Karel ŠONKA

Dept. of Neurology, Charles University, 1st Faculty of Medicine and General University Hospital Prague

Idiopathic hypersomnia 2019

11th annual meeting of Integrated Sleep Medicine Society Japan

Nagoya, October 12, 2019

Conflict of Interest Disclosures
– Authors/Presenters

[x] The authors do not have any potential conflicts of interest to disclose,

OR

[ ] The authors wish to disclose the following potential conflicts of interest related to content in this lecture:

Type of Potential Conflict	Details of Potential Conflict
Grant/Research Support	
Consultant	
Speakers' Bureaus	
Financial support	
Other	

This talk presents material that is related to one or more of these potential conflicts, and the following objective references are provided as support for this lecture:

1.
2.
3.

Short content

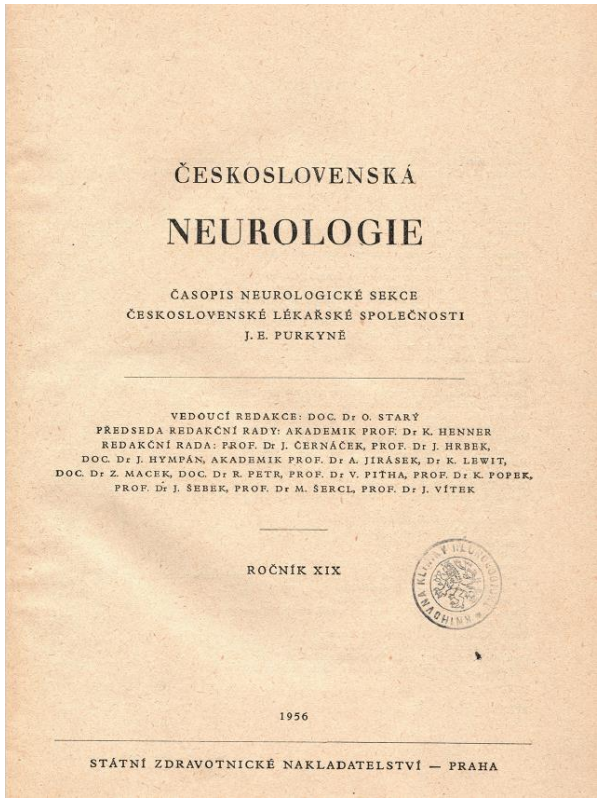
- Idiopathic hypersomnia concepts
- Weakness of ICSD3 diagnostic criteria
- Pathophysiology
- Diagnosis and severity measurement
- Treatment

Idiopathic hypersomnia

- Rare disease with „central„ EDS.
- EDS may be unique symptom of IH.
- Clinical picture of EDS in IH has different manifestations.

History of idiopathic hypersomnia concepts

First description by Bedřich Roth (1919 – 1989) in combination with sleep drunkenness



ČESKOSLOVENSKÁ

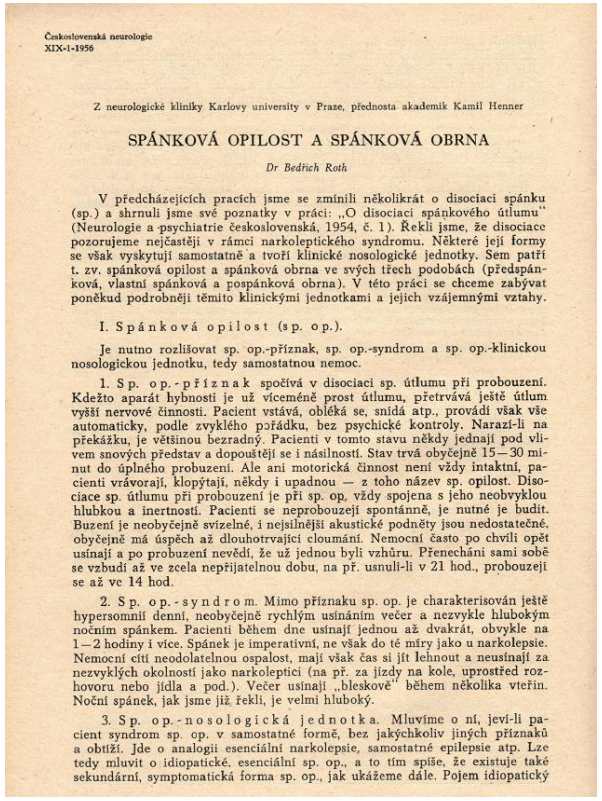
NEUROLOGIE

ČASOPIS NEUROLOGICKÉ SEKCE
ČESKOSLOVENSKÉ LÉKAŘSKÉ SPOLEČNOSTI
J. E. PURKYNĚ

ROČNÍK XIX

1956

STÁTNÍ ZDRAVOTNICKÉ NAKLADATELSTVÍ — PRAHA



Československá neurologie
XIX-1-1956

Z neurologické kliniky Karlovy university v Praze, přednosta akademik Kamil Henner

SPÁNKOVÁ OPILOST A SPÁNKOVÁ OBRNA

Dr Bedřich Roth

V předcházejících pracích jsme se zmínili několikrát o disociaci spánku (sp.) a shrnuli jsme své poznatky v práci: „O disociaci spánkového útlumu" (Neurologie a psychiatrie československá, 1954, č. 1). Řekli jsme, že disociace pozorujeme nejčastěji v rámci narkoleptického syndromu. Některé její formy se však vyskytují samostatně a tvoří klinické nosologické jednotky. Sem patří t. zv. spánková opilost a spánková obrna ve svých třech podobách (předspánková, vlastní spánková a pospánková obrna). V této práci se chceme zabývat poněkud podrobněji těmito klinickými jednotkami a jejich vzájemnými vztahy.

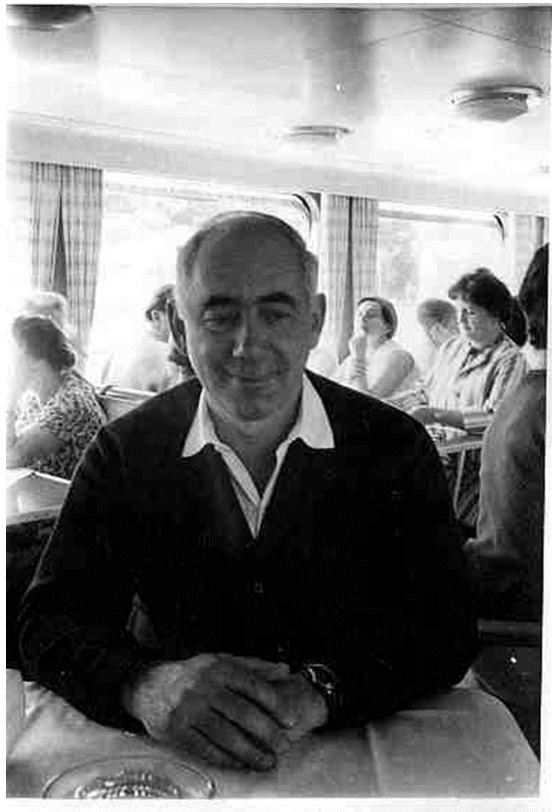
I. Spánková opilost (sp. op.).

Je nutno rozlišovat sp. op.-příznak, sp. op.-syndrom a sp. op.-klinickou nosologickou jednotku, tedy samostatnou nemoc.

1. Sp. op.-příznak spočívá v disociaci sp. útlumu při probouzení. Kdežto aparát hybnosti je už víceméně prost útlumu, přetrvává ještě útlum vyšší nervové činnosti. Pacient vstává, obléká se, snídá atp., provádí však vše automaticky, podle zvyklého pořádku, bez psychické kontroly. Narazí-li na překážku, je většinou bezradný. Pacienti v tomto stavu někdy jednají pod vlivem snových představ a dopouštějí se i násilností. Stav trvá obyčejně 15—30 minut do úplného probuzení. Ale ani motorická činnost není vždy intaktní, pacienti vrávorají, klopýtají, někdy i upadnou — z toho název sp. opilost. Disociace sp. útlumu při probouzení je při sp. op. vždy spojena s jeho neobvyklou hlubkou a inertností. Pacienti se neprobouzejí spontánně, je nutné je budit. Buzení je neobyčejně svízelné, i nejsilnější akustické podněty jsou nedostatečné, obyčejně má úspěch až dlouhotrvající cloumání. Nemocní často po chvíli opět usínají a po probuzení nevědí, že už jednou byli vzhůru. Přenecháni sami sobě se vzbudí až ve zcela nepřijatelnou dobu, na př. usnuli-li v 21 hod., probouzejí se až ve 14 hod.

2. Sp. op.-syndrom. Mimo příznaku sp. op. je charakterisován ještě hypersomnií denní, neobyčejně rychlým usínáním večer a nezvykle hlubokým nočním spánkem. Pacienti během dne usínají jednou až dvakrát, obvykle na 1—2 hodiny i více. Spánek je imperativní, ne však do té míry jako u narkolepsie. Nemocní cítí neodolatelnou ospalost, mají však čas si jít lehnout a neusínají za nezvyklých okolností jako narkoleptici (na př. za jízdy na kole, uprostřed rozhovoru nebo jídla a pod.). Večer usínají „bleskově" během několika vteřin. Noční spánek, jak jsme již řekli, je velmi hluboký.

3. Sp. op.-nosologická jednotka. Mluvíme o ní, jeví-li pacient syndrom sp. op. v samostatné formě, bez jakýchkoliv jiných příznaků a obtíží. Jde o analogii esenciální narkolepsie, samostatné epilepsie atp. Lze tedy mluvit o idiopatické, esenciální sp. op., a to tím spíše, že existuje také sekundární, symptomatická forma sp. op., jak ukážeme dále. Pojem idiopatický



Bedrich Roth, 1959

Sleep drunkeness – nosological entity, hypersomnia - its symptom

Department of Neurology and Center of Clinical Neuroscience
First Faculty of Medicine, Charles University and General University Hospital in Prague

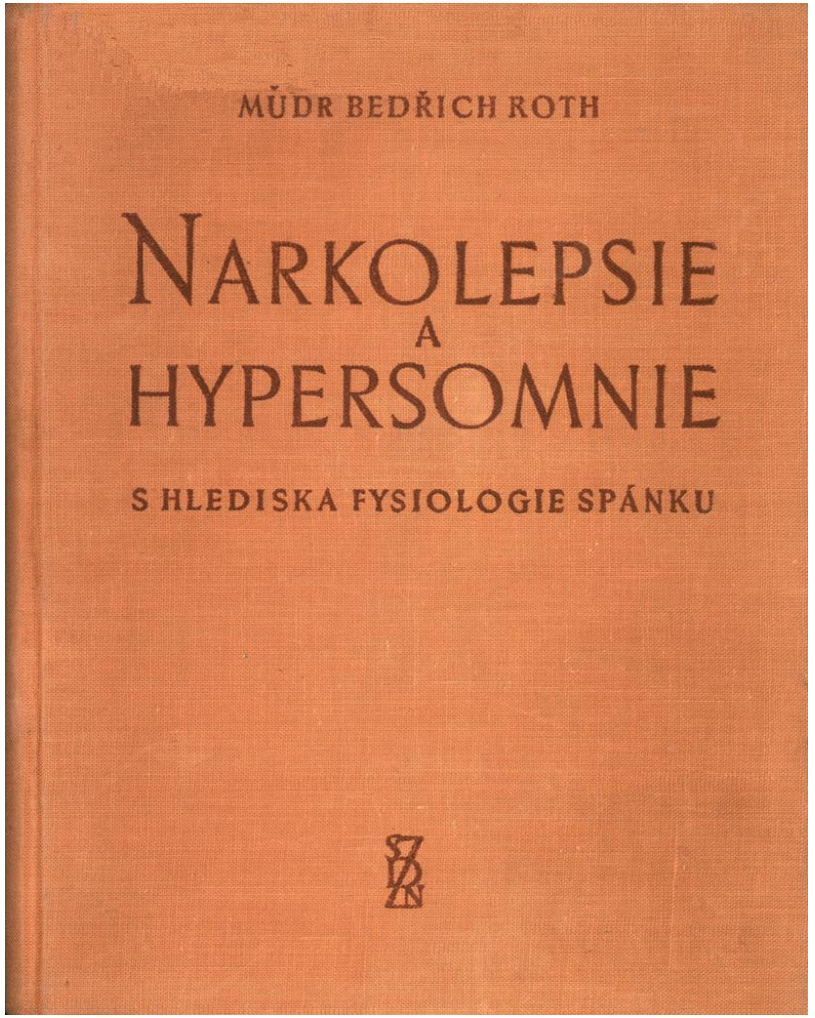
Two forms of postdormitial drunkenness

A sporadic form

Once or a few times in the patient's life time, on suddenly being artificially wakened after insufficient sleep

A form with persistent occurrence which occurs everytime on awakening

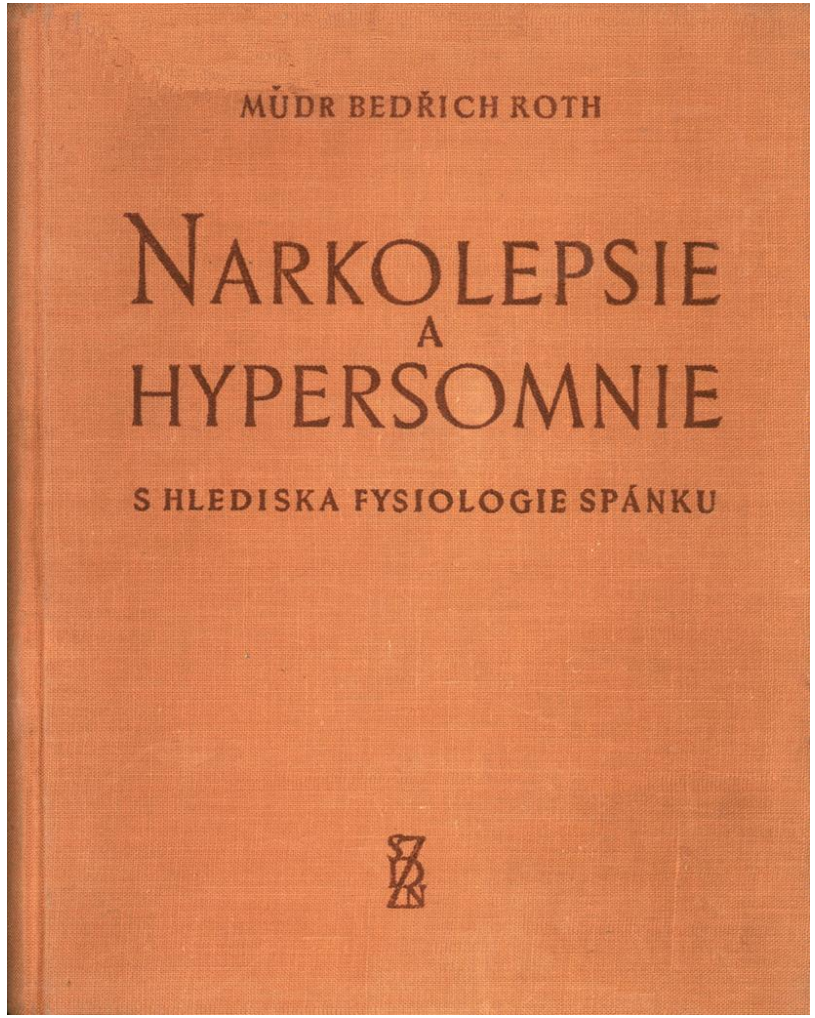
new „clinical entity“



B. Roth, 1957

Sleep drunkenness symptoms:

Nejnápadnějším příznakem onemocnění je porucha probouzení. Pacienti vesměs spí abnormálně hlubokým spánkem a spontánně se nikdy neprobudí v přijatelnou dobu. Je-li nutno, aby vstali v 7 hod. ráno, probudí se, nejsou-li buzeni, až někdy odpoledne nebo i večer. Všichni tito nemocní používají zvlášť silných budíků, většinou několika a mnozí z nich je mají speciálně konstruovány, takže zvoní opětovně a velmi silně. Přesto se budíky u těchto nemocných neosvědčují; buď se nemocní na zvonění neprobudí vůbec, nebo ve stavu rozespalosti budík odstaví a spí dále. Obvykle uspěje až dlouho trvající cloumání, někdy je nutno pacienta posadit nebo postavit a pozorovali jsme dokonce pacienta, kterého rodiče musili nosit ještě spícího do školy. Když se pacient konečně probudí, je rozespalý, desorientován a zmaten a provádí všechny úkony automaticky. Tento stav ustupuje normálnímu stavu bdělosti po různě dlouhé době, obvykle po čtvrt až půl hodině, výjimečně až po hodině. V lehčích případech trvá tento stav jen 5—10 min. a upraví se po omytí studenou vodou. Ve stavu spánkové opilosti jde o převahu útlumu ve sféře vyšší nervové činnosti. Hybnost je zachována a poruchy koordinace a účelnosti jednání, které lze někdy pozorovat, jsou podmíněny útlumem vyšší nervové činnosti. Někdy však postihuje útlum v menší míře i hybnost, nemocní pak vrávorají, klopýtají a padají. — Ve stavu spánkové opilosti jedná někdy pacient pod vlivem snových vidin a představ, abnormálně vnímá a reaguje na zevní podněty, takže i u této formy spánkové opilosti může dojít k trestným činům. Je pochopitelné, že k příznakům spánkové opilosti dochází u těchto nemocných tím spíše, jsou-li buzeni uprostřed nočního spánku.	Sleep drunkenness (awakening difficulties)
Usínání je u samostatné spánkové opilosti abnormálně rychlé a nemocní udávají, že spánek přichází »jako blesk«, jakmile si lehnou. Tak tomu bylo u 12 z našich 13 nemocných a jen jediný pacient udával, že usíná těžko.	Fast falling asleep
Noční spánek je u všech nemocných neobyčejně hluboký a je velmi těžké a někdy skoro nemožné je probudit. Pacienti sami udávají, že abnormální hloubku nočního spánku pociťují nepříjemně a jsou spokojeni, stane-li se spánek v důsledku léčby méně hlubokým.	Deep and uninterruptible night sleep
Denní hypersomnie byla přítomna u všech našich 13 nemocných. U 12 z nich šlo o hypersomnii periodickou, u jednoho nemocného o trvalou hypersomnii somnolentního rázu s občasným usínáním. Záchvaty periodické hypersomnie trvají u samostatné spánkové opilosti obvykle několik hodin. Přehled o trvání záchvatů periodické hypersomnie u našich nemocných dává tabulka č. 107.	Daytime hypersomnia



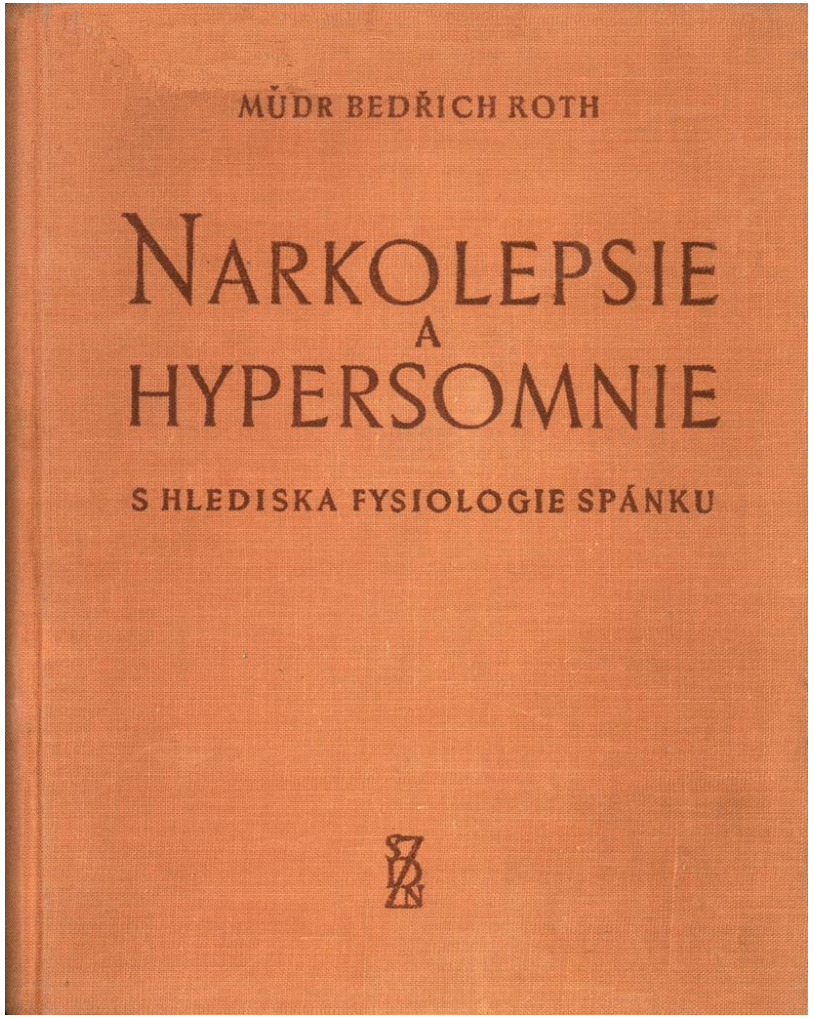
B. Roth, 1957

page 269

Sleep drunkenness symptoms:

Patients rarely waken spontaneously at an appropriate time; they have to be awakened. They usually do not awaken to the ringing of a clock or telephone, or, if the ringing is prolonged, they shut it off and return to sleep. Many patients have special devices for waking them up such as repeating alarm clocks and resonators. In most cases, these devices are ineffective, and the patients have to be awakened by their family members. Awakening procedures must be vigorous and persistent; it is usually necessary to shake the patient repeatedly before he reacts. Even then the patients are confused, disoriented, very slow, and unable to react adequately to external stimuli. If left alone, they often return to sleep and later do not remember having been previously awakened. In most cases, their state improves after washing with cold water, but in many patients SD persists even then...

Usínání je u samostatné spánkové opilosti abnormálně rychlé a nemocní udávají, že spánek přichází »jako blesk«, jakmile si lehnou. Tak tomu bylo u 12 z našich 13 nemocných a jen jediný pacient udával, že usíná těžko.	Fast falling asleep
Noční spánek je u všech nemocných neobyčejně hluboký a je velmi těžké a někdy skoro nemožné je probudit. Pacienti sami udávají, že abnormální hloubku nočního spánku pociťují nepříjemně a jsou spokojeni, stane-li se spánek v důsledku léčby méně hlubokým.	Deep and uninterruptible night sleep
Denní hypersomnie byla přítomna u všech našich 13 nemocných. U 12 z nich šlo o hypersomnii periodickou, u jednoho nemocného o trvalou hypersomnii somnolentního rázu s občasným usínáním. Záchvaty periodické hypersomnie trvají u samostatné spánkové opilosti obvykle několik hodin. Přehled o trvání záchvatů periodické hypersomnie u našich nemocných dává tabulka č. 107.	Daytime hypersomnia



B. Roth, 1957

page 269

History

Existence of the EDS disease different from narcolepsy was mentioned after Roth by some authors

Dement at al 1966,
Berti-Ceroni et al 1967,
Passouant et al 1968

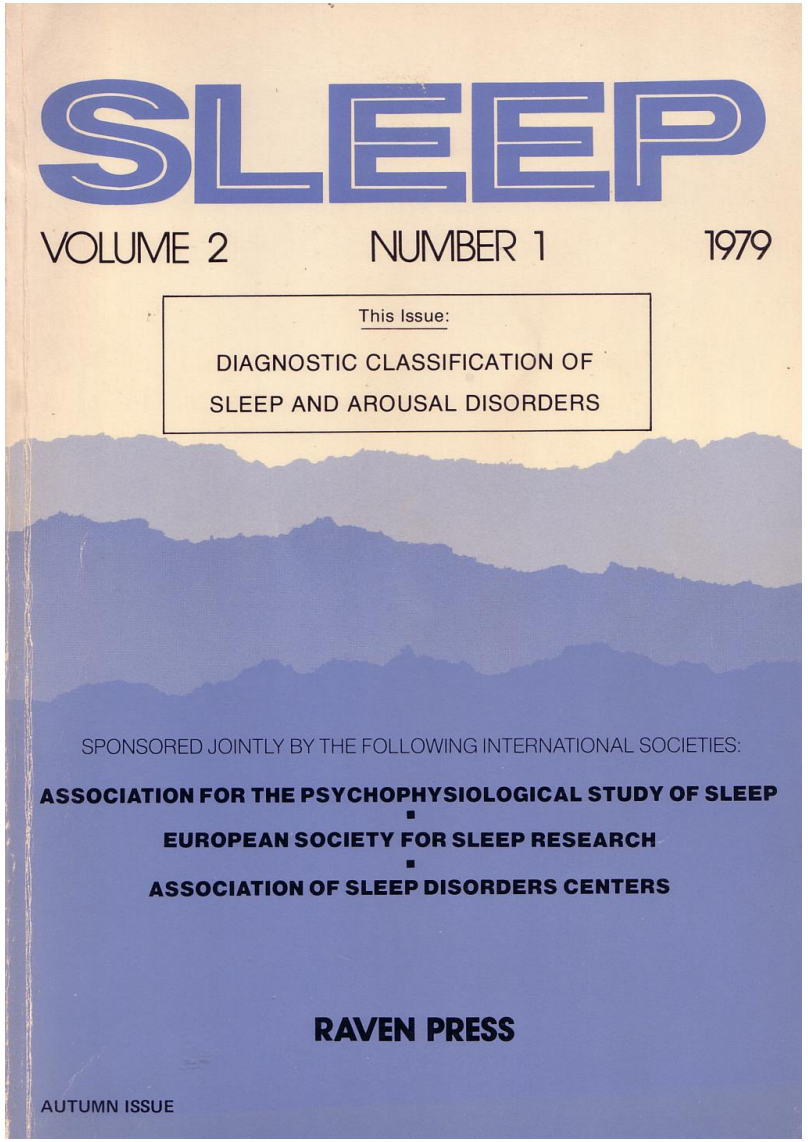
New term

„Hypersomnia with sleep drunkeness“

Roth, Nevšímalová, Rechtschaffen, 1972

B. Disorders of Excessice Somnolence

1. Psychophysiological
2. Associated with Psychiatric Disorders
3. Associated with Use of Drugs and Alcohol
4. Associated with Sleep induced Respiratory Impairment
5. Associated with Sleep-related Myoclonus and RLS
6. Narcolepsy
7. ***Idiopathic CNS Hypersomnolence***
8. Associated with Other Medical, Toxic, and Environmental Conditions
9. Associated with Other DOES Conditions
10. No Disorders of Excessice Somnolence Abnormality



1976: Second concept of idiopathic hypersomnia: Two forms of idiopathic hypersomnia

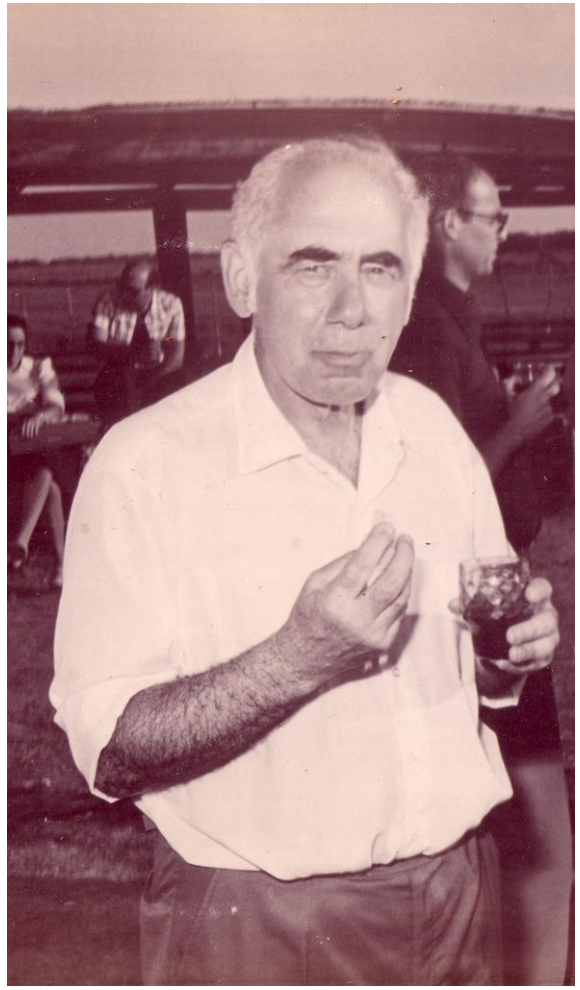
Narcolepsy and Hypersomnia: Review and Classification of 642 Personally Observed Cases

By B. ROTH

DEPARTMENT OF NEUROLOGY, CHARLES UNIVERSITY MEDICAL FACULTY, PRAGUE, CZECHOSLOVAKIA

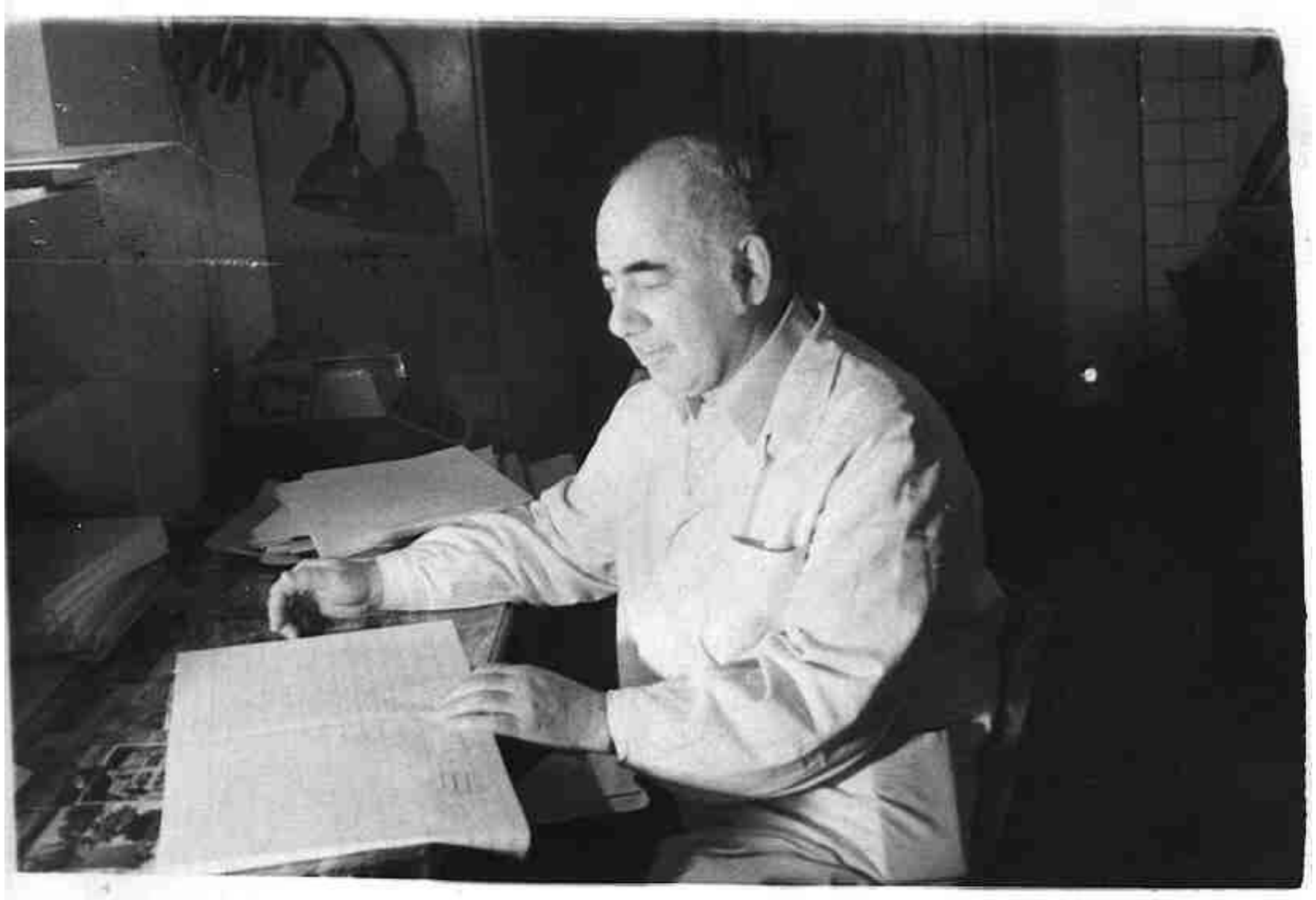
Polysymptomatic form characterized by EDS of one to several hours duration, prolonged night sleep of a 12-18 h duration and great difficulty upon awakening in the morning

Monosymptomatic form characterized by the most prominent and often unique manifestation of EDS of one to several hours duration, however not as irresistible as in narcolepsy



Bedrich Roth, France, 1976

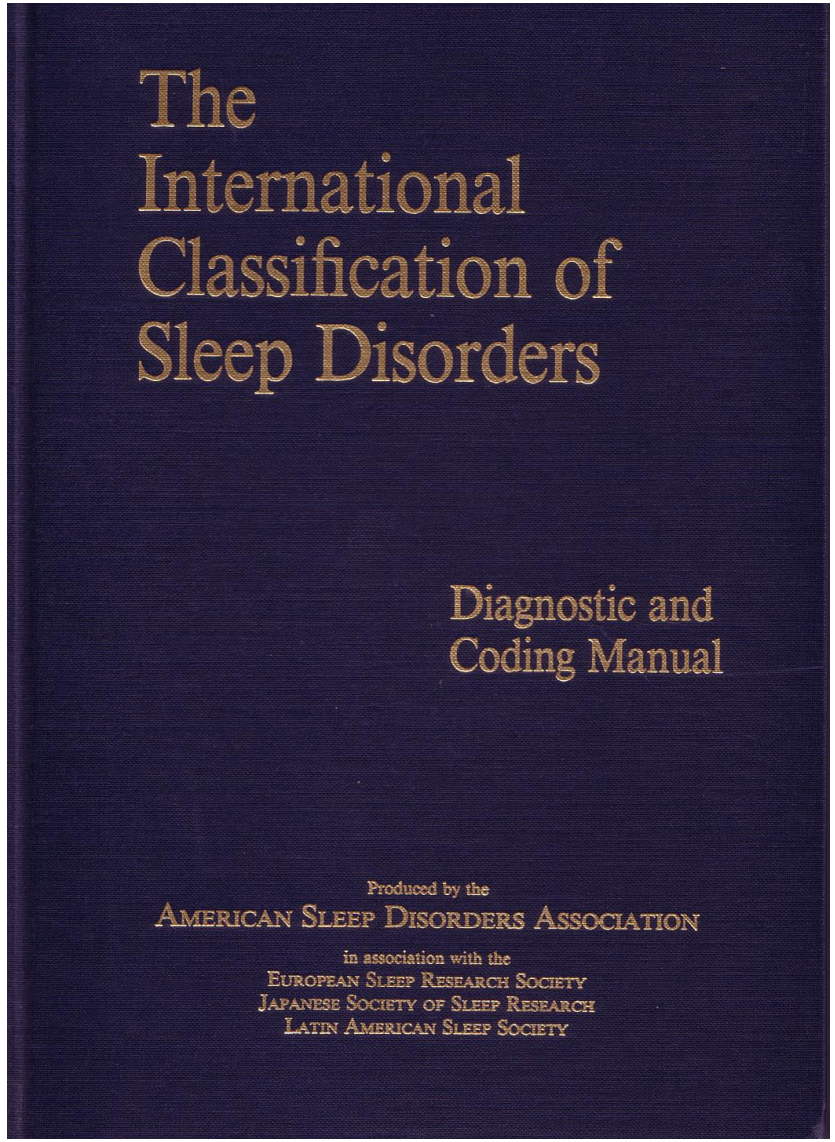
Archives Suisses de Neurologie, Neurochirurgie et de Psychiatrie
Volume 119 (1976), fascicule 1, pages 31–41



Bedrich Roth in his laboratory, 1984.

Dyssomnias, intrinsic sleep disorders

1 Psychophysiological Insomnia
2. Sleep State Misperception
3. Idiopathic Insomnia
4. Narcolepsy
5. Recurrent Hypersomnia
6. ***Idiopathic Hypersomnia***
7. Posttraumatic Hypersomnia
8. Obstructive Sleep Apnea Syndrome
9. Central Sleep Apnea Syndrome
10. Central Alveolar Hypoventilation Syndrome
11. Periodic Limb Movement Disorder
12. Restless Legs Syndrome
13. Intrinsic Sleep Disorder NOS



Rochester, 1990

Brain (1997), **120,** 1423–1435

Idiopathic hypersomnia
A series of 42 patients

Claudio Bassetti and Michael S. Aldrich

Department of Neurology, University of Michigan Medical Center, Ann Arbor, Michigan, USA

n = 28, 11 males and 17 females

« Classic » idiopathic hypersomnia

n = 8 (3 males and 5 females)

« Narcoleptic » -like idiopathic hypersomnia

n = 9 (5 males and 4 females)

« Mixed » idiopathic hypersomnia

n = 11 (3 males and 8 females)

Japanese Society of Sleep Research

Psychiatr Clin Neurosci (1998),52, 125-129

Special Paper

Idiopathic hypersomnia

MICHEL BILLIARD, CORINNE MERLE, BERTRAND CARLANDER, BASILE ONDZE, DANIEL ALVAREZ AND ALAIN BESSET

Department of Neurology B, Gui de Chauliac Hospital, Montpellier, France

n = 23, 9 males and 14 females

« Complete form »

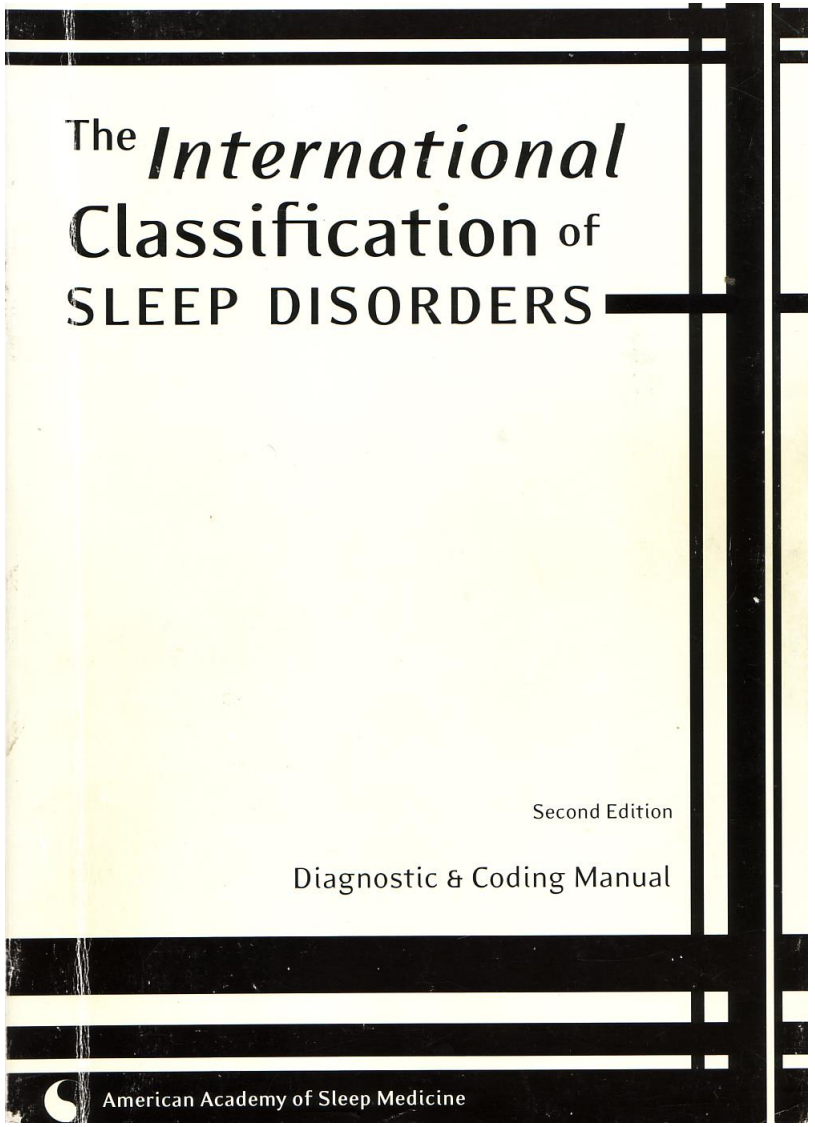
n = 13 (4 males and 9 females)

« Incomplete form »

n = 10 (4 males, 9 females)

3. Hypersomnias of central origin

1. Narcolepsy with cataplexy
2. Narcolepsy without cataplexy
3. Narcolepsy due to medical condition
4. Narcolepsy, unspecified
5. Recurrent hypersomnia
6. ***Idiopathic hypersomnia with long sleep time***
7. ***Idiopathic hypersomnia without long sleep time***
8. Behaviorally induced Insufficient sleep syndrome
9. Hypersomnia due to medical condition
10. Hypersomnia due to drug or substance
11. Hypersomnia not due to substance or known physiological condition (Nonorganic hypersomnia, NOS)



Westchester, 2005

Idiopathic Hypersomnia with and without Long Sleep Time: A Controlled Series of 75 Patients

Sleep 2009

Cyrille Vernet, MSc[1,2,3]; Isabelle Arnulf, MD, PhD[1,2,3]

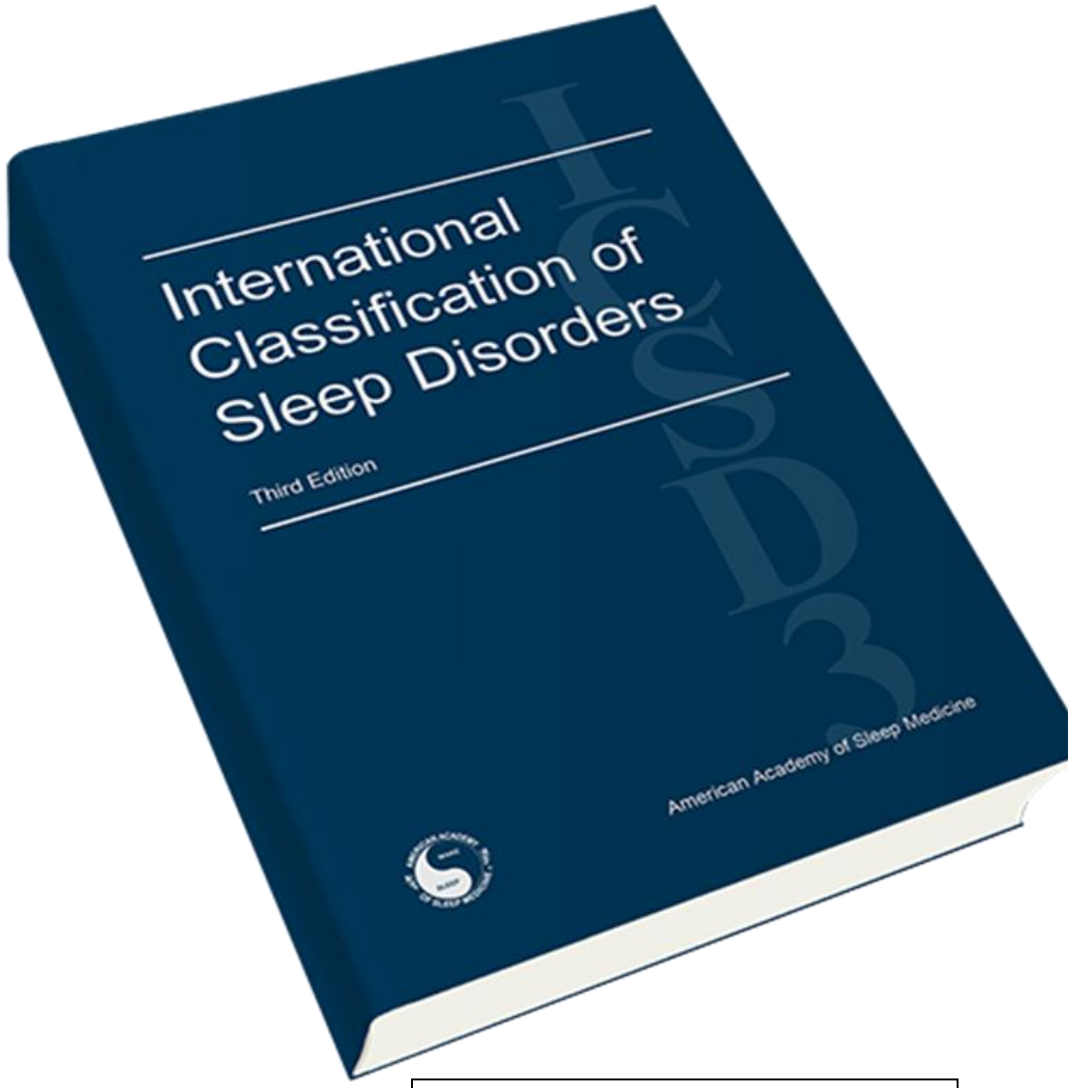
Clinical characteristics	Patients without long sleep time	Patients with long sleep time	P
Number	35	40	
Age, y	39.7 ± 13.0	29.1 ± 9.7	0.0002
BMI, kg/m2	26.1 ± 5.3	22.8 ± 4.1	0.005
Women, %	60.0	67.5	0.63
Hypnagogic hallucinations, %	25.0	23.3	0.88
Sleep paralysis, %	28.6	26.7	0.87
Non refreshing naps, %	45.0	47.6	0.87
Sleep drunkenness, %	23.1	50.0	0.08
Epworth sleepiness score (0-24)	15.0 ± 4.1	14.9 ± 4.3	0.91
Pichot fatigue score (0-32)	26.9 ± 7.9	26.0 ± 8.8	0.75
HAD anxiety (0-21)	9.6 ± 4.1	8.1 ± 4.0	0.29
HAD depression (0-21)	7.5 ± 4.6	6.8 ± 5.4	0.66
Horne-Ostberg score	52.7 ± 10.2	44.0 ± 13.8	0.04
HLA DQB1*0602 positive, %	21.9	26.5	0.78

Sleep measures	Patients without long sleep time	Patients with long sleep time	P
Number	35	40	
Nighttime sleep			
Total sleep time, min	517 ± 60	633 ± 76	< 0.0001
Sleep efficiency, %	89.3 ± 6.7	92.3 ± 5.6	0.04
Latency to, min			
Sleep onset	26.7 ± 26.5	35.1 ± 51.3	0.37
REM sleep	82.8 ± 53.2	80.5 ± 43.5	0.84
Sleep stages, % total			
stages 1-2	56.0 ± 9.4	54.8 ± 9.2	0.59
stages 3-4	20.8 ± 7.9	20.8 ± 8.6	0.97
REM sleep	23.1 ± 5.4	24.3 ± 7.3	0.41
Sleep fragmentation			
Arousals, n/h	10.3 ± 7.1	7.3 ± 4.1	0.15
Periodic legs movements, n/h	10.8 ± 14.7	5.4 ± 8.2	0.13
Apnea/hypopnea, n/h	3.4 ± 4.5	0.9 ± 1.3	0.004
End of the night			
SWS after 06:00, % patients	59.4	61.8	0.88
Time of last SWS episode	8:08 ± 1:26	9:27 ± 1:40	0.02
Sleep during 24-hour monitoring			
Total sleep time, min	635 ± 82	747 ± 82	< 0.0001
Sleep stages, % total			
stages 1-2	58.9 ± 8.5	57.5 ± 9.5	0.52
stages 3-4	19.3 ± 7.2	20.0 ± 8.6	0.68
REM sleep	21.6 ± 5.3	22.5 ± 6.7	0.55

Central Disorders of Hypersomnolence

1. Narcolepsy Type 1
2. Narcolepsy Type 2
3. ***Idiopathic Hypersomnia***
4. Kleine Levin Syndrome
5. Hypersomnia due to a medical disorder
6. Hypersomnia Due to a Medication or Substance
7. Hypersomnia Associated with a Psychiatric Disorder
8. Insufficient Sleep Syndrome

Isolated Symptoms and Normal Variants



Darien, 2014

Idiopathic hypersomnia

alternate name: Idiopathic CNS hypersomnolence

ICSD3 diagnostic criteria (2014)

A. Daily periods of irrepressible need to sleep or daytime lapses into sleep

B. Cataplexy is absent.

C. MSLT + night PSG: < 2 SOREMp

D. The presence of at least one of the following:

1. MSLT: sleep latency of ≤ 8 minutes.
2. Total 24-hour sleep time is ≥ 660 min. on 24-hour PSG *or* by actigraphy in association with a sleep log

E. Insufficient sleep syndrome is ruled out.

F. Not better explained …..

Present time

Criticism of IH classification

- Patterns of two sleepiness forms are different
- Other symptoms are not taken in account
- Not based on aetiopathophysiology

Questions:
(a) Do IH forms represent one entity independent versus NT1 and NT2?
(b) Does exist another grouping of symptom complexes with „central“ EDS.

Original Article

Narcolepsy with and without cataplexy, idiopathic hypersomnia with and without long sleep time: a cluster analysis

Karel Šonka [a,*,1], Marek Šusta [a,b,1], Michel Billiard [c]

Cluster analysis was chosen as a statistical method of partitioning patients sample into relatively homogenous classes.

Patients

Retrospective analysis
Adult patients
No treatment, no concomitant sleep disorders

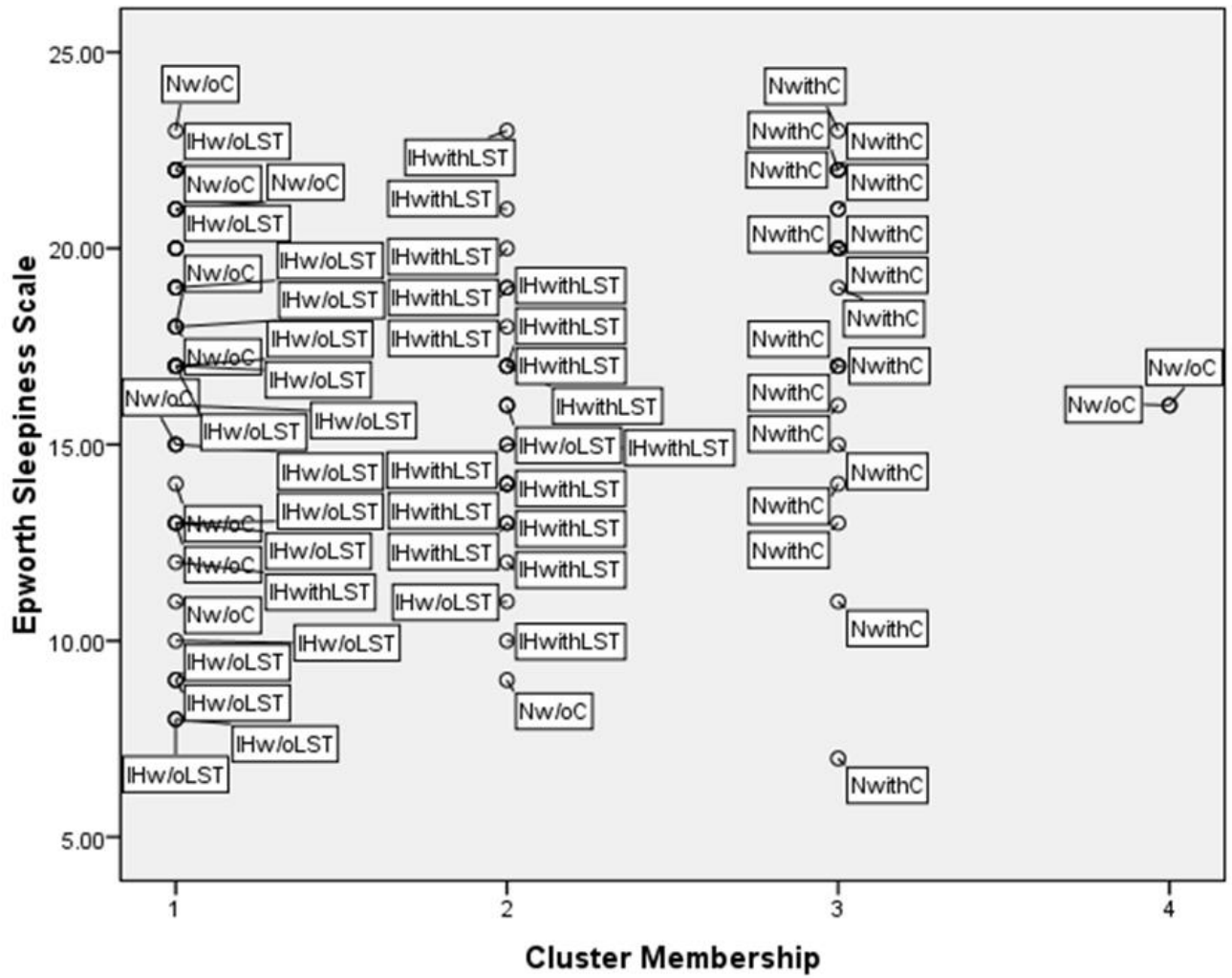
	Diagnosis according to ICSD2			
	IH w/o LST (N=25)	**IH with LST** (N=26)	**N with C** (n=23)	**N w/o C** (N=22)
Men /Women (#)	10/15	7/19	11/12	13/9
Age at examination (years)	41,1 (9,6)	33,0 (11,4)	43,0 (15,7)	45,9 (17,6)
Age at onset (years)	29,4 (9,9)	20.9 (8,6)	22.5 (10,9)	25,5 (15,9)
Disease duration (years)	10,7 (10,5)	13,7 (14,7)	10,1 (8,1)	17,6 (16,0)

Preselection of variables by factor analysis

Variable name	Variable type
Unwanted naps (#)	scale
Irresistible naps duration	Scale
Irresistible unwanted naps	Nominal
Great difficulty waking up from naps	Nominal
Cataplexy	Nominal
MSLT: mean sleep latency	Scale
MSLT: number of SOREMPs	Scale

Not included: Night PSG results because of different protocols.
Differences between working days and weekends because of lack of data.

The analysis was not focused on finding the most relevant symptoms and features for clustering new groups, or on excluding any symptoms from the diagnostic criteria.



Result: Cluster 1 – IH w/o LST + N w/o C
Cluster 2 – IH with LST
Cluster 3 - N with C

ICSD3 spectra of narcolepsy and idiopathic hypersomnia				
	NT 1	NT 2	Idiopathic hypersomnia	
	cataplexy +	no cataplexy		sleep >660 min
MSLT SL (min)	< 8	< 8	< 8	≤ or > 8
MSLT SOREMPs	≥ 2	≥ 2	< 2	< 2

	Hypocretin deficient narcolepsy	Group waiting for the identification	True idiopathic hypersomnia
MSLT SL (min)	< 8	< 8	≤ or > 8
MSLT SOREMPs	≥ 2	≥ 2 or < 2	< 2

PLOS ONE

2015

RESEARCH ARTICLE

Polysomnographic Assessment of Sleep Comorbidities in Drug-Naïve Narcolepsy-Spectrum Disorders—A Japanese Cross-Sectional Study

Taeko Sasai-Sakuma[1,2☯]*, Akihiko Kinoshita[3☯], Yuichi Inoue[1,3☯]

1 Department of Somnology, Tokyo Medical University, Tokyo, Japan, **2** Department of Life Sciences and Bio-informatics, Division of Biomedical Laboratory Sciences, Graduate School of Health Sciences, Tokyo Medical and Dental University, Tokyo, Japan, **3** Japan Somnology Center, Neuropsychiatric Research Institute, Tokyo, Japan

Japanese drug naïve patients with N with C showed higher comorbidity rates and degree of PLMS and polysomnographically diagnosable RBD with excessive motor activity compared to those with **N w/o C or IH w/o LST which were very similar**.

The difference
NT2 versus IH diagnosed by MSLT: number of SOREMp only!

MSLT has demonstrated good sensitivity, specificity, and reliability for NT1 (although between 14%-29% have negative MSLTs), however the test may be less robust for the differentiation of NT2 versus IH.

MSLT has poor reliability in NT2 and IH – the “diagnosis” was reconfirmed in only 30%-47% upon serial MSLT testing.

- Trotti LM et al. Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. J Clin Sleep Med 2013.

- Šonka K et al. The value of repeated non-confirmatory multiple sleep latency test (MSLT) for the diagnosis of narcolepsy. Cesk Slov Neurol N 2014.

- Lopez R et al. Test-retest reliability of the multiple sleep latency test in central disorders of hypersomnolence. Sleep 2017.

- Ruoff C et al. The MSLT is repeatable in narcolepsy type 1 but not narcolepsy type 2: a retrospective patient study. J Clin Sleep Med 2018.

Possible explanations why repeated MSLT in NT2 and IH does not show identical result

- The test is inappropriate for NT2 and IH
- NT2 and IH are not well defined
- NT2 and IH change over time

IH course – a retrospective study

Patients

IH diagnosed previously according to ICSD2/3

No other sleep disorders when diagnosed

Adult age at the diagnosis

Follow-up >1 year

N	44 (17 males, 27 females)
Long sleep duration (600 or 660 min): 18 subjects	
Age at onset	24.7 (±13.0) y.
Age at diagnosis	37.4 (±11.0)
ESS at diagnosis	14.8 (±4.5)
MSLT latency	6.0 (±2.9)
MSLT 1 SOREM	3 (6%)
Night sleep SOREM	0

IH course – a retrospective study. Results.

Night-time - current status

Subj. sleep latency (min)	11.0 (±12.8)
Subj. N of awakenings	1.6 (±3.2)
Subj. sleep not interrupted	31 (72%)

Day-time - current status

EDS everyday 35 (81%)

EDS irresistible 30 (70%)

Nap duration (if any) 55,4 min (±65,9)

Life experience:

Morning sleep drunkenness	28 (65%)
Sleep paralysis	13 (30%)
Hypnagogic hallucinations	9 (21%)

IH course – a retrospective study. Results

Age at follow-up: 42.8 (±12.2) y.

Follow-up duration: 5.4 (±5.2) y.

BMI: 25.8 (±5.8)

Treatment:

Modafinil 12 (26,7%)
Methylphenidate 7 (15,6%)

Antidepressants 6 (13,3%)

Improvement: 12 (28%)

EDS subjectively (nearly/completely) disappeared: 4 (9%) (2 with LST, 2 without LST)

No change over time: 21 (49%)

Worsening: 10 (23%)

Repeated extreme changes of EDS intensity: 1 (2%) - excluded

Diagnosis change: 1 subject – rediagnosed with NT2 (new MSLT) – excluded

Drug effect (life experience):
Modafinil responders 71%
Methylphenidate responders 60%

IH course – a retrospective study. Results

Current status	
ESS (0-24):	13.5 (±4,9)
FSS (0-60):	43.6 (±16,5)
Sleep Inertia Questionnaire (0-150):	59.5 (±20.1)
BDI:	7.3 (±6.6)
Stai II:	23.9 (±2.3)
Morningness-eveningness (16-86):	48.9 (±10.3)
EuQL:	6.9 (±1.9)
Subj. health esteem (0 – 100):	65.4 (±22.8)

New comorbidities	
Depression	11 (26%)
RLS	11 (26%), treated 2
Anxiety	6 (14%)
Hyperprolactinemia	2 (5%)
Bipolar	1 (2%)
Dissociative disorders	1 (2%)
Mental anorexia	1 (2%)
RBD / violent behavior	0
Sleep apnea	?

IH course – a retrospective study. Results
Comparison between groups according subjective severity evolution

	„Improvement“	„no change“	„worsening“
ESS	10.2	13.4	16,5
FSS	37.7	40.1	56.6
BDI	3.75	7.94	10.80
Subj. health esteem (0 – 100)	81.5	65.6	54.5
EuQL	6.0	6.6	8.5

No other statistical differences!

Statistical difference ($p<0.05$)

IH course – a retrospective study. Results
Comparison between groups according subjective severity evolution

	„Improvement“	„no change“	„worsening“
ESS	10.2	13.4	16,5
FSS	37.7	40.1	56.6
BDI			
Subj. he			
EuQL			

Cook JD et al. Identifying Subtypes of Hypersomnolence Disorder: A clustering analysis. Sleep Med in press.

A more severe hypersomnolence phenotype was identified in a cluster that also had elevated depressive symptoms. This cluster endorsed significantly greater daytime sleepiness, sleep inertia, and functional impairment, while displaying longer sleep duration and worse vigilance.

No

<0.05)

NARCOLEPSY AND IDIOPATHIC HYPERSOMNIA

Idiopathic Hypersomnia: A Study of 77 Cases

Kirstie N. Anderson, MB BS, D Phil[1]; Samantha Pilsworth, Bsc[1]; Linda D. Sharples, PhD[1,2]; Ian E. Smith, MA, MD[1]; John M. Shneerson, MA, DM[1]

Sleep 2007

Table 4—Clinical and Polysomnographic Characteristics of Patients Who Spontaneously Improved

Parameter	Chronic idiopathic hypersomnia	Spontaneous improvement	P Value[b]
Subjects, no	66	11	
Sex, male:female	33:33	5:6	1.000
Age of symptom onset, y	17.2 ± 9.5	13.4 ± 8.6	0.216
Duration of symptoms, y	15.9 ± 10.8	20.6 ± 19.6	0.458
Family history	20/66 (30)	6/11 (55)	0.168
Sleep drunk	35/66 (53)	7/11 (64)	0.745
Vivid dreams	14/66 (21)	5/11 (45)	0.127
Hours of night sleep	9.2 ± 1.9	9.3 ± 1.4	0.918
BMI	25 (4)	26.4 (8)	0.709
Initial ESS score off treatment	16.3 ± 3.4	16.6 ± 2.5	0.803
MSLT	8.5 ± 3.1	7.2 ± 2.5	0.205
SOREMPs, no.	7/264	1/44	1.000
Sleep latency, %	12.1 ± 8.5	7.8 ± 4.4	0.103
Sleep efficiency, %	94.4 ± 4.1	94.1 ± 5.2	0.831
Slow-wave sleep, %	22.4 ± 8.7	26.0 ± 8.3	0.204
Number treated	55/66 (80)	8/11 (73)	0.689

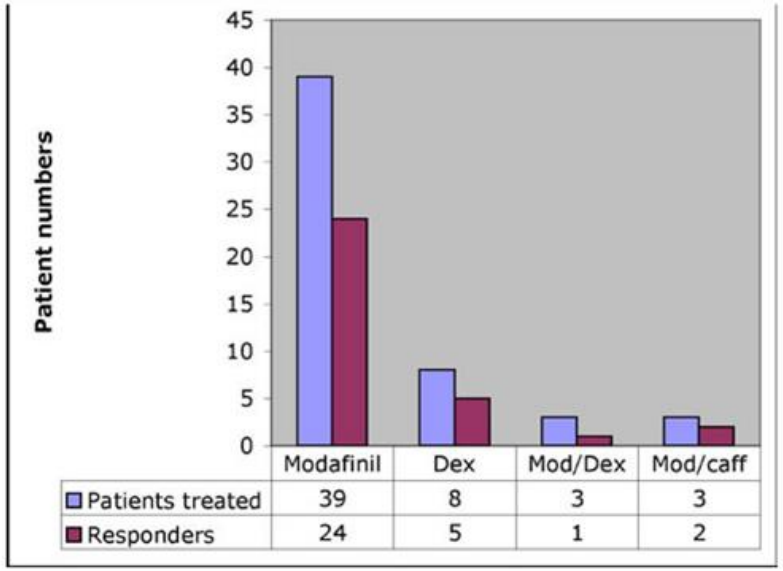


Figure 1—Treatment effects on patients with idiopathic hypersomnia. The figure shows the number of patients treated (blue bars) and the number who improved on treatment with a drop in the Epworth Sleepiness Scale score of > 4 points (red bars). Four different treatments are shown: modafinil (MOD), dexamphetamine (DEX), modafinil and dexamphetamine (MOD/DEX), and modafinil and caffeine (MOD/CAF).

No difference between patients with and without improvement and between therapy responders and nonresponders

IDIOPATHIC HYPERSOMNOLENCE AND SLEEP DURATION

Idiopathic Hypersomnia with and without Long Sleep Time: A Controlled Series of 75 Patients

Cyrille Vernet, MSc[1,2,3]; Isabelle Arnulf, MD, PhD[1,2,3]

Sleep 2009

Patients with LST were younger, slimmer, have lower Horne-Ostberg scores, and would sleep longer on a 24-h basis, with higher sleep efficiency, than patients without LST.

Hypothesis

IH with LTS may be a juvenile form of the same disease, later evolving toward less nighttime sleep.

In favor of this hypothesis: total sleep time during nighttime and during 24 hours slightly decreased with increasing age at diagnosis time.

Pathophysiology

no hypocretin deficiency

(Kanbayashi T et al. Sleep Res. 2002)

no important brain structure impairment

no neurodegeneration

no association with HLA DQB1*0602

(Miyagawa T et al. Human Genome Variation 2015)

Genetics:

IH, or another central disorder of hypersomnolence in family history in 34–38% of IH patients.

New aspects of IH pathophysiology

- Low histamine
- Activity modulation at GABA-A receptors
- Inflamation /autoimmunity
- Circadian system impairment

Low histamine

CSF HISTAMINE LEVELS AND NARCOLEPSY

CSF Histamine Contents in Narcolepsy, Idiopathic Hypersomnia and Obstructive Sleep Apnea Syndrome

Takashi Kanbayashi, MD, PhD[1]; Tohru Kodama, MD, PhD[2]; Hideaki Kondo, MD[1]; Shinsuke Satoh, MD, PhD[3]; Yuichi Inoue, MD, PhD[4]; Shigeru Chiba, MD, PhD[5]; Tetsuo Shimizu, MD, PhD[1]; Seiji Nishino, MD, PhD[6]

[1]Department of Neuropsychiatry, Akita University School of Medicine, Akita, Japan; [2]Department of Psychology, Tokyo Metropolitan Institute for Neuroscience, Tokyo, Japan; [3]Department of Neuropsychiatry, Osaka Medical College, Takatsuki, Japan; [4]Yoyogi Somnology Center, Tokyo, Japan; [5]Department of Neuropsychiatry, Asahikawa University School of Medicine, Asahikawa, Japan; [6]Stanford University Center for Narcolepsy, Palo Alto, CA

Study Objective: To (1) replicate our prior result of low cerebrospinal fluid (CSF) histamine levels in human narcolepsy in a different sample population and to (2) evaluate if histamine contents are altered in other types of hypersomnia with and without hypocretin deficiency.

Design: Cross sectional studies.

Setting and Patients: Sixty-seven narcolepsy subjects, 26 idiopathic hypersomnia (IHS) subjects, 16 obstructive sleep apnea syndrome (OSAS) subjects, and 73 neurological controls were included. All patients were Japanese. Diagnoses were made according to ICSD-2.

Results: We found significant reductions in CSF histamine levels in hypocretin deficient narcolepsy with cataplexy (mean ± SEM; 176.0 ± 25.8 pg/mL), hypocretin non-deficient narcolepsy with cataplexy (97.8 ± 38.4 pg/mL), hypocretin non-deficient narcolepsy without cataplexy (113.6 ± 16.4 pg/mL), and idiopathic hypersomnia (161.0 ± 29.3 pg/mL); the levels in OSAS (259.3 ± 46.6 pg/mL) did not statistically differ from those in the controls (333.8 ± 22.0 pg/mL). Low CSF histamine levels were mostly observed in non-medicated patients; significant reductions in histamine levels were evident in non-medicated patients with hypocretin deficient narcolepsy with cataplexy (112.1 ± 16.3 pg/mL) and idiopathic hypersomnia (143.3 ± 28.8 pg/mL), while the levels in the medicated patients were in the normal range.

Conclusion: The study confirmed reduced CSF histamine levels in hypocretin-deficient narcolepsy with cataplexy. Similar degrees of reduction were also observed in hypocretin non-deficient narcolepsy and in idiopathic hypersomnia, while those in OSAS (non central nervous system hypersomnia) were not altered. The decrease in histamine in these subjects were more specifically observed in non-medicated subjects, suggesting CSF histamine is a biomarker reflecting the degree of hypersomnia of central origin.

Keyword: Histamine, hypocretin/orexin, narcolepsy, idiopathic hypersomnia, CSF

Citation: Kanbayashi T; Kodama T; Kondo H; Satoh S; Inoue Y; Chiba S; Shimizu T; Nishino S. CSF histamine contents in narcolepsy, idiopathic hypersomnia and obstructive sleep apnea syndrome. *SLEEP* 2009;32(2):181-187.

Histamin level dependent on treatment

Enhancement of activity at GABA-A receptors

CSF from patients with IH has been shown to enhance activity at GABA-A receptors in vitro, in excess of that of CSF from controls

Rye DB et al. Sci Transl Med. 2012

Symptoms of IH are reversible in some patients with use of GABA-receptor antagonists or negative allosteric modulators (Clarithromycin and Flumazenil)

Trotti LM et al. Ann Neurol. 2015

Trotti LM et al. J Clin Sleep Med. 2016

Autoimmunity/inflamation

Comorbidity between central disorders of hypersomnolence and immune-based disorders

Lucie Barateau, MD

Neurology, 2017

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 31 October 2018
doi: 10.3389/fneur.2018.00922

Mononucleosis: A Possible Cause of Idiopathic Hypersomnia

*Emilia Sforza, David Hupin and Frédéric Roche**

Service de Physiologie Clinique et de l'Exercice (Pole Hospitalier NOL), CHU Nord, Faculté de Médecine Jacques Lisfranc, Université Jean Monnet, SNA EPIS EA 4607, Université de Lyon, Saint-Étienne, France

OXFORD

Sleep Research Society

SLEEPJ, 2019, 1–9

doi: 10.1093/sleep/zsy223
Advance Access Publication Date: 16 November 2018
Original Article

ORIGINAL ARTICLE

Specific T-cell activation in peripheral blood and cerebrospinal fluid in central disorders of hypersomnolence

Julian Lippert[1,2], Peter Young[1], Catharina Gross[3], Sven G. Meuth[3], Bianca Dräger[1], Anja Schirmacher[1] and Anna Heidbreder[1,*]

[1]Institute for Sleep Medicine and Neuromuscular Disorders, University of Muenster, Germany, [2]Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland and [3]Clinic of Neurology with Institute for Translational Neurology, University of Muenster, Germany

OPEN ACCESS Freely available online

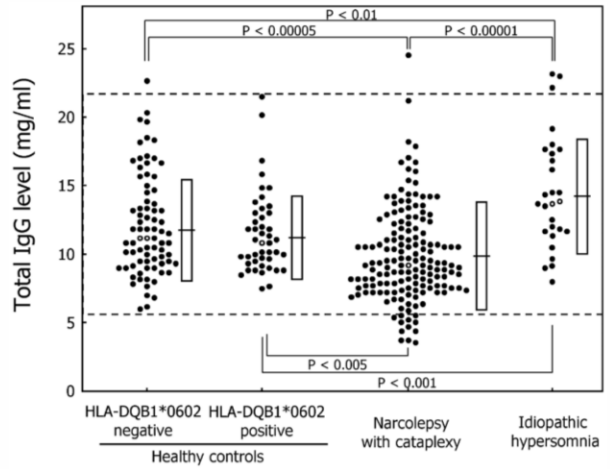
PLoS one

IgG Abnormality in Narcolepsy and Idiopathic Hypersomnia

2010

Susumu Tanaka*, Makoto Honda

Research on the Cause and Treatment of Sleep Disorders, Tokyo Institute of Psychiatry, Tokyo, Japan



Circadian system impairment

A contribution to pathophysiology of idiopathic hypersomnia

S. Nevšímalová[a,*], K. Blažejová[a], H. Illnerová[b], I. Hájek[b], J. Vaňková[a], M. Pretl[a] and K. Šonka[a]

[a]*Department of Neurology, 1st Medical Faculty, Charles University, 12821 Prague 2 (Czech Republic)*
[b]*Institute of Physiology, Academy of Science, 14220 Prague 4 (Czech Republic)*

Phase delay in the rhythm of melatonin and cortisol secretions in 15 patients with IH.

Clinical Neurophysiology, 2010

mRNA expression of several clock genes was impaired in fibroblast cells from IH patients compared to healthy controls.

Lippert J et al. PLoS ONE, 2014

frontiers in Neurology

ORIGINAL RESEARCH
published: 07 June 2018
doi: 10.3389/fneur.2018.00424

Idiopathic Hypersomnia Patients Revealed Longer Circadian Period Length in Peripheral Skin Fibroblasts

Linus Materna[1], Hartmut Halfter[1], Anna Heidbreder[1], Matthias Boentert[1], Julian Lippert[2], Raphael Koch[3†] and Peter Young[1†]*

[1] Division of Sleep Medicine and Neuromuscular Disorders, Department of Neurology, University Hospital Muenster, Muenster, Germany, [2] Department of Neurology, Inselspital, University Hospital Bern, University of Bern, Bern, Switzerland, [3] Institute of Biostatistics and Clinical Research, University of Muenster, Muenster, Germany

Differential diagnosis of IH

- Insufficient sleep syndrome
- The narcolepsies (type 1 and type 2) versus IH
- Delayed sleep phase syndrome
- Hypersomnia associated with a psychiatric disorder
- Hypersomnia due to a medical disorder

Quantifying IH symptoms

- Sleep duration (actigraphy, sleep log)
- MSLT latency
- Sleep Inertia Questionnaire *(Kanady JC et al 2015)*

ARTICLE

Measurement of symptoms in idiopathic hypersomnia

The Idiopathic Hypersomnia Severity Scale

Yves Dauvilliers, MD, PhD, Elisa Evangelista, MD, Lucie Barateau, MD, Regis Lopez, MD, PhD, Sofiène Chenini, MD, Caroline Delbos, Séverine Beziat, and Isabelle Jaussent, PhD

Neurology® 2019;92:e1754-e1762. doi:10.1212/WNL.0000000000007264

Correspondence
Dr. Dauvilliers
ydauvilliers@yahoo.fr

14 item scale

Treatment (off label in EU)

- **Methylphenidate**
- **Modafinil / armodafinil**
- Flumazenil
- Claritromycin
- H3 recetor inversible agonist (pitolisant)
- Gamma hydroxybutyrate
- Solriamfetol (selective dopamine-norepinephrine reuptake inhibitor)
- Light
- Levothyroxine (*Shinno H et al. Sleep Med. 2011)*

Conclusion

- „True“ idiopathic hypersomnia is the disease defined by long sleep and eventually difficulties of awakening.
- Idiopathic hypersomnia defined by MSLT sleep latency only and NT2 are not well studied diseases and perhaps they belongs to one entity or will be grouped in new way when new pathophysiologic explanation and robust biological marker occur.
- Disease course, responsiveness to the stimulants and sleep comorbidities seem not to be markers distinguishing between forms of IH but large studies are lacking.

The classification of narcolepsies and hypersomnias is not closed at present. New forms of hypersomnia may well be identified in the future.

Roth B. Narcolepsy and hypersomnia; review and classification of 642 personally observed cases. Schweiz Arch Neurol Neurochir Psychiat 1976