - Physiologic (organic) hypersomnia, unspecific

Narcolepsy

Epidemiology

Narcolepsy

with cataplexy 0.03-0.05% of the population

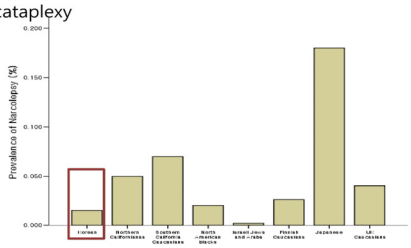
without cataplexy uncertain 0.02-0.034% of the population

Gender: Male = Female

*** Korean**

0.015% narcolepsy with cataplexy

0.034% narcolepsy without cataplexy

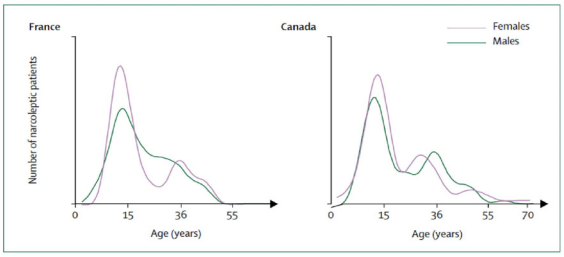


Adopted from Mignot 1998 and Hong 2008

Epidemiology

- Mean age of onset: mid twenties
- Bimodal distribution: Peak around 15 yrs of age and 35 yrs of age

- First-degree relatives have a 1-2% risk of developing narcolepsy (general population 0.02-0.18%)



Mignot, 2007

Clinical symptoms

Tetrad symptoms

Excessive daytime sleepiness

- Sleep attacks occur in bouts lasting sec. and mins
- Irresistible urge to sleep
- Immediate sleep-onset without warning
- Calm, sedentary, boring, sitting -> enhance the risk
- Refreshing nap (<30min, decrease the sleep drive for a few hours)

Cataplexy

- Loss or decrease of m. tone in all striated muscle, except diaphragm
- Trigger: laughter >> joy, elation, surprise, amusement
- Generalized – all m. affected
- Localized – head dropping, jaw dropping, knee buckling, slurred speech
- Attack last sec. to few mins
- Worsen with poor sleep and fatigue

* Status cataplecticus: lasting hours, usually seen on withdrawal from meds.

Clinical symptoms

Tetrad symptoms

Hypnogogic hallucinations (hypnopompic hallucinations)

- ½ ~ 2/3 of narcoleptics
- Simple, complex
- Auditory and tactile hallucinations 도 가능.
- Normal population 에서도 관찰

Sleep paralysis

- Awake but in able to move (last few mins)
- 2/3 of narcoleptics
- Normal population 에서도 관찰

Clinical symptoms

Disturbed nighttime sleep

- Altering nighttime sleep
- Fragmented sleep with multiple arousals
- Nocturnal eating
- Early awakenings
- Overall unrefreshing sleep episodes

Automatic behavior

- ½ narcoleptics
- Carrying on a seemingly purposeful activity
  while having no clear recollection of doing it.
- Appear as wake and responsive or absent-minded
- * Microsleep intrusions

Pathophysiology

- **Hypocretin cell loss**
- **low CSF hypocretin**
- **Autoimmune**
- **HLA-DQB1*0602**

Hypocretin

Hypocretins: (hypocretin 1, hypocretin 2)
promote arousal and wakefulness
regulation of feeding, sleep-wakefulness, muscle tone, locomotoion, regulation of feeding behavior, and neuroendocrine, and autonomic functions.

Hypocretin neurons:
70,000 neurons located in the posterior and lateral hypothalamus.

Hypocretin receptors:
HCRTR1 -hypothalamus, ventral tegmental area, dorsal raphe nucleus locus ceruleus and hippocampus (hypocretin 1>>>hypocretin 2)

HCRTR2 -thalamic and subthalamic nuclei, medulla oblongata, diagonal band, ventral tegmental area, dorsal raphe nucleus tuberomammillary nucleus and (hypocretin 1 and 2)

Bonnavion, 2010 bassetti lancet Neurol, 2005

Hypocretin

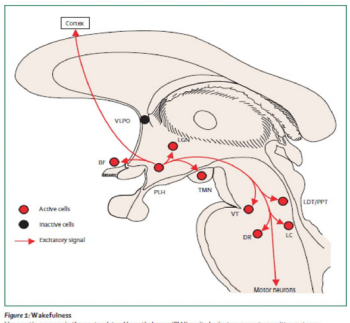


Figure 1: Wakefulness
Hypocretin neurons in the posterolateral hypothalamus (PLH) excite brainstem neurotransmitter systems: serotoninergic cells in the dorsal raphe (DR), norepinephrinergic neurons in the locus coeruleus (LC), cholinergic cells in the basal forebrain (BF) and the LDT/PPT, histaminergic cells in the tuberomammillary nucleus (TMN), and dopaminergic cells in the substantia nigra and the ventral tegmentum (VT). These neurotransmitter systems send excitatory signals via forebrain and thalamus to the cortex, and inhibit sleep -active neurons in the ventrolateral preoptic (VLPO) area (not shown). Activated local glutamatergic neurons (LGN) in the hypothalamus stimulate hypocretin neurons in a positive feedback loop. Hypocretin neurons also innervate spinal motor neurons.

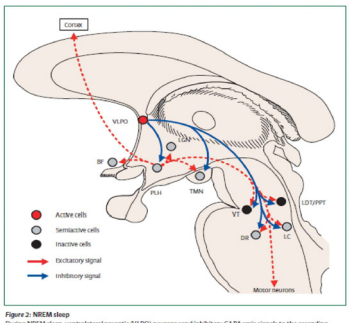


Figure 2: NREM sleep
During NREM sleep, ventrolateral preoptic (VLPO) neurons send inhibitory GABAergic signals to the ascending arousal system (dorsal raphe nucleus [DR], ventral tegmental area [VT], latenodorsal tegmental and pedunculopontine areas [LDT/PPT], locus coeruleus [LC], tuberomammillary nucleus [TMN]) and to hypocretinergic cells. The inhibition of these brainstem neurotransmitter systems lead to a reciprocal disinhibition of ventrolateral preoptic firing. Hypocretin, TMN, DR, and LC neurons are not completely silent during NREM sleep: there is still an inhibition of REM -active LDT/PPT neurons and a minor stimulation of motor neurons. BF - basal forebrain; LGN-local glutamatergic neurons; PLH-posterolateral hypothalamus. Dotted lines indicate decreased activity.

VLPO (ventrolateral preoptic nucleus)

GABA 억제

PLH (posterolateral hypothalamus)

Hypocretin

Activation of monoaminergic neurons (=> wakefulness)

LDT/PPT (Laterodrosal/pedunculopontine tegmental area, cholinergic)
LC (locus ceruleus, norepinephrine)
DR (dorsal raphe nucleus, serotonin)
VT (ventral tegmental area, dopamine)
TMN (tumberomammillary nucleus, histamine)

Hypocretin

Animal studies

Rodents - narcolepsy with cataplexy
Hypocretin knock out mice, Hypocretin-receptor knockout mice,
Genetic ablation of hypocretin neurons

Canine - narcolepsy with cataplexy
Autosomal Recessive (Canarc1) HCRTR2 mutation
Sporadic case with lo CSF hypocretin-1 in CSF

Humans

One case report of patient with a mutation in hypocretin related genes.
Most cases of human narcolepsy – not by hypocretin gene mutation

Mignot et al., neurology 2001, 2000

Hypocretin cell loss / low CSF hypocretin

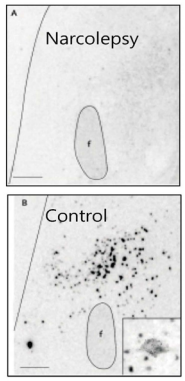
Hypocretin cell loss & Low CSF hypocretin-1 level

Cause of hypocretin cell death remains unknown

*** HLA-DQB1*0602 positivity**
: strong genetic association with selected HLA alleles
: suggest possible autoimmunity

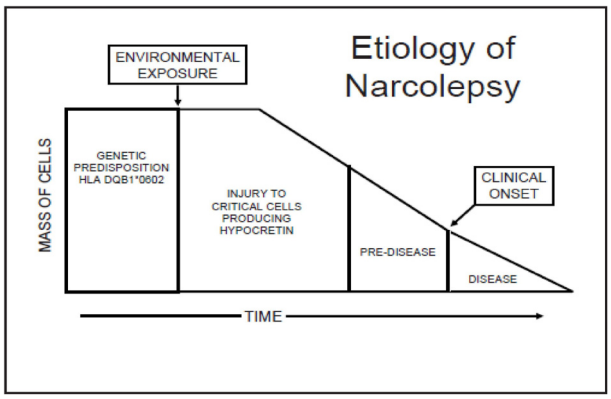
*** Post infectious narcolepsy**
: Streptococcus pyogenes
: Influenza A H1N1 infection and H1N1 vaccination

⇒ However no serum/CSF autoantibodies against pre-prohypocretin



Peyron 1998

Pathophysiology



Longstreth et al., *SLEEP* 2007;30(1):13-26.

Diagnosis - ESS

Epworth Sleepiness Scale (ESS)

Evaluate the subjective level of daytime sleepiness

8 questions each score 0-3

>10 is considered indicative of excessive daytime sleepiness

>15 is common in untreated narcolepsy patients

한국형 주간졸음척도 (KESS)

단순한 피곤함과는 다르게 다음의 상황에서 얼마나 깜박 졸거나 혹은 잠들어버릴 것 같습니까? 이것은 최근에 일상생활을 참고하시기 바랍니다. 비록 최근에 이런 상황에 처하지 않았다 하더라도, 그 상황에서 얼마나 영향을 받을지 생각해 보십시오. 각 상황에서 가장 적절한 숫자를 선택하여 한 개씩만 표시하시기 바랍니다.	깜박 졸 가능성			
	전혀 0	조금 1	상당히 2	매우 많이 3
앉아서 책 (신문, 잡지, 서류 등)을 읽을 때				
TV 볼 때				
공공장소 (모임, 극장 등)에서 가만히 앉아 있을 때				
정차 없이 1시간 동안 운행 중인 차 (자동차, 버스, 열차)에 승객으로 앉아 있을 때				
오후에 주위상황이 허락되어 쉬려고 누워 있을 때				
앉아서 상대방과 이야기할 때				
반주를 곁들이지 않은 점심식사 후 조용히 앉아 있을 때				
교통 혼잡으로 몇 분 동안 멈춰선 차 안에서				

Johns, 1991, Cho, sleep breath 2011

Diagnosis - SSS

Stanford Sleepiness Scale (SSS)

Quantify the subjective sleepiness of patients throughout the day

당신은 지금 얼마나 졸리다 고 생각하십니까?
다음 중 당신의 현재 느낌과 가장 가까운 번호 한가지만, 선택하여 주십시오.

1. 전혀 졸리지 않고 정신이 맑고 활기참을 느낀다.
2. 최상의 상태는 아니지만 집중해서 일을 할 수 있다.
3. 정신을 차리고는 있지만, 다소 나른해진 상태이다.
4. 약간 정신이 몽롱하고 기운이 없다.
5. 몽롱해서 정신을 집중할 수가 업고, 정신을 계속 차리고 있기가 힘들다.
6. 졸리고 멍한 상태이며, 눕고 싶다.
7. 눈을 뜨고 있지만, 깨어 있을 수가 없다. 금새 잠들 것 같다.

Hoddes & Zarcone, 1972

Diagnosis – Ullanlinna Narcolepsy Scale

Ullanlinna Narcolepsy Scale

1. When laughing, becoming glad or angry or in an exciting situation, have the following symptoms suddenly occurred?

	Never	1-5 times during Lifetime	Monthly	Weekly	Daily or Almost Daily
Knees Unlocking	☐	☐	☐	☐	☐
Mouth Opening	☐	☐	☐	☐	☐
Head Nodding	☐	☐	☐	☐	☐
Falling Down	☐	☐	☐	☐	☐

2. How fast do you usually fall asleep in the evening?

>40 min 31-40 min 21-30 min 10-20 min <10 min

3. Do you sleep during the day (take naps)?

☐ No need ☐ I wanted but cannot sleep ☐ Twice weekly or less
☐ On 3-5 days weekly ☐ Daily or almost daily

4. Do you fall asleep unintentionally during the day?

Situation	Never	Monthly or less	Weekly	Daily	Several times Daily
Reading	☐	☐	☐	☐	☐
Travelling	☐	☐	☐	☐	☐
Standing	☐	☐	☐	☐	☐
Eating	☐	☐	☐	☐	☐
Other Unusual	☐	☐	☐	☐	☐

Scale ranging : 0 to 4
Total scores : 0 to 44

Higher score
: narcoleptic tendencies

: cutoff 14 have high sensitivity and specificity.

Hublin et al.

Diagnosis – HLA

Human Leukocyte Antigen (DQB1*0602, DQB1*0301)

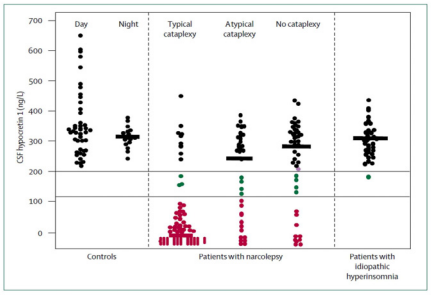
HLA DQB1*0602
- 85-95% of patients with narcolepsy with cataplexy
- 40-60% of patients with narcolepsy without cataplexy
- 12-34% general population

* Homozygous: 2-4배 risk increase
* Ethnic origin 과 관계 없음.

HLA genes: present antigens to the rest of the immune system
HLA genes are highly polymorphic

Diagnosis – CSF Hypocretin

CSF Hypocretin-1
< 110 pg/mL or absence of detectable hypocretin



Narcolepsy w/ cataplexy
Specificity: 99%, Sensitivity: 87-89%
Narcolepsy w/o cataplexy and mild or atypical cataplexy
Specificity 99%, Sensitive 16%

Mignot, lancet 2007

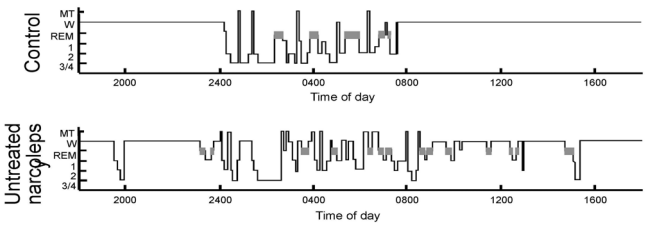
Diagnosis – PSG

Polysomnography

Short sleep latency
Short REM sleep latency
Fragmented REM sleep
Stage 1 sleep extended
Disruption of normal sleep pattern with frequent awakenings.
REM sleep without atonia, PLMS, and even sleep disordered breathing

Littner 2005, Singh 2006, Geisler 2006 Mignot 2006

Diagnosis – PSG



Normal	Narcolepsy
Non-Rapid eye movement (NREM) and rapid eye movement (REM) sleep alternate through the night, with an approximately 90 minute cycle Four to five cycles 4.8 minutes of daytime sleep	Short sleep latency Short REM sleep latency Fragmented REM sleep Stage 1 sleep extended Disruption of normal sleep pattern with frequent awakenings. 44 minutes of daytime sleep

Mignot 2007, Rogers et al. *Sleep*. 1994;17:590.

Diagnosis –MSLT

Multiple Sleep Latency Test

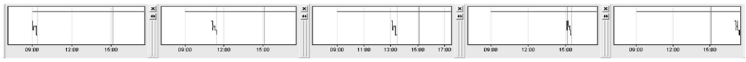
assess physiologic **sleep tendency** in the absence of alerting factors.
" try to fall asleep"
Overnight PSG – ensure sufficient sleep without sleep deprivation
5번의 20 minute nap 각각의 Sleep latency 및 SOREM 측정

Narcolepsy:
SOREM (sleep onset REM): REM occurring within 15 mins of sleep onset
SL (Sleep latency) shorter than 8 mins

Normal population: SL <8 mins 30%, SOREM 2-4%)

Littner 2005, Singh 2006, Geisler 2006 Mignot 2006

Diagnosis – MSLT



Daytime naps	SSS	ESS	Sleep latency	REM latency	Sleep stage
1st trial	4	23	1 min	1 min 30 sec	N1, 2, R
2nd trial	-	-	4 min	1 min	N1, 2, R
3rd trial	-	-	3 min	1 min	N1, 2, R
4th trial	-	-	2 min	30sec	N1, 2, R
5th trial	-	-	5 min	30sec	N1, 2, R
Mean sleep latency				3 min	
Number of sleep-onset REM (SOREM)				5	
Mean REM sleep latency				54 sec	

Diagnosis – MWT

Maintenance of Wakefulness Test

Measure individual's ability to stay awake
Assess the response to treatment

Protocol

40 minute protocol - 4 trials separated by 2-hour intervals
recline 자세, quiet-dark room
"sit still and remain awake for as long as possible"
: sleep latency 측정

Interpretation

Sleep latency <8 min abnormal
8-40 min: uncertain significance

97.5% healthy subjects ≥8 min
42% of healthy subjects stay awake for entire 40 min trial

Littner 2005, Singh 2006, Geisler 2006 Mignot 2006, Kushida 2008

Diagnostic Criteria For Narcolepsy

Narcolepsy With Cataplexy
A. Excessive daytime sleepiness
B. Definite history of cataplexy
C. MSLT optional but advised
D. Hypersomnia not better explained by another disorder

Narcolepsy Without Cataplexy
A. Excessive daytime sleepiness
B. Typical cataplexy is not present
C. Abnormal MSLT required
D. Hypersomnia not better explained by another disorder

Narcolepsy Due to Medical Condition
A. Excessive daytime sleepiness
B. Definite history of cataplexy, abnormal MSLT, or low CSF hypocretin-1 levels
C. Underlying medical or neurological disorder accounts for daytime sleepiness
D. Hypersomnia not better explained by another disorder

The International Classification of Sleep Disorders: Diagnostic and Coding Manual.

Diagnostic criteria

Narcolepsy with Cataplexy

A Excessive daytime sleepiness present for at least 3 months

B Definite history of cataplexy, i.e., loss of muscle tone triggered by laughter or strong emotions (less than 2 mins)

C Should be confirmed by MSLT preceded by an overnight PSG consisting of at least 6 hours of sleep.
A sleep latency ≤ 8 minutes + two or more sleep-onset REM periods (SOREMP) are considered abnormal.
Alternatively a decreased CSF hypocretin level (≤ 110 pg/mL) or one third of mean normal control value.

D The hypersomnia is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

MSLT, Multiple Sleep Latency Test; PSG, polysomnogram; REM, rapid eye movement; CSF, cerebrospinal fluid

Diagnostic criteria

Narcolepsy with Cataplexy

A Excessive daytime sleepiness present for at least 3 months

B Cataplexy is absent or very doubtful

C Should be confirmed by MSLT preceded by an overnight PSG consisting of at least 6 hours of sleep.
A sleep latency ≤ 8 minutes + two or more sleep-onset REM periods (SOREMP) are considered abnormal.

D The hypersomnia is not better explained by another sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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Treatment

No cure

Medications can manage symptoms
- Stimulants (mostly dopaminergic)
- Antidepressants (mostly noradrenergic)
- Sodium oxybate (xyrem)

Life style changes can mange symptoms
- Schedule sleeping times
- Regular napping time (15-30 min)
- Avoid substance usage (alcohol etc)
- Get regular exercise

Pharmacologic Treatment of Excessive Daytime Sleepiness

Drug	Dosage	Comment	Common AE
Stimulant			
D-Amphetamine	5-10mg (max 60mg) 1-2/day (아침, 점심)	Increase monoamine release (DA>NE>>5HT)	Palpitation, Tachycardia, elevated BP, anorexia, weight loss, insomnia, psychosis, potential for abuse
Methamphetamine	5-10mg (max 60mg) 1-2/day (아침, 점심)	Similar to amphetamine, but more lipophilic with inc. central penetration	Same but high abuse potential, more anorexigenic
Methylphenidate	10-20mg (max 60mg) 1-2/day (아침, 점심)	Similar to amphetamine	Same but less abuse potential, less anorexigenic
Wake promoting agents			
Modafinil	100-200mg (max 400mg) 1-2/day (아침, 점심)	Little addictive potential	Headache, Nausea, insomnia
Other			
Sodium oxybate	1.5g at bed time and 2-4 hours later (max 9g)	EDS, cataplexy and sleep disruption 모두 효과적	Headache, Nausea, dizziness, enuresis, can worse SDB

Adopted from Kushida 2009

Pharmacologic Treatment of Cataplexy

Drug	Dosage	Comment	Common AE
Tricyclics			
Imipramine	10-25mg Bedtime (max 125-150mg)	Efficacious but relatively high doses are generally needed.	Dry mouth, constipation, drowsiness
Protriptyline	5-10mg Bedtime (max 60mg)		
Clomipramine	10-25mg Bedtime (max 10-150mg)		
SSRI			
Fluoxetine	10-20mg Morning (max 60mg)	Efficacious but relatively high doses are generally needed.	Nausea, insomnia, diarrhea
Fluvoxamine	25-50mg Morning (max 300mg)		
SSNRI			
Venlafaxine	75mg morning (max 375mg)	most effective First choice	Nausea, constipation, somnolence, dry mouth, dizziness

Adopted from Kushida 2009

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- **Idiopathic Hypersomnia With Long Sleep Time**
- **Idiopathic Hypersomnia Without Long Sleep Time**
  - Behaviorally induced insufficient sleep syndrome
  - Hypersomnia due to medical condition
  - Hypersomnia due to drug or substance
  - Hypersomnia not due to substance or known physiologic condition (nonorganic hypersomnia)
  - Physiologic (organic) hypersomnia, unspecific

Recurrent Hypersomnia

Kleine-Levin Syndrome

Hypersomnia

few days to several weeks (2days ~ 4weeks)
sleep for 16-18 hours/day
waking only to eat and void – wt gain of few Kg during the episode
Cognitive ab.: unreality, confusion, hallucination
Behavior ab.: binge eating, hypersexuality, irritability, aggressiveness

Termination: amnesia, transient dysphoria, elationwith insomnia

Between episodes: normal sleep and general behavior
* 1-10 / year

Menstrual-related Hypersomnia

Last one week with rapid resolution at the time of menses

Idiopathic Hypersomnia with Long Sleep Time
Idiopathic Hypersomnia w/o Long Sleep Time

Unknown etiology diagnosis of exclusion

EDS with adequate total sleep time and normal overnight sleep architecture
Idiopathic hypersomnia with long sleep time : long ≥10 hr
Idiopathic hypersomnia wo long sleep time : normal (>6 but ≤ 10).

Unrefreshing sleep with difficulty waking up
Unrefreshing nap, and usually longer (3-4 hr) than narcoleptic patients

Normal CSF hypocretin level

Diagnosis	Symptoms	Diagnostic Criteria		
Narcolepsy with cataplexy	3months EDS Recurrent Nap (refreshing)	Cataplexy (+) ϕ	PSG (TST>6hr) MSLT MSL≤ 8 min; ≥2 SOREMPs	CSF hypocretin-1 ≤ 110pg/ml, or 1/3 of mean normal control values
Narcolepsy wo cataplexy		Cataplexy (-) ϕ		
Idiopathic hypersomnia with long sleep time	3months EDS	Nocturnal sleep ≥10 hours (prolonged) ϕ ¥	PSG major sleep periods (≥10hr)	MSLT MSL≤ 8 min; < 2 SOREMPs
Idiopathic hypersomnia wo long sleep time		Nocturnal sleep >6 but ≤ 10 hours (Normal) ϕ ¥	PSG normal sleep periods (>6 but ≤ 10)	

ϕ No medical or mental disorder accounts for the symptom
¥ Symptoms do not meet the diagnostic criteria of other sleep disorders causing excessive sleepiness

Behaviorally induced insufficient sleep syndrome

Persistently fail to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness

Voluntary, albeit unintentional, Chronic sleep deprivation

Vacation, weekend, holiday -> markedly extended sleep time

Common problem in adolescents

Insufficient sleep time:
daytime sleepiness
concentration problems,
lowered energy level

Tx: Behavior modification

Hypersomnia Due to Medical Condition

Medical condition directly causing the hypersomnia
: head trauma, stroke, encephalitis, inflammatory conditions, tumors, genetic diseases, neurodegenerative diseases.

Hypersomnia Due to Drug or Substance

Hypersomnia due to substance abuse, stimulant withdrawal, sedative abuse

Hypersomnia Not Due to Substance or Known Physiological Condition (Nonorganic hypersomnia, NOS)

Hypersomnia associated with mental disorders