Date: 2023.9.16 Sat. - 17 Sun

Venue: Pacifico Yokohama North
[Room G312+G313]
Minato Mirai, Nishi-ku, Yokohama 220-0012, JAPAN

President: Takashi Kanbayashi
Organizing Committee: Yuichi Inoue, Makoto Honda

Greeting

We are extremely happy to invite you to participate in the 3rd Asian Narcolepsy and Hypersomnolence Society Meeting (ANHS) as a satellite meeting to joint congress of the 45th Annual Meeting of Japanese Society of Sleep Research / the 30th Annual Meeting of Japanese Society for Chronobiology held on Sep.15 (Fri) - Sep.17 (Sun), 2023, at Yokohama, Japan.

Since 2006, many Asian researchers interested in the field of narcolepsy and hypersomnolence have gathered together in the Asian Narcolepsy Forum to share their passion and future perspectives. To upgrade and extend our activities and research arena, key members of the Asian Narcolepsy Forum reached a decision to found ‘Asian Narcolepsy and Hypersomnolence Society (ANHS).

The 1st Asian Narcolepsy & Hypersomnolence Society (ANHS) was held on March 24(Fri)-25(Sat), 2017, at Seoul, Korea. It was organized by Prof Seung Chul Hong who is the first President of ANHS.
The 2nd Asian Narcolepsy and Hypersomnolence Society Meeting (ANHS) was held on March 30(Sat)-31(Sun), 2019, at Taipei, Taiwan. It was organized by Prof. Yu-Shu Huang who is the 2nd President of ANHS.
Both meetings were great success and we set up the aim & goals to center on cooperative research, training and education in Asia.

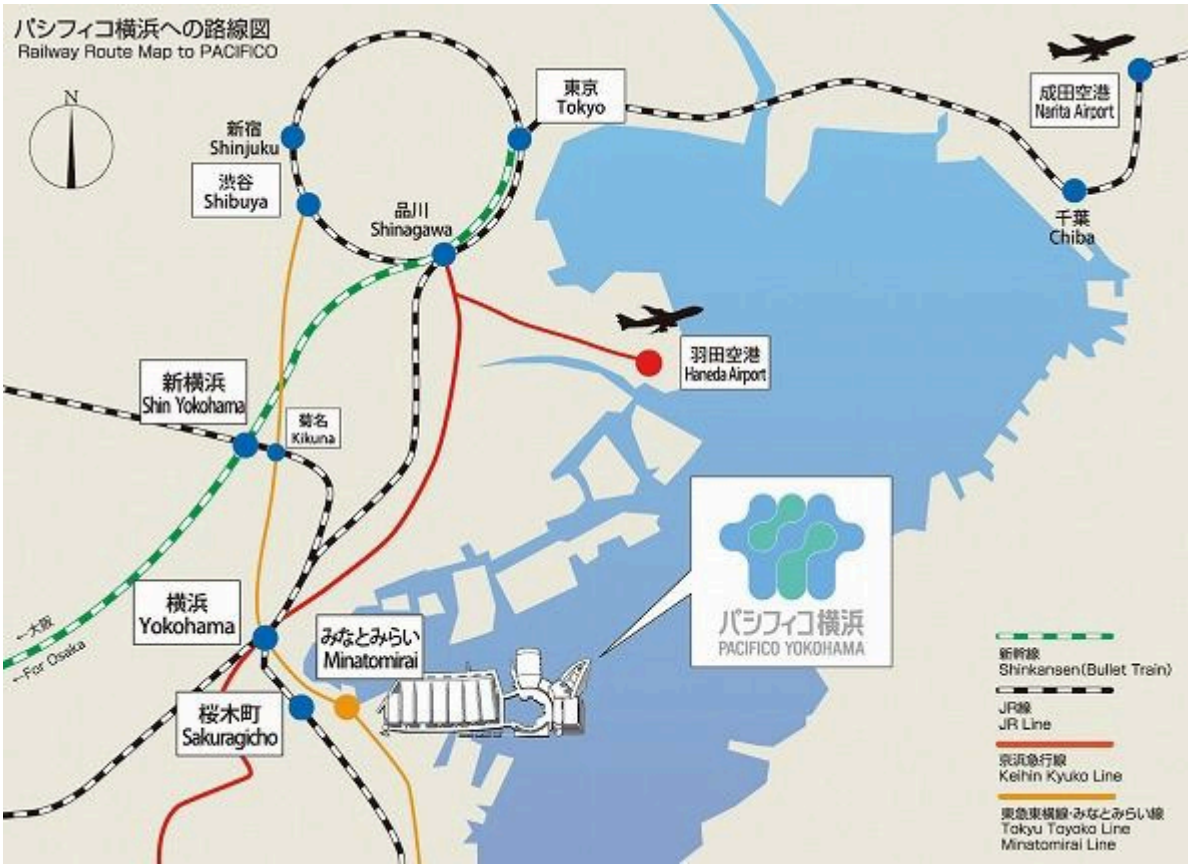
We plan to invite most renowned researchers, most updated perspective in the field of narcolepsy and hypersomnia. The recent trends in research and treatment will be shared and discussed. We believe this meeting provides an excellent opportunity to share the new scientific findings and promote collaborations among the Asian researchers.

Takashi Kanbayashi (Professor, Tsukuba University / IIIS)
Yuichi Inoue (Professor, Department of Somnology, Tokyo Medical University)
Makoto Honda (Project Leader, Sleep Disorders Project, Tokyo Metropolitan Institute of Medical Science)

Meeting Sponsorship

Takeda

Access to the Venue

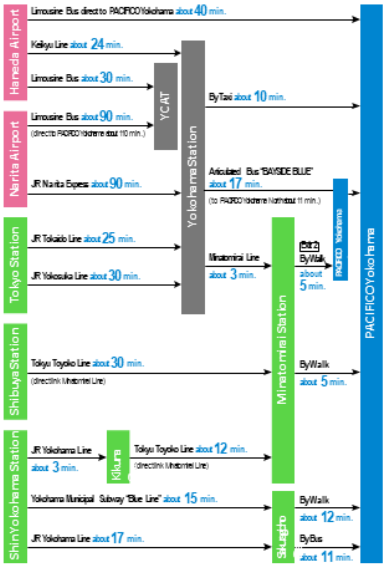


Floor Plan

PACIFICO YOKOHAMA

PACIFICO YOKOHAMA ACCESS GUIDE

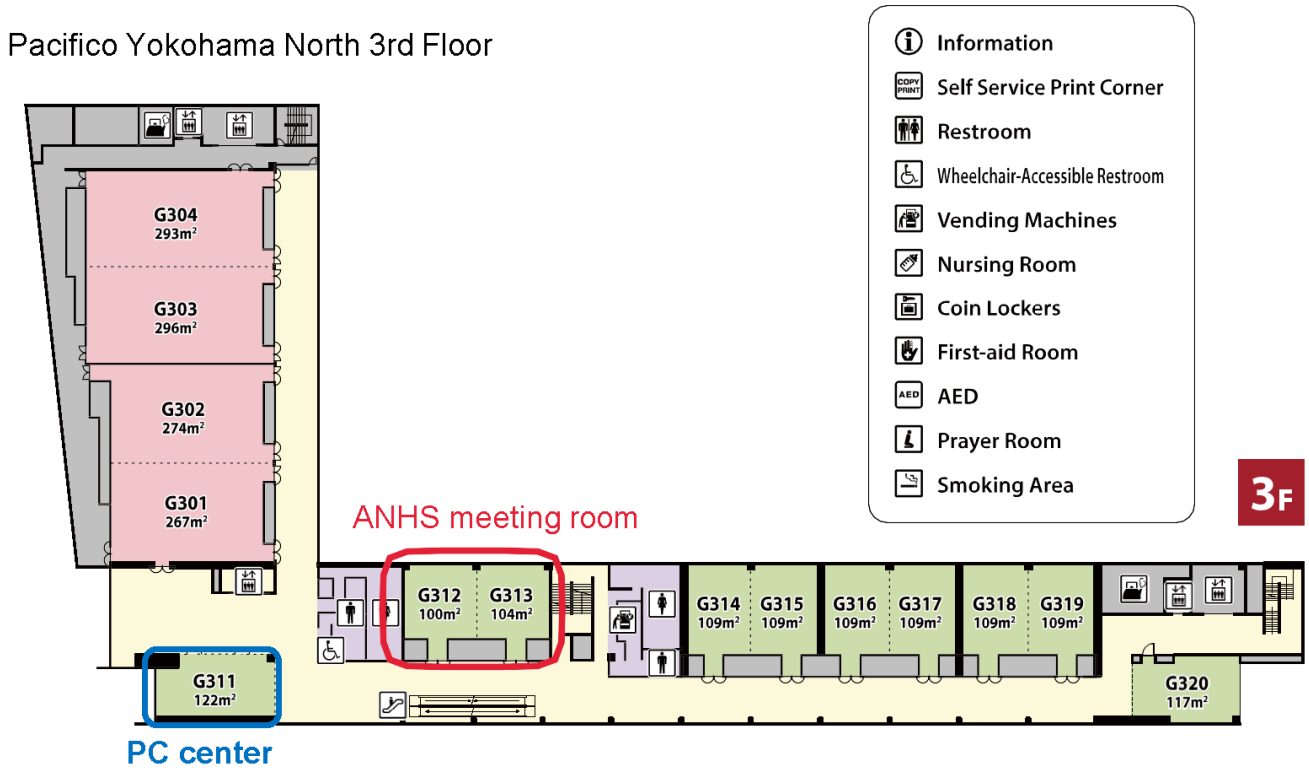
About 40 minutes by direct limousine bus from Haneda Airport
Nearest stations: Minatomirai Line Minatomirai Station / JR Sakuragicho Station
1-1-1 Minato Mirai, Nishi-ku, Yokohama 220-0012, Japan Tel: +81-45-221-2155 (General Information)
*To PACIFICO Yokohama North: 1-1-2, Minato Mirai, Nishi-ku, Yokohama



Parking Lot Information
Minatomirai Public Parking Lot
Rinko Park Parking Lot
Bus / Large Vehicle Parking Lot
North Parking Lot

2023.8

Pacifico Yokohama North 3rd Floor



Information for presenters

Please register your presentation file either to the PC in ANHS meeting room or to the PC center in JSSR/JSC office at least 30 min before your talk. Only USB is available as a media. If you bring your own laptop (for example to show the movies), please check the connection beforehand.

Assignment time for the presentations is 20 minutes including question-and-answer period (40 minutes for lunch-on seminar and special seminar).

Schedule at a glance

Sat Sep16, 2023

<JSSR-JSC meeting> (at 3F G301+G302)
Breakthrough Prize Lecture Meeting 10:30-12:00
Chair: Professor Mayumi Kimura
Professor Emmanuel Mignot: Pathophysiology of human narcolepsy
Professor Masashi Yanagisawa: Searching for the molecular substrate for "sleepiness"

<ANHS meeting> (at 3F G312+G313)
Lunch on Seminar 12:30-13:10
Chair: Professor Yun Kwok Wing
Professor Yuichi Inoue: Clinical characteristics of narcolepsy type 2

Symposium 1 13:20-15:00
Symptoms and Courses of Narcolepsy and Hypersomnia
Chairs: Professors Fang Han, Seung Chul Hong

Symposium 2 15:10-16:30
Diagnosis and New Biomarkers of Narcolepsy and Hypersomnia
Chairs: Professors Seung Bong Hong, Makoto Honda

Symposium 3 16:40-18:00
Psychiatric and Neurological comorbidities in Narcolepsy and Hypersomnia
Chairs: Professors Yun Kwok Wing, KI-Young Jung

[Gala Dinner (Social Gathering in conjunction with the banquet of JSSR/JSC)18:30
Venue:Pacifico Yokohama Intercontinental hotel ballroom]

Welcome convivial gathering (for the participants of 3rd ANHS meeting only) 19:30-21:30
Restaurant “Ginza Hakobune“ next to Washington Hotel, Yokohama Sakuragicho

Sun Sep17, 2023

Symposium 4 8:30-10:10
Epidemiology/Comorbidity of Narcolepsy and Hypersomnia
Chairs: Professors Seung-Chul Hong, Yuichi Inoue

Symposium 5 10:20-11:40
Psychosocial Aspects of Narcolepsy and Hypersomnia
Chairs: Professors Yu-Shu Huang, Makoto Honda

Special Lectures (Lunch on) 11:50-13:10
Chair: Professor Seiji Nishino
Professor Fang Han: Flu and Narcolepsy - cataplexy: new evidence from China Narcolepsy Network
Professor Yun Kwok Wing: Epidemiology of hypersomnolence – a reflective thinking

Symposium 6 13:20-14:20
Treatment of Narcolepsy and Hypersomnia
Chairs: Professors Seung Bong Hong, Takashi Kanbayashi

Closing Remark, Group Photo 14:20-14:30

Board Meeting 14:30-15:00

Scientific Program

Sat Sep16, 2023

12:00 registration open [in front of Room G312+G313]

Lunch on Seminar 12:30-13:10

Chair: Professor Yun Kwok Wing

Clinical Characteristics of Narcolepsy Type 2

Yuichi Inoue Department of Somnology, Tokyo Medical University, Tokyo, Japan

Sponsored by Aculys Pharma, Inc.

Symposium 1 13:20-15:00

Symptoms and Courses of Narcolepsy and Hypersomnia

Chairs: Professors Fang Han, Seung Chul Hong

1. **Different Course of Narcolepsy Diagnosed by Multiple Sleep Latency Test: a Single Center Experience**
   Seung-Chul Hong Department of Psychiatry, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea
2. **Clinical and Polysomnographic Features in Narcolepsy Cataplexy Patients with and without HLA-DQB1*0602**
   Qidi Ding Department of Sleep Medicine, Peking University People's Hospital, Beijing, China
3. **Differential Characteristics of Repeated Polysomnography and Multiple Sleep Latency Test Parameters in Narcolepsy Type 1 and Type 2 Patients: a Longitudinal Retrospective Study**
   Young-Chan Kim Department of Psychiatry, College of Medicine, St. Vincent's Hospital, The Catholic University of Korea
4. **Electromyographic Finding of Narcolepsy**
   Taeko Sakuma Department of Clinical Laboratory Science, Faculty of Medical Technology, Teikyo University, Tokyo, Japan
5. **Diurnal Changes in Blood Pressure and Heart Rate in Children with Narcolepsy with cataplexy**
   Jingyu Wang Division of Sleep Medicine, Peking University People's Hospital, Beijing, China
   Department of Respiratory and Critical Care Medicine, Binzhou Medical University Hospital, Binzhou, China

Coffee Break

Symposium 2 15:10-16:30

Diagnosis and New Biomarkers of Narcolepsy and Hypersomnia

Chairs: Professors Seung Bong Hong, Makoto Honda

1. **Evaluation of Sleepiness in Idiopathic Hypersomnia**
   Makoto Honda Sleep Disorders Project, Tokyo Metropolitan Institute of Medical Science, Tokyo / Koishikawa Tokyo Hospital, Institute of Neuropsychiatry, Tokyo, Japan
2. **Characteristic of Novel Sleep EEG Biomarkers with Central Disorders of Hypersomnolence**
   Bi Taoran Peking University People's Hospital, China
3. **Altered DNA Methylation in Narcolepsy**
   Mihoko Shimada Genome Medical Science Project (Toyama), National Center for Global Health and Medicine (NCGM), Tokyo, Japan
4. **A Genetic Variant in *prepro-orexin* is Associated with Idiopathic Hypersomnia**
   Taku Miyagawa Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan

Coffee Break

Symposium 3 16:40-18:00

Psychiatric and Neurological Comorbidities in Narcolepsy and Hypersomnia

Chairs: Professors Yun Kwok Wing, KI-Young Jung

1. **Characteristics of Hypersomnia due to Inflammatory Demyelinating Diseases of the Central Nervous System**
   Hideaki Ishido International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba / Hakusuikai Hatsuishi Hospital, Japan
2. **Hypersomnia and Major Depressive Disorder**
   Yun Kwok Wing Li Chiu Kong Family Sleep Assessment Unit, Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China
3. **Hypersomnia Specific Belief and Psychotherapy for Hypersomnia**
   Megumi Hazumi National Center of Neurology and Psychiatry, Japan
4. **ADHD and Narcolepsy**
   Wakako Ito Koishikawa Tokyo Hospital, Tokyo. Institute of Neuropsychiatry, Tokyo, Japan

18:30(-20:30)
Gala Dinner (Social Gathering in conjunction with the banquet of JSSR/JSC)
Venue:Pacifico Yokohama Intercontinental hotel ballroom

19:30-21:30
Welcome convivial gathering (for the participants of 3rd ANHS meeting only)
（Restaurant "**Ginza Hakobune**" next to Washington Hotel, Yokohama Sakuragicho）

Sun Sep17, 2023

8:00 registration open [in front of Room G312+G313]

Symposium 4 8:30-10:10

Epidemiology/Comorbidity of Narcolepsy and Hypersomnia

Chairs: Professors Seung-Chul Hong, Yuichi Inoue

1. **Narcolepsy is Associated with an Increased Risk of HLA-Related Autoimmune Disease: Evidence from a Nationwide Healthcare System Database in South Korea**
   Jihye Oh Department of Psychiatry, College of Medicine, The Catholic University of Korea, Suwon, South Korea
2. **Narcolepsy and the Risk of Pregnancy Complications: Based on Nationwide Healthcare System Database in South Korea**
   Suhyung Kim Department of Psychiatry, St.Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, South Korea
3. **Markedly Increased Risk of Colorectal Cancer and Decreased Risk of All Malignancies in Patients with Narcolepsy: A Nationwide Population-Based Cohort Study**
   Jihyung Lee Department of Psychiatry, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, South Korea
4. **Factors Associated with Metabolic Disorders of Narcolepsy Type 2**
   Kunihiro Futenma Department of Neuropsychiatry, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan
5. **Epidemiology and Burden of Narcolepsy in Taiwan: by Taiwan's National Health Insurance Research Database and Clinical Hospital Database**
   Yu-Shu Huang Department of Psychiatry and Sleep Center, Chang Gung Memorial Hospital, Taipei, Taiwan.

Coffee Break

Symposium 5 10:20-11:40

Psychosocial Aspects of Narcolepsy and Hypersomnia

Chairs: Professors Yu-Shu Huang, Makoto Honda

1. **The Impact of COVID-19 and Lockdown in Patients with Narcolepsy**
   Wei-Chih Chin Department of Psychiatry and Sleep Center, Chang Gung Memorial Hospital, Taipei, Taiwan
2. **The Impact of COVID-19 Vaccination and Virus Infection on Sleep Problems in Narcolepsy**
   Shuang Yue Division of Sleep Medicine, Peking University People's Hospital, Beijing, China
3. **Psychological Problems of Narcoleptic Patients in Korea.**
   Seung Bong Hong Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
4. **Risks and Accidents of Patients with Narcolepsy: A Study of Taiwan's National Health Insurance Research Database and Clinical Hospital Database**
   Tsun-Yi Ruan Department of Psychiatry and Sleep Center, Chang Gung Memorial Hospital, Taipei, Taiwan.

Special Lectures (Lunch on) 11:50-13:10

Chair: Professor Seiji Nishino

1. **Flu and Narcolepsy - cataplexy: new evidence from China Narcolepsy Network**
   Fang Han Division of Sleep Medicine, Peking University People's Hospital, Beijing, China
2. **Epidemiology of hypersomnolence – a reflective thinking**
   Yun Kwok Wing Li Chiu Kong Family Sleep Assessment Unit, Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China.

Symposium 6 13:20-14:20

Treatment of Narcolepsy and Hypersomnia

Chairs: Professors Seung Bong Hong, Takashi Kanbayashi

1. **The Treatment Strategy of Pediatric Narcolepsy**
   Hang Chung Department of Psychiatry and Sleep Center, Chang Gung Memorial Hospital, Taipei, Taiwan
2. **The Effect of Aripiprazole on The Difficulty Waking Up in The Morning**
   Takashi Kanbayashi International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba. Ibaraki Prefectural Medical Center of Psychiatry, Japan
3. **Efficacy and Safety of Modafinil in Patients with Idiopathic Hypersomnia without Long Sleep Time: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Comparison Study**
   Yuichi Inoue Department of Somnology, Tokyo Medical University, Tokyo / Yoyogi Sleep Disorder Center, Japan

Closing Remark, Group Photo 14:20-14:30

President Takashi Kanbayashi

Board Meeting 14:30-15:00

Abstracts

Sat September 16, 2023

Lunch on seminar (Sponsored by Aculys Pharma, Inc.)

Clinical Characteristics of Narcolepsy Type 2

Yuichi Inoue

Department of Somnology, Tokyo Medical University, Tokyo, Japan

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Narcolepsy type 2 (NT2) differs from classic and typical narcolepsy, now termed narcolepsy type 1 (NT1), in that it lacks cataplexy and decreased cerebro-spinal fluid orexin levels. Because of the lack of characteristic disease markers other than the findings of multiple sleep latency test (MSLT), the diagnosis of NT2 is not easy, and its prevalence and clinical significance have not been well understood.

On nocturnal polysomnographic (PSG) findings, patients with NT1 have a characteristically high frequency of sleep onset REM period (SOREMP) and a markedly shallow and fragmented sleep structure, whereas patients with NT2 have a relatively lower frequency of SOREMP than those with NT1, and sleep architecture is considered less impaired as similar to idiopathic hypersomnia without long sleep time (IH). The appearance rate of SOREMPs on MSLT sessions is somewhat lower in NT2 patients especially cases being negative for HLA-DQB1*06:02 . In addition, the reproducibility of the presence of SOREMPs on MSLT is somewhat low, and SOREMP frequencies sometimes decrease when tested at two time points at intervals, which often forces a change in diagnosis from NT2 to IH. These findings impresses that the increase in REM propensity is thought to be at a lower level in NT2 than in NT1, possibly corresponding to a lower frequency of REM sleep-related symptoms (hypnagogic hallucination and sleep paralysis) in patients with NT2 than in NT1.

Symposium 1: Symptoms and Courses of Narcolepsy and Hypersomnia

Symposium 1-1

Different Course of Narcolepsy Diagnosed by Multiple Sleep Latency Test: A Single Center Experience

Seung-Chul Hong, **Hong-Shik Chun**

Department of Psychiatry, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, Korea

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Objectives:
Several studies have raised questions about the diagnostic validity of the narcolepsy using multiple sleep latency test (MSLT). In this study, we investigated the diagnostic change in narcolepsy type 1 (NT 1) and narcolepsy type 2 (NT 2) when we use multiple sleep latency tests with long-term interval.
Methods:
In this retrospective study, the demographic characteristics, polysomnography (PSG), and MSLT parameters were compared at the baseline between the NT1 and NT 2 patients. Then, MSLT re-tests were conducted with a mean follow-up of 8.48 years in patients with NT 1 and 7.05 years with NT 2.
Results:
Seventy-four patients (58 with NT1 and 16 with NT2) were investigated in this study. At the baseline, demographic data showed a larger BMI value, more sleep paralysis, and hypnogogic hallucination in NT 1 compared to NT 2. Also, at baseline MSLT, shorter mean sleep latency (MSL) and higher number of Sleep onset rapid eye movement periods (SOREMPs) were observed in the NT 1 than those of the NT 2. On follow-up MSLT, 6.9% (n=4) patients with NT1 and 50% (n=8) patients with NT2 did not satisfy the previous diagnosis.
Conclusions:
The result of MSLT was observed not to be stable in the diagnosis of NT 2 at the repeat study. Therefore, it suggests the need of new tests in addition to MSLT for the diagnostic consistency in NT2 and idiopathic hypersomnia.

Symposium 1-2

Clinical and Polysomnographic Features in Narcolepsy Cataplexy Patients with and without HLA-DQB1*0602

Ding Qidi, Zhang Chi, Shuai Wu, Shuang Yue, Long Zhao, Yuhua Zuo, Bing Zhao, Xueli Zhang, Xiaosong Dong, Fang Han

Department of Sleep Medicine, Peking University People's Hospital, Beijing, China

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Background:
Narcolepsy cataplexy has a strong link with HLA-DQB1*06:02. However, the narcolepsy cataplexy patients without DQB1*06:02 is yet to be elucidated.
Methods:
Fifty narcolepsy patients with clear cut cataplexy and negative HLA-DQB1*0602 were recruited from the Sleep Center of Peking University People's Hospital. And one hundred and ninety-seven narcolepsy patients with clear cut cataplexy and positive HLA-DQB1*0602 were selected as controls, with sex and visiting age matched. All participants underwent clinical evaluation by a sleep specialist and completed nocturnal polysomnography, multiple sleep latency tests and Epworth sleepiness scales. HLA-DQB1*0602 was tested using a real-time PCR assay.
Results:
There was a lower rate of hypnagogic hallucinations in the HLADQB1*0602 negative group (63.45%) than in the positive group (48%, P=0.02). The sleep latency was longer for the DQB1*0602-negative group versus the positive group (17.88 ± 49.65min vs 6.34 ±9.93min). We found increased sleep efficiency (90.80 ± 11.61% vs 87.36 ± 10.69%) and reduced wake periods after sleep onset (32.00± 27.27min vs 58.90 ±44.42min) in the DQB1*0602-negative group versus the positive group.
In the MSLT, the number of SOREMs in DQB1*0602-negative group was 3.43 ± 1.17 min less than the 4.06 ±1.25min in the positive group.
Conclusion:
In conclusion, our study indicates a longer sleep latency and less sleep disruption for narcolepsy cataplexy subjects without DQB1*0602.

Symposium 1-3

Differential Characteristics of Repeated Polysomnography and Multiple Sleep Latency Test Parameters in Narcolepsy Type 1 and Type 2 Patients: a Longitudinal Retrospective Study

Yoo Hyun Um[1], Young-Chan Kim[1], Jihye Oh[2], Sung-Min Kim[1], Tae-Won Kim[1], Ho-Jun Seo[1], Jong-Hyun Jeong[1], Seung-Chul Hong[1]

[1]Department of Psychiatry, College of Medicine, St. Vincent's Hospital, The Catholic University of Korea, 93, Jungbu-daero, Paldal-guGyeonggi-do, Suwon-si, 16247, Republic of Korea.
[2]Department of Psychiatry, College of Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea.

Purpose:
Narcolepsy is a chronic disorder and its phenotype is dichotomized into narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2). The clinical course and pathophysiological mechanisms of these two clinical entities and their differences are not adequately defined. This study aimed to explore the differential longitudinal patterns of polysomnography (PSG) and multiple sleep latency test (MSLT) in NT1 and NT2.
Methods:
In this retrospective study demographic characteristics, PSG, and MSLT parameters at baseline and follow-up were compared between NT1 and NT2 patients. Patients with both follow-up MSLT and PSG were selected for sub-group analysis. Baseline and follow-up MSLT and PSG parameters were compared.
Results:
Of 55 patients with narcolepsy, mean follow-up periods were 7.4 ± 3.5 years for NT1 and 5.5 ± 2.9 for NT2. Demographic data showed increased body mass index and prevalence of sleep paralysis in NT1. Baseline PSG characteristics between NT1 and NT2 showed decreased sleep latency ($p = 0.016$) and REM latency ($p = 0.046$) in NT1 group when compared with NT2. Nocturnal SOREMP on PSG was more prevalent in NT1 ($p = 0.017$), and half of NT2 patients with nocturnal SOREMP on PSG changed their diagnoses to NT1. On follow-up PSG, NT1 displayed reductions in sleep stage N2 ($p = 0.006$) and N3 ($p = 0.048$), while wake after sleep onset (WASO) ($p = 0.023$) and apnea-hypopnea index (AHI) ($p = 0.007$) were significantly increased.
Conclusion:
Differential MSLT and PSG characteristics of NT1 and NT2 in at baseline and follow-up indicate that NT1 and NT2 are distinct disease phenotypes, and that they present with a contrasting course of disease.

Symposium 1-4

Electromyographic Finding of Narcolepsy

Taeko Sakuma[1,2]

[1] Department of Clinical Laboratory Science, Faculty of Medical Technology, Teikyo University, Tokyo, Japan
[2] Department of Somnology, Tokyo Medical University, Tokyo, Japan

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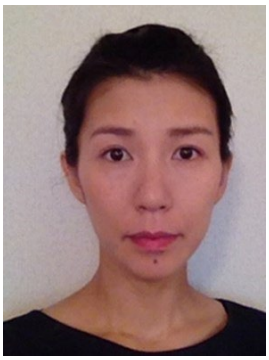
Movement disorders or parasomnia are often comorbid with human narcolepsy. Especially, REM sleep without atonia has been reported as diagnosable marker of NA recently. We will talk about comorbidity rate, polysomnigraphically diagnosible rapid eye movement sleep behavior disorder/REM sleep without atonia and periodic limb movements during sleep in Japanese drug-naïve patients with narcolepsy-spectrum disorders.
A total of 158 consecutive drug naïve patients with NT1, 295 patients with NT2 and 395 patients with idiopathic hypersomnia without long sleep time were enrolled. From retrospectively analyzed data of nocturnal polysomnography and multiple sleep latency test, higher rates of periodic limb movements during sleep ($\geq 15 h^{-1}$) (10.2%) and polysomnographically diagnosable rapid eye movement sleep behavior disorder (1.9%) were found in patients with NT1. They had more severe periodic limb movements during sleep especially during rapid eye movement sleep and higher percentages of REM sleep without atonia than the other two patient groups. In the present large sample study, Japanese drug naïve patients with NT1 showed the highest comorbidity rates of periodic limb movements during sleep, polysomnographically diagnosable rapid eye movement sleep behavior disorder and REM sleep without atonia among those with the other narcolepsy-spectrum disorders; the rates were lower than those for Western patients.



Symposium 1-5

Diurnal Changes in Blood Pressure and Heart Rate in Children with Narcolepsy with Cataplexy

Jingyu Wang[1,2], Zhihui Yan[3], Xiaosong Dong[1], Jing Li[1], Long Zhao[1], Xueli Zhang[1], Changjun Lv[2], Ziyan Zhao[3], Kingman P. Strohl[4], Fang Han[1]

[1] Division of Sleep Medicine, Peking University People's Hospital, Beijing, China
[2] Department of Respiratory and Critical Care Medicine, Binzhou Medical University Hospital, Binzhou, China
[3] Institute of Materia Medica, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinnan, China
[4] Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Case Western Reserve University, and Cleveland Louis Stokes VA Medical Center, Cleveland, Ohio, USA

The hypocretin neurons in the lateral hypothalamus are connected not only to brain alertness systems but also to brainstem nuclei that regulate blood pressure and heart rate. The premise is that regulation of blood pressure and heart rate is altered and affected by methylphenidate, a stimulant drug in children with narcolepsy with cataplexy.
The changes in 24-hr ambulatory systolic and diastolic blood pressure and heart rate were compared among pre-treated narcolepsy with cataplexy patients (40 males, 10 females), with mean age 10.4 ± 3.5 years (M ± SD, range 5–17 years) with values from 100 archival age–sex–body mass index matched controls.
Patients had a lower diurnal systolic blood pressure (6.5 mmHg; p = 0.000) but higher heart rate (+11.0 bpm; p = 0.000), particularly evident in the waketime, while diastolic blood pressure was comparable. With methylphenidate (18 mg sustained release at 08:00 hours), patients with narcolepsy with cataplexy had higher systolic blood pressure (+4.6 mmHg, p = 0.015), diastolic blood pressure (+3.3 mmHg, p = 0.005) and heart rate (+7.1 bpm, p = 0.028) during wake time, but nighttime cardiovascular values were unchanged from pre-treated values; amplitude variation in cardiovascular values was unchanged over 24 hr.
In conclusion, children with narcolepsy with cataplexy had downregulation blood pressure profile but a higher heart rate, and lesser non-dipping profiles. Daytime methylphenidate treatment increases only waketime blood pressure and further elevated heart rate values

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Symposium 2
Diagnosis and New Biomarkers of Narcolepsy and Hypersomnia
Symposium 2-1

Evaluation of Sleepiness in Idiopathic Hypersomnia

Makoto Honda[1,2] Wakako Ito[2]

[1] Sleep Disorders Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
[2] Koishikawa Tokyo Hospital, Institute of Neuropsychiatry, Tokyo, Japan

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Background:
Sleepiness is not unidimensional. Sleep/Wake are independently regulated so that there could be at least two types of sleepiness: hyperfunction of sleep centers and hypofunction of wake centers in the brain.
ICSD-3-TR defined objective measures for two types of pathological sleepiness; sleep prolongation with 24-hour total sleep time ≥660 min and high sleep propensity with mean sleep latency ≤8 min on the MSLT. In order to clarify the characteristics of sleep prolongation type sleepiness, we performed 3-day sleep studies as one of the routine clinical examination.
Subjects and Methods:
Participants were 105 patients suspected of idiopathic hypersomnia with long sleep time who were evaluated by 3-day sleep studies (unattended 24hr PSG followed by PSG and MSLT) in Seiwa Hospital/Koishikawa Tokyo Hospital from January 2017 to May 2023 and gave written informed consents for the study. They were 21.3±7.5 years old, BMI 20.7±3.4 and female/male=60/45. Clinical and PSG variables were compared to search for the markers of pathological sleepiness.
Results:
Eighty-one of 105 patients showed sleep prolongation with 24hrPSG TST≥660min and 21 of 105 showed high sleep propensity with MSLT mSL <8min. Twenty-one patients did not fulfil the criteria of pathological sleepiness and 84 were diagnosed as hypersomnia, 22.6% (19/84) of them showed both types of sleepiness (sleep prolongation and high sleep propensity). Search for the associated variables with sleep prolongation in 24hr PSG revealed that MSLT mSL is negatively correlated with 24hr TST (r=-0.27, p=0.004).
Conclusions:
We confirmed our previous report that pathological sleepiness determined with 24hr PSG and MSLT reflected different aspects of sleepiness and recommended to perform 24hr PSG for patients suspected of idiopathic hypersomnia with long sleep time. However the significant correlation of sleep prolongation and sleep propensity indicates that both were not completely independent. The significance/meaning of MSLT mSL needs to be reconsidered for those with sleep prolongation.

Symposium 2-2

Characteristic of Novel Sleep EEG Biomarkers with Central Disorders of Hypersomnolence

Bi Taoran, Han Fang

Peking University People's Hospital, China

Study Objectives:
In this study, we use novel biomarkers of sleep depth to study the continuous and dynamic Electroencephalography characteristics in narcolepsy type 1 (NT1), narcolepsy type 2 (NT2) and idiopathic hypersomnia (IH).

Methods:
Participants were 16- to 64-year old and drug free: 103 subjects with NT1, 28 with NT2,19 with IH and 77 controls. We compared the following novel biomarkers from polysomnogram recordings among these subjects: a continuous index of sleep depth (odds-ratio-product, ORP), dynamics of sleep recovery following arousals and continuous sleep microarchitecture based on different sleep depth levels. The relationship between sleep depth and the level of cerebrospinal fluid (CSF) orexin was investigated by multiple linear regression.

Results:
NT1 patients had significantly higher ORP values in all sleep stages and remarkable right shift sleep microarchitecture: less deep sleep, more wake-sleep transitional state and higher sleep propensity during wakefulness. NT2 also had higher ORP values, decreased deep sleep and increased transitional state compared with controls, but not as severe as in NT1. In IH group, only the higher ORP values in N3 stage and reduced deep sleep were abnormal. CSF orexin level was strongly related to ORP values in the central disorders of hypersomnolence groups.

Conclusions:
NT1, NT2 and IH have special nocturnal sleep features, but only NT1 demonstrate remarkably light sleep depth and abnormal sleep architecture. The level of CSF hcrt-1 was associated with a significant decrease in ORP in hypersomnolence.

Symposium 2-3

Altered DNA Methylation in Narcolepsy

Mihoko Shimada[1,2],**Taku Miyagawa**[2],**Katsushi Tokunaga**[1],**Makoto Honda**[2,3]

[1] Genome Medical Science Project (Toyama), National Center for Global Health and Medicine (NCGM), Tokyo, Japan

[2] Sleep Disorders Project, Department of Psychiatry and Behavioral Sciences, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan

[3] Koishikawa Tokyo Hospital, Institute of Neuropsychiatry, Tokyo, Japan

Narcolepsy type 1 (NT1) is a hypersomnia that is caused by the loss of orexin-producing cells in the posterior hypothalamus, but the pathogenesis is still unclear. DNA methylation is an important mechanism of epigenetics, and in mammals, it mainly involves the addition of a methyl group to the 5-carbon atom of the pyrimidine ring of cytosine. DNA methylation changes under the influence of both genetic and environmental factors, and generally, methylation upstream of genes shows a negative correlation with gene expression. Atypical narcolepsy (ADCA-DN) is reported to be caused by mutations in DNMT1, a DNA methylation enzyme, and it has been reported that one of the associated SNPs reported in the genome-wide association study (GWAS) for NT1 affects the expression of DNMT1. DNA methylation is a relatively stable modification, and the effect at the time of NT1 onset might be detected as “epigenetic memory”. We performed an epigenome-wide association study (EWAS) on DNA methylation in two brain regions: the lateral hypothalamus and the temporal cortex. We also studied two types of immune cells, CD4+ T cells and CD8+ T cells, because the presence of auto-reactive cells in these two immune cell types has been previously reported in NT1.

In the brain analyses, we identified 77 differentially methylated regions (DMRs) in the lateral hypothalamus, with the top association being a DMR in the myelin basic protein (MBP) region. In contrast, only five DMRs were detected in the temporal cortex analysis. Genes annotated to DMRs in the lateral hypothalamus were significantly associated with pathways related to fatty acid response or metabolism. Furthermore, we found a significant overlap between the CpG sites associated with NT1 and those of multiple sclerosis.

In the immune cell analyses, we identified 15 replicated NT1 DMRs in CD4+ T cells and 5 DMRs in CD8+ T cells, including regions associated with chemokine-related genes, CCL5 and CCR4. Although many of the associated methylation regions were common to both cell types, the degree of association tended to be stronger in CD4+ T cells. Further, more than 80% of NT1-associated methylation sites were found to be hypomethylated in patients, and these sites were significantly less abundant in promoter regions, 5'UTR and CpG Island. In addition, we conducted an integrated analysis of the EWAS data, incorporating genotype and gene expression data from all samples utilized in this study, with the objective of identifying NT1-related genetic regions with greater certainty. As a result, we detected the association of genes involved in the pathway related to immune response of IL-3 via JAK/STAT, suggesting the involvement of immune-related genes such as NFKB1 and JAK1. Each of the genetic factors detected in this study using various approaches suggests the involvement of the immune system and immune cell migration.

Symposium 2-4

A Genetic Variant in *prepro-orexin* is Associated with Idiopathic Hypersomnia

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Idiopathic hypersomnia (IH) is a rare heterogeneous disorder characterized by prolonged and disabling excessive daytime sleepiness (intolerable sleepiness in the daytime). The etiology of IH is poorly understood. No susceptibility loci associated with IH have been clearly identified, despite the tendency for familial aggregation of IH. No significant associations between IH and human leukocyte antigen (HLA) alleles have also been observed. Orexin (hypocretin) is a neuropeptide that regulates sleep-wake cycles and rapid eye movement (REM) sleep. Narcolepsy type 1 is caused by the loss of orexin-producing neurons in the hypothalamus, leading to low or undetectable levels of orexin-A in the cerebrospinal fluid (CSF). Unlike patients with narcolepsy type 1, patients with IH show normal levels of orexin-A in the CSF. Pathogenic mutations in prepro-orexin and orexin receptor-1 (OX1R) and -2 (OX2R) were not identified in patients with narcolepsy type 1, except for one rare severe case. Genetic variants in prepro-orexin, OX1R, and OX2R have not been studied in IH. In this study, we focused on rare missense and loss-of-function variants in these genes to search for genetic factors of IH because no significant associations with common variants in these gene regions were observed in our genome-wide association study (GWAS).

We performed a variation screening of these genes and an association study for IH in a Japanese population, with replication (598 patients and 9826 controls). We identified a rare missense variant (g.42184347T>C; p.Lys68Arg; rs537376938) in the cleavage site of prepro-orexin that was associated with IH (minor allele frequency of 1.67% in cases versus 0.32% in controls, $P = 2.7 \times 10^{-8}$, odds ratio = 5.36). We searched for minor allele frequencies of p.Lys68Arg in populations other than the Japanese population using databases. The minor allele frequencies in the Han Chinese, European (non-Finnish), African, South Asian and European (Finnish) populations were 0.34%, 0.003%, 0%, 0%, and 0%, respectively, suggesting that this variant is an East Asian-specific mutation. Two forms of orexin (orexin-A and -B) are generated from cleavage of one precursor peptide, prepro-orexin. The difference in cleavage efficiency between wild-type (Gly-Lys-Arg; GKR) and mutant (Gly-Arg-Arg; GRR) peptides was examined by assays using proprotein convertase subtilisin/kexin (PCSK) type 1 and PCSK type 2. In both PCSK1 and PCSK2 assays, the cleavage efficiency of the mutant peptide was lower than that of the wild-type peptide. We also confirmed that the precursor peptides consisting of orexin-A and orexin-B bound together transmitted less signaling through orexin receptors than mature orexin-A and orexin-B peptides.

These results indicate that a subgroup of IH is associated with decreased orexin signaling, which is believed to be a hallmark of narcolepsy type 1.

Symposium 3
Psychiatric and Neurological Comorbidities in Narcolepsy and Hypersomnia

Symposium 3-1
Characteristics of Hypersomnia Due to Inflammatory Demyelinating Diseases of The Central Nervous System

Hideaki Ishido[1,2] Shigeru Chiba[1,3,4] Tomoyuki Miyamoto[5] Seiji Nishino[6] Haruhisa Honda[2] Takashi Kanbayashi[1,4]

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Background
This study investigated neuromyelitis optica spectrum disorder and related conditions, focusing on cerebrospinal fluid orexin-A (CSF-OX) levels and their impact on hypersomnia.
Methods
We conducted retrospective case-control and case series studies, analyzing 50 hypersomnia patients and 68 controls. Significant findings included more cases of neuromyelitis optica spectrum disorder, diencephalic syndrome, and use of adrenocorticosteroid therapy in the hypersomnia group.
Results
The median CSF-OX value was 160.5 pg/mL, and the MRI hypothalamus-to-caudate nucleus ratio (MRI H/C ratio) was 127.6. Key risk factors for hypersomnia were hypersomnolence and an MRI H/C ratio >130%. Treatment led to a recovery in CSF-OX values.
Conclusion
The study indicated that even intermediate CSF-OX levels could trigger hypersomnia in central nervous system inflammatory demyelinating diseases. Adrenocorticosteroid therapy was found to improve CSF-OX levels, contributing to understanding mechanisms beyond cataplexy or sleep paralysis. The combined use of CSF-OX levels and MRI H/C ratio was proposed to identify severe cases with diencephalic syndrome.

Symposium 3-2

Hypersomnia and Major Depressive Disorder

M Cheung, JWY Chan, JCC Tsang, YK Wing

Li Chiu Kong Family Sleep Assessment Unit, Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China

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Background:
Hypersomnia is a recognised but under investigated sleep problem in major depression disorder (MDD). Existing studies are limited by small sample sizes and loose definitions that have defined hypersomnia as “excessive sleepiness” without taking into consideration of the subjects’ prior sleep pattern.

Method:
A cohort of psychiatric patients who were diagnosed of MDD were identified by consecutive sampling over a 2-month psychiatric clinic-attendance. Diagnosis of MDD was ascertained by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P). A tighter definition of hypersomnia, defined as an excessive daytime sleepiness (EDS) despite an adequate night-time sleep duration of at least 7 hours. The severity of depression and symptoms suggestive of atypical depression were assessed. Each subject also completed a battery of questionnaires including Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS), Insomnia Severity Index (ISI), reduced version of the Morningness-Eveningness Questionnaire (rMEQ), and 1-week sleep diary.

Results:
Among 252 recruited subjects, 28 (prevalence of 11.1%) met the stringent criteria of hypersomnia. The hypersomnia subjects represented a unique subgroup of MDD patients. Among those with adequate sleep duration, hypersomnia subjects were found to have higher depression and anxiety scores, more negative perceptions towards their sleep problems, higher rates of suicidal ideations and more likely to meet a diagnosis of atypical depression ($P<0.05$). Stepwise logistic regression demonstrated that depression severity and atypical depression were independent correlates of hypersomnia. Hypersomnia was an independent predictor of a 3-fold increase in the risk of non-remission in depression (adjusted OR 3.06; 95% CI 1.09-8.58; p=0.034)

Conclusions:
MDD with hypersomnia represented a subgroup patients with more severe clinical profile, higher non-remission rate and atypical features.

Symposium 3-3

Hypersomnia Specific Belief and Psychotherapy for Hypersomnia

Megumi Hazumi
National Center of Neurology and Psychiatry, Japan

Patients with hypersomnia often have mental health problems after its onset. Hypersomnia-specific negative beliefs are suspected to develop in patients with hypersomnia, as they often undergo adverse experiences and are susceptible to stigmatic thinking related to their symptoms. Furthermore, such negative beliefs specific in hypersomnia induced by such experience and thinkingare hypothesized to be associated with mental health problems. Therefore, we aimed to identify hypersomnia-specific negative beliefs using qualitative analyses; we developed and validated the Hypersomnia-Specific Beliefs scale to investigate the associations between such beliefs and mental health problems.

From the qualitative analysis with the interviews for 11 individuals with narcolepsy type 1 (NT1) and idiopathic hypersomnia (IH), three beliefs consisting of 12 thoughts were identified: "aversion toward doze," "hypersensitivity toward others," "reactions about my doze," and "sense of defeat caused by doze." The Hypersomnia-Specific Beliefs (HSB) scale with three sub-scales was developed based on the result of qualitative research. The reliability, validity, and discriminant ability of the HSB scale were verified through a questionnaire survey of 166 patients with NT1 and IH and 375 controls. Furthermore, the HSB score was associated with depressive symptoms, social anxiety, mental health, and subjective sleepiness.

Considering the specificity of the HSB score in individuals with hypersomnia and its impact on mental health problems, it is important to offer patients with high HSB scores psycho-social support services in addition to pharmacological treatment.

Symposium 3-4

ADHD and Narcolepsy

Wakako Ito[1,2] and Makoto Honda[1,2,3]

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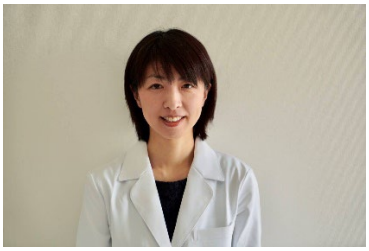
Attention-deficit/hyperactive disorder (ADHD), characterized by inattention, hyperactivity, and impulsivity, often coexists sleep problems. Among sleep problems, cumulative data shows that excessive daytime sleepiness (EDS) is related to ADHD. A recent study showed that sleep latency, assessed by the Multiple Sleep Latency Test (MSLT) was shorter in children with ADHD than in the control group irrespective of the presence/absence of sleep disturbances. On the other hand, ADHD symptoms in pediatric narcolepsy patients found that in the control group, 4.8% had clinically significant ADHD symptoms, narcolepsy type 1 had 19.7% with ADHD symptoms, and narcolepsy type 2 had 35.3% with ADHD symptoms. This shows a higher prevalence of ADHD symptoms among narcolepsy patients. Thus, ADHD and hypersomnia often coexist, and there are some shared characteristics reported between both conditions in neurochemical modulation, electroencephalogram, and genetic link.

First, there is substantial evidence that the underlying mechanisms in neurochemical modulation of arousal and attention considerably overlap. Methylphenidate, a central nervous system stimulant, is known to maintain wakefulness, and is effective in alleviating symptoms of ADHD by blocking the reuptake and increasing the release of dopamine and norepinehrine. The activation of the system is involved in the action mechanism in pharmacological treatment not only for narcolepsy but also for ADHD.

Second, some studies showed that relative theta power or theta/beta power ratio in the electroencephalogram, which was used as a marker of central nervous system arousal, was elevated in children and adults with ADHD. These findings suggest that arousal dysregulation is possibly related to the underlying mechanism in inattentive symptoms in ADHD. On the other hand, studies involving quantitative electroencephalogram (QEEG) analysis in individuals with narcolepsy have shown increased delta and theta power during wakefulness. In essence, narcolepsy and ADHD exhibit similar brainwave patterns, suggesting a potential link between arousal regulation and ADHD symptoms.

Third, recent evaluation using polygenic risk scores, derived from genome-wide association study (GWAS) data of narcolepsy patients, has shown a correlation between higher polygenic risk scores and higher scores for hyperactivity and inattentive symptoms, indicating a genetic link between narcolepsy onset risk and ADHD symptoms.

In this way, ADHD and sleepiness often coexist, and both conditions share significant similarities. This is because narcolepsy (EDS) and ADHD symptoms may share a common underlying mechanism.



Sat September 17, 2023

Symposium4 Epidemiology/Comorbidity of Narcolepsy and Hypersomnia

Symposium 4-1

Narcolepsy is Associated with an Increased Risk of HLA-Related Autoimmune Diseases: Evidence from a Nationwide Healthcare System Data in South Korea

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4Department of Environmental Horticulture, College of Natural Science, The University of Seoul, Korea

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Study Objectives:
To determine the incidence rate of narcolepsy in South Korea and closely examine the relationship between narcolepsy, which is believed to be an autoimmune response, and other systemic autoimmune diseases.
Methods:
We examined data from the South Korean nationwide health insurance claims database from 2010 to 2019. Our study included patients with narcolepsy as well as age- and sex-matched controls without narcolepsy. We estimated the incidence of narcolepsy and the odds ratio of narcolepsy and associated autoimmune comorbidities in South Korea.
Results:
We identified 8710 patients with narcolepsy (59.8% men and 40.2% women). The incidence of narcolepsy was 0.05%. Patients with narcolepsy were at a significantly high risk of ankylosing spondylitis, rheumatoid arthritis, and Sjögren's syndrome, which diseases are known to be related to human leukocyte antigen (HLA) genes.
Conclusions:
Narcolepsy is closely related to systemic autoimmune diseases, particularly those related to HLA genes.

Symposium 4-2

Narcolepsy and the Risk of Pregnancy Complications: Based on Nationwide Healthcare System Database in South Korea

Suhyung Kim, Jihye Oh, Seung-Chul Hong

Department of Psychiatry, St.Vincent's Hospital, College of Medicine, The Catholic University of Korea

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Study Objectives:
Narcolepsy is known as an autoimmune disease which altered metabolic functions. It is believed that narcolepsy makes more pregnancy complications. However clinical evidence in narcolepsy patients, especially in pregnant women, is limited. We aim to find out whether there is relationship between narcolepsy and pregnancy complications.

Methods:
We examined data from the South Korean nationwide health insurance claims database from 2010 to 2019. Out study included women narcolepsy patients who gave birth, and age- and sex- matched controls without narcolepsy. We estimated the odds ratio of narcolepsy with pregnancy complications and control group with pregnancy complications using multivariate logistic regression analysis.

Results:
Our study included 1,836 women with narcolepsy who gave birth and 29,496 women who gave birth without narcolepsy. We found that women with narcolepsy have a slightly high risk of preterm birth (OR, 1.191; 95% CI, 1.034-1.372). Patients with narcolepsy were at a significantly lower risk of spontaneous abortion, caesarean and gestational diabetes (OR, 0.763; 0.682-0.854, OR, 0.679; 95% CI, 0.560-0.824 and OR, 0.656; 95% CI, 0.556-0.774, respectively).

Conclusions:
This study is the first study about pregnancy complications in narcolepsy patients in South Korea. We found that preterm birth happened more in the patient with narcolepsy during pregnancy. But patient had lower risk of spontaneous abortion, caesarean, gestational diabetes compared to heath control group. These findings suggest that narcolepsy is not a definite risk factor for pregnancy complications. Further research is needed to investigate the reasons why narcolepsy patients had lower risk of spontaneous abortion, caesarean, gestational diabetes compared to health control.

Symposium 4-3

Markedly Increased Risk of Colorectal Cancer and Decreased Risk of All Malignancies in Patients with Narcolepsy: A Nationwide Population-Based Cohort Study

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Background:
Interest in the relationship between cancer epidemiology and sleep has been increasing in the scientific community. Among sleep disorders, orexin, a neuropeptide whose deficient production plays a role in causing narcolepsy, has been suggested to play a role in autoimmune digestive disorders such as Chrohn's disease, as well as digestive tract cancers. So in this study, we deduced the relationship between narcolepsy and colorectal cancer as well as malignancies using the Nationwide Health Insurance Service (NHIS) database.

Materials and methods:
The Korean National Health Insurance Service (NHIS) claims database from 2010 to 2019 was used. International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) was used to extract data on colorectal cancers, all malignancies and narcolepsy. The NT1 cohort and the controls were propensity score matched in a 1:10 ratio for sex, age, and medical comorbidities. Incidence rate of colorectal and all malignancies and Hazard ration were calculated for both group.

Results:
The incidence rate of NT1 in South Korea from years 2010 to 2019 was 1.127 per 100,000 person-year. The incidence of all malignancies was 664.1 (95% CI, 660.6 - 667.6) and 708.9 (95% CI, 692.4 - 725.7) for NT1 patients and controls, respectively (p=0.0002). The adjusted HR for developing any type of cancer was 0.67 (95% CI 0.64 - 0.70) for NT1 patients in comparison with the controls.
The incidence of colorectal malignancy was 285.2 (95% CI 282.3 - 288.1) and 123.5 (95% CI 112.4 - 125.9) for NT1 patients and controls, respectively (p<0.0001). The adjusted HR of developing colorectal malignancy was 1.77 (95% CI 1.48 - 2.11) for NT1 patients in comparison with the controls

Conclusion:
Sex, age, and comorbidity-matched cohort of NT1 patients showed a markedly increased risk of developing colorectal malignancy in comparison with the general population. In contrast, NT1 patients showed a significantly reduced risk of developing any type of malignancy in comparison with the general population.

Symposium 4-4
Factors Associated with Metabolic Disorders of Narcolepsy Type 2

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Narcolepsy (NA) is a disorder that causes intolerable drowsiness. NA is classified into NA type 1 (NA1) and NA type 2 (NA2) based on the presence or absence of orexin deficiency in the spinal fluid. Almost all patients with NA1, which is deficient in orexin, are HLA-DQB1*06:02 positive. NA1 is thought to be an autoimmune disease in which orexin-producing cells in the hypothalamus selectively drop out. Orexin is also involved in the regulation of energy metabolism, and NA1 shows the development of metabolic diseases such as obesity and type 2 diabetes. However, the pathogenesis of NA2, which is said to be free of orexin deficiency, is heterogeneous and unclear in many respects, with an HLA-DQB1*06:02 expression rate of approximately 40%. It is also unclear whether NA2 causes the same metabolic diseases as NA1. Recently, the existence of HLA-DQB1*06:02 positive NA2 with moderately low orexin levels (110-200 pg/mL) that do not meet the diagnostic criteria for NA1 (110 pg/mL or less) on CSF examination has been reported (Postiglione et al. sleep. 2022). NA1 and HLA-DQB1*06:02 positive NA2 may have a continuum of pathology.

We conducted a cross-sectional survey on physical complications and HLA-DQB1*06:02 positivity in 83 NA2 patients aged 35 years or older attending a sleep specialist medical institution in Japan under the working hypothesis that the presence of metabolic complications differs depending on HLA-DQB1*06:02 positivity. In this study, we provisionally defined a patient with a metabolic syndrome related disorder (MRD) as a patient with at least one of the following conditions: hypertension, diabetes, or dyslipidemia. Logistic regression analysis showed that MRD in NA2 was significantly associated with the positivity of HLA-DQB1*06:02 independent of age, gender, and BMI obstructive sleep apnea ($p<0.05$). The pathogenesis of HLA-DQB1*06:02 negative NA2 without orexin deficiency is unknown, but it should be noted that HLA-DQB1*06:02 positive NA2 may develop metabolic disease similar to NA1. The research on this presentation was initiated after approval by the ethics committee of the Neuropsychiatric Research Institute in Tokyo, Japan (Approval number 143).

Symposium 4-5

Epidemiology and Burden of Narcolepsy in Taiwan: by Taiwan's National Health Insurance Research Database and Clinical Hospital Database

Yu-Shu Huang

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Introduction:
Narcolepsy is a chronic brain disease with the cerebral dysfunction in modulating the mechanism of sleep and awakening. Previous studies showed the disease burden of narcolepsy can be high. Besides the medical cost, impairment and economic loss related to narcolepsy, both medical and psychiatric comorbidities are common in patients with narcolepsy. In this study, we used a clinical narcolepsy cohort conducted in Chang Gung Memorial Hospital to validate data of the Taiwan's National Health Insurance Research Database. This study aims to investigate the prevalence and incidence of narcolepsy in Taiwan, as well as its disease burden including medical and psychiatric comorbidities.
Subject:
(1) To assess the incidence and prevalence of patients with narcolepsy type 1(NT1), narcolepsy type 2(NT2), and idiopathic hypersonic(IH) in Taiwan. (2) Characterize and assess the patient journey among those with NT1 and NT2; (3) Assess treatment patterns and burden of illness among patients with NT1 and NT2, and to explore the long-term outcomes of narcolepsy and IH patients in Taiwan.
Results:
The cohort database collected 404 patients' information. The distribution of patients in this database are 68 patients with IH (17.00%), 209 patients with NT1 (52.25%), and 121 patients with NT2 (30.50%), respectively. A total of 26,780 patients with IH, NT1 and NT2 were retrieved from in the NHIRD by ICD9/ICD10 code between 2009-2019. With a total of 1009 patients with NT1 and NT2, considering that the calculated precision of narcolepsy by NHIRD is 47.7%, estimated prevalence of narcolepsy in Taiwan is around 0.91 per 10,000 people. Most common psychiatric comorbidities include anxiety disorder in group NHIRD and clinical database (12% and 30%) and depression (13% and 19%). Obstructive sleep apnea is common (25% and 27%). Common physical comorbidities include diabetes mellitus (5%), hypertension (11%), and cardiovascular disease (6% and 5%).
Discussion:
Consider the precision rate of validation, estimated prevalence of narcolepsy in Taiwan is lower than that in Hong Kong. The result indicates that narcolepsy can be under-diagnosed or treated inadequately in Taiwan. But the disease burden including medical and psychiatric comorbidities should be reminded.
Support: Taiwan National Science and Technology Council and Takeda Pharmaceutical Company

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Symposium 5: Psychosocial Aspects of Narcolepsy and Hypersomnia

Symposium 5-1
The impact of COVID-19 and Lockdown in Patients with Narcolepsy

Wei-Chih Chin

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Introduction:
Mental health issues related to the COVID-19 lockdown has been investigated, and sleep is of particular concern, along with a new term, COVID-somnia, which describes sleep problems directly or indirectly related to COVID-19. Patients with previously diagnosed sleep disorders can be more vulnerable during this period of time, such as those with narcolepsy. Using data from our cohort study, we investigated changes in the quality of life and the symptom severity of patients with narcolepsy during lockdown.
Subjects:
(1) to investigate the changes of the Short Form 36 Health Survey questionnaire (SF-36), the Epworth Sleepiness Scale (ESS), the visual analog scale (VAS) for hypersomnolence, the VAS for cataplexy and sleep diary during Taiwan's 2021 lockdown, compared with the non-lockdown period.
(2) to analyze subgroup differences of the impact of the lockdown by narcolepsy subtype, sex, and age.
Results:
A total of 120 patients with narcolepsy were recruited; 80 of the patients had NT1 (mean age 25.25 ± 6.79 years; 60% male) and 40 had NT2 (mean age 22.16 ± 6.64, 53% male). During the lockdown period, the ESS score of total patients was decreased ($p = 0.039$) and body mass index was increased ($p = 0.02$). The NT1 group decreased significantly ($p1 = 0.017$), especially in men ($p1 = 0.016$) and adults ($p1 = 0.04$); scores for the VT domain of the SF-36 increased significantly in male and adult patients with NT2 ($p1 = 0.048$ and 0.012). Additionally, male patients with NT2 exhibited significantly decreased scores in the physical and emotional role functioning domains ($p1 = 0.028$, 0.024). The children and adolescents with NT1 had significantly decreased scores in the general health domain of the SF-36, but no significant change was noted in that of adults ($p1 = 0.027$, $p2 = 0.012$).
Discussion:
Both negative and positive impacts of Taiwan's 2021 lockdown were found. The improvements of daytime hypersomnolence and vitality highlight that a more flexible but structured daily routine with adequate sleep time should be considered for this population even in the nonlockdown periods.

Symposium 5-2

The Impact of COVID-19 Vaccination and Virus Infection on Sleep Problems in Narcolepsy

Shuang Yue, Xiaosong Dong, Chi Zhang, Fang Han

Division of Sleep Medicine, Peking University People's Hospital, Beijing, China.

Background:
The COVID-19 pandemic and vaccinations have caused sleep-related problems. The impact of COVID-19 vaccination and infection on patients with narcolepsy symptoms remained to be studied. The special procedure to control COVID-19 in China allows us to survey on this issue.
Methods:
From 1 Dec 2022 to 30 May 2023, we conducted a questionnaire survey of sleep problems in patients with narcolepsy using Chinese version of Narcolepsy Severity Scale (Li, 2021), OSAHS patients were evaluated as controls. Sleep problems includes EDS, insomnia, nightmares, hypnotic use, fatigue.
Results:
145 were narcolepsy patients. The number of people vaccinated and infected with COVID-19 was 90.7% and 85.9%, respectively. Compared with OSA patients, daytime sleepiness increased 9.2% in narcolepsy patients after vaccination and 6.1% in OSAHS. The number of people who had poor sleep quality after vaccination with narcolepsy and OSA was 9.2% and 7.9%, respectively. The number of patients with sleepiness increased significantly after infection (6.3% vs 18.2%, $p<0.05$). Patients with narcolepsy also had an increased rate (15.7%) of poor sleep quality after infection than those in the OSA group (9.9%). In patients with narcolepsy, sleepiness and disturbed nighttime sleep are the main symptoms that worsen after vaccination and infection.
Conclusions:
Compared with OSA, COVID-19 vaccination and infection have greater effects on hypersomnia and insomnia in patients with narcolepsy than OSA, and the symptoms of hypersomnia and disturbed nighttime sleep are mainly observed.

Symposium 5-3

Psychological Problems of Narcoleptic Patients in Korea

Seung Bong Hong

Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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Chronic diseases are frequently comorbid with depression that can worsen the associated health outcomes and alter the quality of life of patients. However, in narcolepsy, an endogenous origin of mood disturbances has been suspected. ORX deficiency could induce psychological impairments through several neurobiological pathways. Moreover, nocturnal REM sleep latency is reduced while REM sleep pressure and sleep fragmentation are increased in narcolepsy type 1 and in major depression. Currently, narcolepsy management is only symptomatic, and patients require lifelong treatments with psychostimulants and often anticataplectic drugs. Most anticataplectic drugs (e.g., tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and selective serotonin reuptake inhibitors) also have mood-modifying effects. A cross-sectional study showed that patients with narcolepsy type 1 treated with stimulants and anticataplectic drugs presented more depressive symptoms and poorer quality of life than those treated with stimulants alone.

The prevalence of insomnia, depression, anxiety problem and suicidal thought in narcoleptic patients was investigated at single sleep disorder center in Korea. 151 patients had insomnia severity index and showed normal in 43 (28.5%), subthreshold insomnia in 59 (39.1%) and clinical insomnia (moderate) in 39 (25.8%) and clinical insomnia (severe) in 10 (6.6%). 142 patients with narcolepsy had BDI-2 test and the result showed 65 (45.8%) normal mood (BDI-2 score: 0-13), 26 (18.3%) mild depression, 30 (21.1%) moderate depression and 20 (14.1%) severe depression. 75 patients had GAD-7 test and the result was normal in 37 patients (49.3%), mild anxiety in 18(24%), moderate anxiety in 15 (20%) and severe anxiety in 5 (6.7%). Out of 77 patients who responded to suicidal ideation question, 17 (22.1%) showed suicidal ideation. These results indicate that psychosocial aspects of narcoleptic patients should be tested and managed appropriately.

Symposium 5-4

Risks and Accidents of Patients with Narcolepsy: A Study of Taiwan's National Health Insurance Research Database and Clinical Hospital Database

Tsun-Yi Ruan

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Introduction:
Narcolepsy is a central hypersomnia and previous studies have reported high comorbidities disease burdens. Besides, daytime somnolence and cataplexy can also result in risks and accidents. In this study, we used a clinical narcolepsy cohort to track prevalence of various risks and accidents of study participants in the Taiwan's National Health Insurance Research Database.
Subject:
To investigate the prevalence of comorbidities, injuries and accidents of patients with narcolepsy type 1(NT1), narcolepsy type 2(NT2), and idiopathic hypersomnia(IH), compared with age and gender matched controls.
Results:
The narcolepsy cohort group included 386 participants and the control group consisted of 772 age and gender matched controls. Significantly more physical and psychiatric comorbidities were found in the narcolepsy cohort group, along with more psychotropic use. The narcolepsy cohort group also had significantly more injuries and transport accidents. Other accidents such as drowning or burning didn’t show significant difference.
Discussion:
The findings of high physical and psychiatric comorbidities are consistent with previous studies and highlight the importance of comprehensive assessment and treatment for narcolepsy patients. Besides, high injuries and transport accidents can result from hypersomnolence. Prevention of injureis and accidents should be discussed and medication treatment should be tailored individually according to different patients’ needs.

Support: Taiwan National Science and Technology Council and Takeda Pharmaceutical Company

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Special Lecture 1

Flu and Narcolepsy - cataplexy: new evidence from China Narcolepsy Network.

Fang Han

Division of Sleep Medicine, Peking University People's Hospital, Beijing, China.

The influenza A virus subtype H1N1 pandemic surfaced in the year of 2009. With the first reports of a clearly increased incidence of narcolepsy in Scandinavian children, the H1N1 vaccine named Pandemrix was suggested to be the culprit. However, research groups from China with a low vaccination grade as well as different vaccine reported a more modest increase in narcolepsy incidence, which was replicated in areas like Taiwan, the United States, and several other European countries. Recently, our groups consolidated one major piece of this puzzle by collecting the incidence of narcolepsy on a large scale over a 20-year period in mainland China with data from multiple sleep centers. A possible role for the H1N1 virus itself was thus emphasized. This is also supported by several mechanism studies. Increased incidences were mainly reported in children, and to a lesser extent in adults.

There are evidences imply that H1N1 virus infection or vaccination against H1N1 is not the sole trigger. Hypocretin-deficient narcolepsy also existed in the last century before 2009 H1N1pandemic, seasonal effect on narcolepsy onset persisted during the past 20years in our dataset, and children narcolepsy were often seen in our clinic. Multiple other candidates have been suggested. Streptococcal infection was not related to narcolepsy in China. A spatial and temporal analysis between narcolepsy onset and national flu data from China CDC give more clue of the new possible triggers, and the outbreak of COVID-19 globally also may influence narcolepsy onset in some way.

Special Lecture 2

Epidemiology of hypersomnolence – a reflective thinking

Yun Kwok Wing

Li Chiu Kong Family Sleep Assessment Unit, Department of Psychiatry, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China

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Epidemiology study will help to inform the prevalence, incidence and potential etiological factors of a disease. The epidemiology of hypersomnolence has a wide range of disorders from the rare narcolepsy and idiopathic hypersomnia to common insufficient sleep problem. While the population survey suggested about 40% of adolescents might have excessive daytime sleepiness, only 0.05% of narcolepsy was reported in community survey in Hong Kong. The current lecture will focus on the current global epidemiological data especially from the methodological perspectives on how we may improve the precision and refinement of the epidemiology of hypersomnolence – a much neglected sleep problem.

Symposium 6 Treatment of Narcolepsy and Hypersomnia

Symposium 6-1

The Treatment Strategy of Pediatric Narcolepsy

I Hang Chung

Department of Psychiatry and Sleep Center, Chang Gung Memorial Hospital, Taipei, Taiwan

Introduction:

Pediatric narcolepsy is a chronic sleep-wakefulness disorder. Its symptoms frequently begin in childhood. Symptoms of pediatric narcolepsy include excessive sleepiness, cataplexy, sleep paralysis, sleep terror, and hypnagogic or hypnapompic hallucinations. These symptoms impaired children's function and negatively influenced their social interaction, studying, quality of life, and may further lead to emotional and behavioral problems. Therefore, early diagnosis and intervention are essential for children's development. With our review, pediatric narcolepsy's treatment approach should include medication, behavioral modification, and education/mental support.

Subject/Method:

We investigated and reviewed previous studies about pediatric narcolepsy via Pubmed, Cochrane library and other medical journal resources. With our review, we wish to present a comprehensive treatment strategy for pediatric narcolepsy.

Through our clinical experience, we modify an applicable behavioral model for treating pediatric narcolepsy:

(1) Regular sleep/wake schedule
(2) Modified sleep environment
(3) Relaxation before bedtime & wake-up routine
(4) Risk prevention
(5) Educating people around children with narcolepsy
(6) Mental support

Results:

Narcolepsy is a chronic neurological disorder that currently has no cure. The goal of treatment is to reduce daytime sleepiness and other disturbing symptoms and improve daytime function and quality of life. Treatment plans for childhood narcolepsy should be comprehensive and typically involve pharmacological and non-pharmacological approaches. Only sodium oxybate had been proven effective in pediatric patients through randomized placebo-controlled studies. Other wake promoting medications and antidepressants are used as off-label, and still warrant more studies to prove their efficacy and investigate possible side effects in pediatric narcolepsy. When prescribing medications for pediatric narcolepsy patients, it is important to acknowledge evident-based safety and the growth issues within each medication. It is also important to provide sufficient psychological counseling and behavioral modification for pediatric narcolepsy patients in multiple environments, and to enhance the cooperation between school teachers, family members, and the medical team.

Discussion:

Treatment of pediatric narcolepsy should involve the use of medication, behavior modification, education, and mental support. Although psychosocial interventions such as behavior modification is shown to benefit patients and the family, prospective long-term follow-up is necessary to evaluate the prognosis of outcome of children with narcolepsy.

Support: Taiwan National Science and Technology Council

Symposium 6-2
The Effect of Aripiprazole on The Difficulty Waking Up in The Morning

Takashi Kanbayashi[1,2], Roushi Li[1], Hideaki Ishido[1,3], Shigeru Chiba[1,2,4], Yuta Konno[1], Aya Imanishi[5], Yuki Omori[6], Taisuke Ono[7], Hideaki Kondo[1,8], Mayumi Kimura[1]

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Hypersomnolence can be divided into two main categories: excessive daytime sleepiness and prolonged total sleep time. Narcolepsy is representative of the former, while the latter is idiopathic hypersomnia with prolonged sleep time. In addition, there are other patients, mainly young adults, who also fall asleep late, sleep for longer periods of time, and are unable to wake up in the morning. They are diagnosed with delayed sleep phase syndrome. I imagine that this is common in Japan and East Asia. Effective treatment for these patients with prolonged sleep duration has been scarce. Recently, aripiprazole (APZ), a second-generation antipsychotic, has been shown to be effective as a treatment when used in small doses. For example, a patient with idiopathic hypersomnia who went to bed at 1:00 a.m. and woke up at 12:00 a.m. and took naps during the day was treated with 1 mg of APZ and went to bed at midnight and woke up at 8:00 a.m. He no longer needed naps during the day. A similar effect was observed in patients with delayed sleep phase syndrome. Since APZ is a dopamine partial agonist, it was thought that a small amount of APZ would activate dopamine and shorten the sleep time, but this alone could not explain the earlier sleep onset time. In this August, Li et al. reported that APZ reduces signaling from the suprachiasmatic nucleus, making it more attuned to the light-dark cycle instead. Now that we have clarified the mechanism of action, we would like to work on further establishment of therapeutic methods.

Symposium 6-3

Efficacy and Safety of Modafinil in Patients with Idiopathic Hypersomnia without Long Sleep Time: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Comparison Study

Yuichi Inoue [1 2]

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[2] Yoyogi Sleep Disorder Center, Tokyo, Japan

Background:
Few treatments are available for patients with idiopathic hypersomnia (IH). Modafinil, an established psychostimulant for the treatment of narcolepsy, was tested for efficacy and safety in Japanese patients with IH without long sleep time.
Methods:
This multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study was conducted at 20 institutions in Japan. Patients who met the diagnostic criteria of IH in the International Classification of Sleep Disorders (second edition) were included. The study comprised a 17-day observation period and a 3-week treatment period during which modafinil (200 mg) or placebo was administered orally once daily (in the morning). The primary efficacy endpoint was the change in mean sleep latency on the Maintenance of Wakefulness Test (MWT). Adverse events (AEs) were also recorded to evaluate safety.
Results:
In total, 123 patients were eligible for this study, and 71 were randomized to receive modafinil (N =34) or placebo (N =37). Patients treated with modafinil experienced a significantly prolonged mean sleep latency on the MWT at the end of the study compared with placebo (5.02 min, 95% confidence interval: 3.26-6.77 min; $p < 0.001$). AEs occurred in 58.8% (20/34) and 27.0% (10/37) of patients in the modafinil and placebo groups, respectively. Frequent AEs in the modafinil group were headache (n = 6), dry mouth (n =3), and nausea (n =3); no clinically significant AEs occurred.
Conclusion:
Modafinil was shown to be an effective and safe treatment for excessive daytime sleepiness in patients with IH without long sleep time.

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