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HOT TOPICS IN EUROPEAN NARCOLEPSY RESEARCH

1.

Introduction: the hypothalamus as bedroom of the brain

G.J. Lammers

Department of Neurology and Clinical Neurophysiology. Leiden University Medical Center. The Netherlands.

The origin of the name 'narcolepsy' is well documented. It was coined, in 1880, by Jean-Baptiste Edouard Gelineau, a French physician who described a patient with complaints that are still recognized as typical for narcolepsy with cataplexy. The word narcolepsy is derived from the Greek words *narke* (meaning numbness, stupor) and lambanein (meaning to seize). The origin of the name 'hypothalamus' is also well established. It was coined, only in 1893, by the Swiss anatomist Wilhelm His for the portion of the diencephalon inferior to the thalamus. In contrast, the origin of the name 'thalamus' is not clear. It can be found in medical manuscripts from the end oft he 18th century. Intriguing, however, is its meaning: the receptacle of a flower or bedroom (derived from the Greek word thalamos and the later Latin word thalamus). A better name could not have been chosen for this part of the brain, but this can only be concluded with our current knowledge about the function of the (hypo) thalamus: the thalamus is instrumental for generating wake, and the hypothalamus for the regulation of sleep and wake. In fact, von Economo already proofed this in the 1910's. Unfortunately, it took us almost 90 years to rediscover his knowledge and to identify precisely which structures, projections and transmitters are responsible for the 'bedroom-function' of the (hypo)thalamus, and which disturbance causes narcolepsy.

2.

Hypocretinergic regulation of sleep-wakefulness states: narcoleptic signs emergence based on insufficient hypocretin actions in the pontine tegmentum

M. Garzón

Department of Anatomy, Histology and Neuroscience. Medical School UAM. Madrid, Spain.

Perifornical area (PeF) contains hypocretinergic neurons linked to narcolepsy and projects to pontine tegmentum areas involved in sleep-waking control. We here report neural mechanisms by which dysfunction of hypocretin (Hcrt) neurons innervating the pontine tegmentum could elicit narcoleptic signs. We used sleep recordings in free cats, electrophysiological unit recording in anesthetized rats, anatomical tracing and immunohistochemistry. Our study targets were the dorsal (dRPO) and ventral (vRPO) divisions of oral pontine tegmentum, respectively implicated in wakefulness and REM sleep. Hcrt-1 microinjection in dRPO increased wakefulness and decreased NREM and REM sleep. In contrast, Hcrt-1 in vRPO suppressed REM sleep as sole significant effect. To determine cellular mechanisms underlying such actions, we examined electrophysiological activity of d/RPO/vRPO neurons after PeF stimulation and local hypocretin application. PeF stimulation elicited orthodromic responses in dRPO and vRPO. Accordingly, anatomical tracing showed PeF retrogradely-labeled neurons, some of which contained hypocretin, from both tegmental areas. Hcrt-1 application in dRPO provoked increase in dRPO neurons activity and decrease in EEG delta activity that were blocked by a Hcrt-1R antagonist. Quite the opposite, Hcrt-1 in vRPO induced an inhibition, which was blocked by bicuculline, indicating that Hcrt-1 inhibitory action may involve $GABA_A$ receptors activation. Collectively, these data suggest that PeF hypocretin-containing neurons may enhance wakefulness by activating dRPO neurons with ascending projections, and also impair REM sleep generation by a GABA-mediated inhibition of vRPO neurons. Absence of Hcrt signaling in narcolepsy would impair those actions, thus leading in dRPO to somnolence and hypovigilance and in vRPO to REM sleep disinhibition. Support: BFU2009-06991.

3.

Narcolepsy-cataplexy and comorbid autoimmune diseases

F.J. Martínez Orozco [b], C. de Andrés [a], I. Villalibre [b], J.L. Vicario [c], M. Fernández Arquero [b], R. Peraita Adrados [a]

[a] Sleep Unit. Clinical Neurophysiology and Neurology Department. Gregorio Marañón University Hospital. Complutense University of Madrid (UCM). [b] Sleep Unit. Clinical Neurophysiology and Immunology. San Carlos University Hospital. UCM. [c] Histocompatibility. Blood Center of the Community of Madrid. Madrid, Spain.

Introduction. There are no reports on the association between sporadic and familial narcolepsy-cataplexy (NC) and other neurological and non-neurological autoimmune HLA class II–associated diseases; therefore, there is no evidence for the autoimmune hypothesis of NC. **Aim.** We present the comorbid autoimmune diseases (AD) associated with NC studied in our sleep unit during the last 25 years. **Patients and methods.** 155 NC Caucasian patients with a mean age at diagnosis of 39.1 ± 17.8 years (range, 6-70) were assessed using the clinical history, physical and neurological examinations, sleep questionnaires, neuroimaging studies, and HLA class II antigen typing. Diagnosis was confirmed by an overnight polysomnographic recording followed by a MSLT (sleep latency ≤ 8 minutes, ≥ 2 SOREMPs) or by detection of Hcrt-1 levels in CSF. We found 24 patients (out of 155) with one or more AD associated. They were matched for gender and age at onset of NC symptoms with other NC patients (all sporadic cases) without AD. **Results.** 24 patients with NC + AD (15.48%), 50% women, 1 familial and 23 sporadic cases, had idiopathic thrombocytopenic purpura (1 case); multiple sclerosis (1 case); systemic lupus erythematosus (1 case); psoriasis (2 cases); multinodular goiter (1 case); Crohn disease (1 case); atopic dermatitis (3 cases); allergic asthma and or allergic rhinitis (15 cases). Two patients had a suspected autoimmune disorder: Peyronie disease, and idiopathic recurrent facial palsy. In 12 cases the diagnosis of the AD preceded the EDS. In 4 cases, both EDS and AD appeared simultaneously. In the patient with systemic lupus erythematosus, NC appeared 10 years later and MRI was normal. The age at diagnosis of narcolepsy was made 8 earlier in NC + AD patients but the difference was not significant, whereas we found significant differences in the severity of cataplexy of NC + AD compared to

NC patients. **Conclusion.** NC was associated with AD in 15.48% of cases, and the prevalence of these AD is overrepresented in our series. We found that age at diagnosis was made 8 years earlier in NC + AD patients and that cataplexy was significantly more severe.

4.

Environmental risk factors for narcolepsy with cataplexy in a series of 54 patients

R. del Río Villegas [a], R. Peraita Adrados [b]

[a] Sleep Unit. Clinical Neurophysiology Service. La Paz University Hospital. Autonomous University of Madrid (UAM). [b] Sleep and Epilepsy Unit. Clinical Neurophysiology Service. University Hospital Gregorio Marañón. Complutense University of Madrid (UCM). Madrid, Spain.

Introduction. Epidemiological studies emphasize the importance of environmental risk factors in the etiology of narcolepsy with cataplexy (NC) in genetically predisposed patients. **Aim.** To replicate literature findings in a case-control study using controls matched for age at onset and gender. **Patients and methods.** All patients were recruited through our sleep units, and the diagnosis of NC fulfilled the criteria of the ICSD. A Picchioni's questionnaire was self-administered to 54 patients, and we specifically determined the stressor factors and infectious diseases one year before the onset of the first potentially related symptom. The questionnaire consisted of 54 environmental risk factors and 42 infectious diseases items. Data from questionnaires were matched with 84 control participants recruited from non-related family members. We asked the control group about the risk factors appearing the year before. **Results.** The questionnaire was answered by 54 patients (55.6% males) with a mean age at onset of first symptom of 21,6 ± 9,3 years and mean age at diagnosis of 35,3 ± 14,5 years, and 84 controls. Several of the stressors factors carried a significant risk including changed school, major changes in sleeping habits. Chicken pox and strep throat were the most frequent infectious diseases. There were no differences in number of factors between cases and controls. **Conclusion.** The significant differences in risk factors in our NC series were changed school, major change in sleeping habits and of the infectious diseases chickenpox and strep throat. Prospective epidemiological studies will be encouraged despite the low prevalence of NC in the context of EU-NN.

5.

How genetic characterization of narcolepsy and hypersomnia is useful on phenotype definition

A. Martins da Silva [a,c], J. Lopes [a], J. Ramalheira [a], C. Carvalho [b,c], D. Cunha [b,c], P.P. Costa [c,d], B.M. Silva [b,c]

[a] Serviço Neurofisiologia. Hospital Santo António/CH Porto. [b] Laboratório de Imunogenética/ICBAS. [c] UMIB/ICBAS. Universidade do Porto. [d] Instituto Nacional Saúde Ricardo Jorge. Porto, Portugal

Introduction. The determination of HLA class II genotype is widely used to confirm the diagnosis of narcolepsy with or without cataplexy. It is known from studies carried out in the 80's and 90's that genetic markers, particularly HLA-DR2 (HLA-DRB1*15) and later DQB1*06:02, are strongly associated with susceptibility to narcolepsy (N). First studies in 1984 showed values of 100% of positive HLA-DR2 (Langdon et al; Lancet 1984) in narcoleptic patients with cataplexy (NC). Mignot et al (Sleep 1997) found values of 76.1% of HLA-DQB1*06:02 positive in NC and 40.9% in N. More recent studies emphasize difference between children and adults for HLA-DQB1*06:02. Values of 93.7% (adults) vs 92.6% (children) in NC and a frequency of 78,6% in adults vs 52.9% in children were found in N (Nevsimalova et al; J Neurol 2013). The dissemination of HLA genotyping was the result of two convergent reasons: i) the method is reliable, easy to perform and reassures the clinician; ii) the assay is less invasive than other methodologies, namely those involving **cerebrospinal fluid (**CSF) samples. Another contributing factor is the wide acceptance of the hypothesis of an autoimmune origin for Narcolepsy (a clinical field in which the relevance of HLA system is generally accepted). This hypothesis finds support in the virtually absent levels of hypocretin peptides in the CSF of patients with NC, which is postulated to be due to the autoimmune destruction of hypocretin producing neurons (Burgess et al; J Neurosci 2012). **Aims.** To evaluate the contribution of genetic markers (HLA) to the differential diagnosis between narcolepsy with (NC) or without cataplexy (N) and hypersomnia (H) and their relevance in the context of our population (Northern Portugal). **Patients and methods.** A cohort of 113 patients with sleep and hypersomnia complaints were observed at the Outpatient Sleep Clinic from Hospital Santo António/CH Porto and were assessed by clinical, night sleep polygraphic recording, MSLT on the following day, blood sampling in a routine method. Data from laboratory parameters was confronted with the clinical diagnostic hypothesis. Clinical reevaluation of the patients was considered if results did not match. Of these patients, classified as NC, N or H (according to ICSD2, 2005), 38 were NC (age at testing: mean, 32.8 years; median, 30 years); 13 N (age at testing: mean, 34.2 years; median: 36 years); 62 patients had H (age at testing: mean, 38.2 years; median, 40 years). We used a control population (CP) of 206 reportedly healthy individuals from the same geographic origin. The allele frequencies of the control population were confirmed and compared with a larger cohort of another population (2500 individuals) from the central and south regions of the country. **Results.** The frequency of HLA-DQB1*06:02 allele was overrepresented in N and NC patients (46% and 71% respectively), as expected, and the *p* value is extremely significant for NC ($p < 0.0000$). HLA-DQB1*02 frequency was also increased in the population with H when compared with the CP (55% vs 34%; $p = 0.00396$). Interestingly the frequency of the HLA-DQB1*03 allele was decreased in the NC vs CP group (34% vs 56%; $p = 0.012153$). No differences were found in the HLA-DQB1*06:03 frequency between the cohort of patients and the control population. **Conclusions.** The HLA-DQB1*06:02 allele, a susceptibility factor to other autoimmune disorders (e.g.: MS, SLE, sarcoidosis, sclerosing cholangitis), was confirmed as a susceptibility allele also to NC in our population. The frequency of this allele in our NC patients (71%) is within the range of other studies. This value is lower when compared to studies concerning only patients with severe cataplexy (frequencies between 85-95%). Some of the differences could be due to phenotypic uncertainty or to the clinical picture evolution in different age groups (Nevsimalova et al; J Neurol 2013). Also a modification of hypocretin levels, by circadian or other oscillations and the influence of environmental factors (infections, head trauma, immunization) can be involved. The role of the potential regeneration of CNS tissue is also a subject to be explored. Given these uncertainties, genetic characterization has the potential to enhance the ability to carry out differential diagnosis among diverse excessive daytime sleepiness phenotypes, helping in the distinction of diverse entities corresponding to fundamentally different biological processes. Finally a matter to be explored is the role of HLA-DQB1*06:03 allele, considered by some authors as a protective factor to NC (Hor et al; Nat Genet 2010) (Van der Heide et al; Sleep 2012). Our study did not confirm this assumption.

6.

Genetic factors in narcolepsy

M. Tafti

Center for Integrative Genomics. University of Lausanne. Lausanne, Switzerland.

Narcolepsy with cataplexy is tightly associated with HLA-DQB1*06:02. For over two decades no other major genetic factors was associated with narcolepsy. The discovery of hypocretin neurotransmission pathway and mutations in hypocretin receptor 2 in canine narcolepsy, opened up a new field of molecular genetics of narcolepsy. By using a transgenic mouse model, we have shown that hypocretin neurons are enriched in Tribbles Homolog 2 protein (TRIB2) and that

narcolepsy patients diagnosed early after first symptoms have auto-antibodies against TRIB2. Together with the HLA association, these findings are interpreted as suggestive of an autoimmune disease. Genome-wide association studies also found associations with variants in TCRA, P2RY11, CTSH, and TNFSF4, all with immune-related functions. It was also shown that a large number of HLA-DQB1*06:02 controls carry the HLA-DQB1*06:03, which confers a strong protection against narcolepsy. Search for causative genes in familial forms of narcolepsy has also identified a mutation in MOG in a single large family, and in DNMT1 in three families with autosomal dominant cerebellar ataxia, deafness and narcolepsy. Ongoing next generation exome sequencing of both familial and sporadic narcolepsy patients might reveal new mutations causally linked to the condition.

7.

Glucose and fat metabolism in narcolepsy and the effect of sodium oxybate: a hyperinsulinaemic-euglycemic clamp study

C.E.H.M. Donjacour [a], N.A. Aziz [a], F. Roelfsema [b], S. Overeem [c,d], A. Kalsbeek [e,f], H. Pijl [b], G.J. Lammers [a]

[a] Department of Neurology. [b] Department of Endocrinology and Metabolic Diseases. Leiden University Medical Centre. Leiden. [c] Radboud University Medical Centre. Nijmegen. [d] Centre for Sleep-Wake Disorders Kempenhaeghe. Heeze. [e] Netherlands Institute for Neuroscience. Hypothalamic Integration Mechanisms. Amsterdam. [f] Department of Endocrinology and Metabolism. Academic Medical Centre of the University of Amsterdam. Amsterdam, The Netherlands.

Introduction. Hypocretin (orexin) deficiency causes narcolepsy, a condition characterized by excessive daytime sleepiness, cataplexy, and fragmented nocturnal sleep. Although narcolepsy is associated with obesity it is uncertain whether this is caused by changes in glucose and fat metabolism. Therefore, we performed a detailed analysis of systemic energy homeostasis in narcolepsy patients, and additionally, investigated whether it was affected by three months of sodium oxybate (SXB) treatment. **Patients and methods.** Nine hypocretin deficient patients with narcolepsy-cataplexy (seven males), and nine healthy sex, age, and weight matched controls were enrolled. A hyperinsulinaemic-euglycemic clamp combined with stable isotopes ([6,6-2H2]-glucose and [2H5]-glycerol) was performed at baseline. In seven patients (five males) a second study was performed after three months of SXB treatment. **Results.** Glucose disposal rate (GDR) per unit serum insulin was significantly higher in narcolepsy patients compared to individually matched controls (1.6 ± 0.2 vs 1.1 ± 0.3 µmol/kgFFM/min/mU×L; $p = 0.024$), whereas β-cell function was similar ($p = 0.50$). Basal steady state glycerol appearance rate tended to be lower in narcolepsy patients (5.2 ± 0.4 vs 7.5 ± 1.3 µmol/kgFM/min; $p = 0.058$), suggesting a lower rate of lipolysis. After SXB treatment, GDR tended to decrease (1.4 ± 0.1 vs 1.1 ± 0.2 µmol/kgFFM/min/mU×L; $p = 0.063$), and endogenous glucose production decreased as well (0.24 ± 0.03 vs 0.16 ± 0.03 µmol/kgFFM/min/mU×L; $p = 0.028$), suggesting a twofold effect on insulin sensitivity. SXB treatment significantly increased lipolysis (4.9 ± 0.4 vs 6.5 ± 0.6 µmol/kgFFM/min; $p = 0.018$), possibly contributing to weight loss in narcolepsy patients (–5.2 ± 2.0 kg; $p = 0.075$). **Conclusion.** Our findings suggest that narcolepsy patients are more insulin sensitive, and tend to have a lower rate of lipolysis, than weight matched controls. After SXB treatment lipolysis increased body weight decreased, and insulin sensitivity decreased to the level of healthy controls. **Support.** This study was supported by a grant from UCB Pharma.

8.

Pediatric narcolepsy: data from the French cohort Narcobank

M. Lecendreux, S. Lavault, F. Benazzouz, P. Franco, I. Arnulf, Y. Dauvilliers

National Reference Center for Narcolepsy, Idiopathic Hypersomnia and Kleine-Levin Syndrome. Paris, France.

Introduction. Narcolepsy with cataplexy (NC) in children is frequently under-diagnosed. Young patients often show dramatic impairment in their well-being, social skills and academic performance. Under-recognition and undertreatment of narcolepsy represents a significant unmet medical need in childhood. **Aim.** To conduct a descriptive analysis of a large sample of pediatric narcoleptic patients. **Subjects and methods.** Pediatric data were extracted from a National French multicentre research program on narcolepsy (PHRC AOM07-138) that has enrolled a cohort of 544 narcoleptic patients, and which includes 109 pediatric patients. **Results.** Mean age ± SD at diagnosis was 11.6 ± 3.1 years. All children presented with EDS, 80% with cataplexy, 40% with hypnagogic hallucinations and 24% reported sleep paralysis and 16% dyssomnia. 31% had received (A) H1N1 vaccine prior to disease onset. School difficulties and grade repetition were found in respectively 36% and 23% of the sample. Obesity was found to be more common before the age of 10 years-old. Overall mean BMI ± SD was 23.2 ± 5.2. HLA DQB1*0602 was found in 91% of the sample. Overall mean CSF Hcrt levels ± SD were 31 ± 46 pg/mL ($n = 20$) but were lower in obese children ($p = 0.023$). PSG-MSLT parameters significantly differed in children with or without cataplexy. Compared to controls, narcoleptic patients showed more impairment when assessing ADHD symptoms and depression. Sleepiness was found to be a predictor of ADHD symptoms and depression. **Conclusion.** Narcolepsy in children and adolescents should be considered as a serious disorder. Evidence-based treatment guidelines for the treatment of narcolepsy in children have yet to be established. **Support.** PHRC AOM07-138, French health Ministry; promotor: Assistance Publique-Hôpitaux de Paris.

9.

The endocrine-metabolic spectrum in childhood narcolepsy

F. Poli [a], F. Pizza [a], E. Mignot [b], R. Ferri [c], U. Pagotto [d], S. Taheri [e], E. Finotti [a], F. Bernardi [f], P. Pirazzoli [f], A. Cicognani [f], A. Balsamo [f], L. Nobili [g], O. Bruni [h], G. Plazzi [a]

[a] Department of Neurological Sciences. University of Bologna. IRCCS Istituto delle Scienze Neurologiche di Bologna. Bologna, Italy. [b] Stanford Center for Sleep Sciences. Stanford University. Stanford, CA, USA. [c] Department of Neurology. IRCCS Oasi Institute for Research on Mental Retardation and Brain Aging. Troina, Italy. [d] Endocrinology Unit. Department of Clinical Medicine. S. Orsola-Malpighi General Hospital. Bologna, Italy. [e] School of Clinical and Experimental Medicine. University of Birmingham. Birmingham, United Kingdom. [f] Pediatric Clinic. S. Orsola-Malpighi General Hospital. Bologna, Italy. [g] Centre for Epilepsy Surgery C. Munari. Centre of Sleep Medicine. Department of Neuroscience. Niguarda Hospital. Milan, Italy. [h] Department of Developmental Neurology and Psychiatry. Sapienza University. Rome, Italy.

Aim. We analyzed the potential predictive factors for precocious puberty and for obesity in childhood narcolepsy with cataplexy (NC). **Patients and methods.** Forty-three children/adolescents with NC versus 52 age-matched obese children as controls. All patients underwent clinical interview, polysomnographic recordings, cerebrospinal fluid hypocretin-1 measurement, and human leukocyte antigen typing. Height, weight, arterial blood pressure, Tanner pubertal stage, lipid and glucose plasma profiles were measured. If an altered pubertal development was clinically suspected, plasma concentrations of hypothalamic-pituitary-gonadal axis hormones were also determined. **Results.** NC patients showed a high prevalence of overweight/obesity (74%), twice than the general pediatric population (36%) and of precocious puberty (17%), near 1000 times than the general population (0.015%). Moreover, the odds ratio for developing precocious puberty in NC versus obese controls was 10.2. Isolated signs of accelerated pubertal development (thelarche, pubic hair, advanced bone age) were also present (41%). Precocious puberty was

significantly predicted by a younger age at first NC symptom onset, but not by overweight/obesity. Also overweight/obesity was predicted by younger age at diagnosis; additional predictors for overweight/obesity (i.e. short disease duration, younger age at weight gain and lower high-density lipoprotein cholesterol) did not include precocious puberty. NC symptoms, pubertal signs appearance, and body weight gain developed in close temporal sequence. **Conclusion.** NC occurring during prepubertal age is frequently accompanied by precocious puberty and overweight/obesity, suggesting an extended hypothalamic dysfunction. The severity of these comorbidities and the potential related risks in adulthood require a prompt multidiagnostic approach and a tailored therapeutic management.

10.

Narcolepsy treatment: burden and disabilities of the disease

G. Mayer

Hephata Klinik.
Schwalmstadt-Treysa, Germany.

The psychosocial consequences of narcolepsy have been described in detail by Broughton et al in 1981. Within the past years many authors have confirmed this data and added new aspects. There are significant negative effects upon performance, promotion, earning capacity, fear of or actual job loss, increased disability insurance, falling asleep at work, loss or leaving a job, unemployment and being without a partner. Due to the long latency between the disease onset and diagnosis of 3-18 years many chances for adequate medical support cannot be provided and many patients fail in private and professional domains. Excessive daytime sleepiness is the most impairing symptom. Many doctors are consulted before patients receive a correct diagnosis, and even when diagnosis is established it is difficult to find an experienced doctor who can provide the personalized medical management. Depression, obesity, metabolic dysfunction, impaired concentration and impaired verbal and information recall are further burdens. An increased risk for traffic, household and work accidents restrains untreated patients from social and professional functions and influences their lives negatively. There is a need to supply narcolepsy patients with early diagnosis, counseling, effective medication and proper instruments that enable them to learn and progress in professional as well as social life.

11.

Motor discontrol during sleep in narcolepsy

J. Santamaría

Neurology Service. Hospital Clínic. Barcelona, Spain.

The classic narcoleptic tetrad includes hypersomnia, cataplexy, sleep paralysis, and hypnagogic hallucinations. Less well known problems are sleep fragmentation and REM sleep behavior disorder (RBD). When RBD is associated to a neurological disorder it is more often seen in Parkinson's disease, dementia with Lewy bodies and multiple system atrophy, but it can also occur in narcolepsy. In contrast to idiopathic and parkinsonism-related RBD, the parasomnia in patients with narcolepsy is equally common in males and females, it is associated with less vigorous dream enacting behaviors, and appears earlier than the typical age for idiopathic RBD (the sixth decade). Only narcoleptic patients with cataplexy present this parasomnia, what suggests a possible role of hypocretin deficiency in the generation of these behaviors in narcolepsy. In contrast to idiopathic RBD, RBD in narcolepsy does not herald evolution into a neurodegenerative disorder. In our experience, whereas PSG in idiopathic RBD confirms the diagnosis in the majority of patients, in narcolepsy it is more common to have complaints suggestive of RBD than to have video-PSG confirmation of the problem. This is the reverse of what happens in patients with PD or DLB, where PSG often shows the parasomnia even in patients that deny it. It is likely that hypocretin neurons are centrally involved in motor control during wakefulness and sleep in humans, and its deficiency causes a dysfunctional control of motor activity that may manifest as cataplexy during wakefulness and RBD during sleep.

12.

The EU-NN narcolepsy-cataplexy retrospective database: clinical and polysomnographic characteristics

J. Haba Rubio [a], G. Luca [b], and the European Narcolepsy Network (EU-NN)

[a] Center for Investigation and Research in Sleep. Centre Hospitalier Universitaire Vaudois. [b] Center for Integrative Genomics. University of Lausanne. Lausanne, Switzerland.

Aim. To describe the clinical and polysomnographic characteristics of narcolepsy with cataplexy (NC). **Patients and methods.** We analyzed data of 1099 patients coming from European Narcolepsy Network (EU-NN) affiliated sleep centers. All had typical unambiguous sporadic narcolepsy with clear cut cataplexy, they were HLA DQB1*06:02 positive and from European origin. **Results.** 54.8% of patients were men and 45.2% women. Mean age at excessive daytime sleepiness (EDS) onset was 22.7 ± 11.8 years, age at cataplexy onset was 25.80 ± 12.84 years. Age at diagnosis was 36.87 ± 17.13 years, mean delay between onset of symptoms and diagnosis was 14.6 ± 14.3 years. Two thirds had frequent or very frequent (> 1/week) cataplexy attacks. Hypnagogic/hypnopompic hallucinations were experienced by 63.1%, sleep paralysis by 52.6%, both symptoms by 43.6%. Mean total sleep time at the polysomnograpy was 411.7 ± 80.4 min, sleep efficiency was 83.8 ± 11.5%. Mean REM sleep latency (REM SL) was 54.5 ± 65.3 min, 34.9% of patients had SOREMP during the polysomnography (REM SL < 15 min). MSLT mean sleep latency was 3.9 ± 3 min and the percentage of SOREMPs was 65.9 ± 27.2%. Laboratory criteria currently used to diagnose NC (MSLT latency < 8 min, ≥ 2 SOREMPs) were present in 87.2%. CSF hypocretine levels (n = 294) were < 110 pg/mL in 96.3% of the cases. **Conclusion.** This study provides a detailed description of the clinical and polysomnographic characteristics of a large homogeneous group of NC patients. The long delay between the onset of symptoms and diagnosis implies that many cases remain undiagnosed. A better knowledge of the nosology of NC may allow earlier diagnosis of this disabling condition.

13.

The EU-NN narcolepsy-cataplexy prospective database

G. Luca [a], M. Tafti [a], R. Khatami [b]

[a] Center for Integrative Genomics. University of Lausanne. Lausanne, Switzerland. [b] Center of Sleep Medicine and Sleep Research. Barmelweid Klinik. Barmelweid, Switzerland.

The EU-NN narcolepsy-cataplexy database is aiming at collecting complete information on narcolepsy patients with demographic, clinical, polysomnographic, and biological data. The primary goal is a better phenotypic description of narcolepsy, as well as to provide resources for future research. So far, 440 cases were included from Austria, Czech Republic, Finland, France, Germany, Italy, Netherlands, Scotland, Spain and Switzerland. Here we report some preliminary results on the advantages of having data from standardized diagnostic evaluation as well as from prospective follow-up visits. Sleepiness, sleep disturbances, polysomnographic data and other clinical variables were compared between sessions. Subjective daytime sleepiness (Epworth Sleepiness Scale) was significantly lower in follow-up visits compared with diagnostic visit at inclusion (one-way RM ANOVA; p = 0.008); and at the first follow-up less patients tend to report the presence of disturbed sleep (McNemar test; p = 0.05). The effect of the different treatments could not be established due to the reduced number of cases available in each treatment group. Response to treatment and the effects of different therapeutic regimes will be an important step in further collecting systematic information. Having such detailed

information about the symptoms and the evolution of the disease and from a large number of patients will provide a more accurate description of narcolepsy with cataplexy.

14.

How to evaluate sleepiness. The value of diagnostic tests in narcolepsy

K. Sonka

Department of Neurology. First Faculty of Medicine. Charles University and General University Hospital. Prague, Czech Republic.

Daytime sleepiness is the key symptom of narcolepsy and also one with the greatest effect on the patients' life. Depending on clinical needs, sleepiness is explored using observation, clinical interview, scales (namely Epworth Sleepiness Scale), neurophysiological measurements including Multiple Sleep Latency Test (MSLT), Maintenance of Wakefulness Test (MWT), daytime continuous polysomnography and pupillography and with psychomotor reaction time (RT) tests – Oxford Sleepiness Resistance Test (OSLER) and Sustained Attention to Response Task (SART). MSLT shows sleep propensity and, in narcolepsy, shortened REM sleep latency. MSLT is the golden standard of sleepiness rating, and MSLT results (mean sleep latency ≤ 8 min, two or more sleep onset REM periods –SOREMp) are part of the diagnostic criteria of narcolepsy. The sensitivity and specificity of MSLT for narcolepsy are 0.78 and 0.93 respectively. Repeated MSLT increases its sensitivity. Analysis of sleep onset characteristics at MSLT helps to differentiate narcolepsy from idiopathic hypersomnia – narcoleptics fall asleep faster. The ability to stay awake is measured with MWT. Rather than for diagnosis, MWT is more appropriate for unattended napping assessment. Spontaneous daytime sleep and the occurrence of multiple daytime SOREMp measured with continual daytime polysomnography correlate with MSLT findings in narcolepsy. Pupillographic results also correlate well with MSLT, but in the absence of normative values the clinical uses of pupilography are limited. OSLER was validated against the MWT. SART is complementary to MSLT, and does not only provide information about RT, but also about the capability of decision-making.

15.

Narcolepsy-cataplexy induced by a cow milk oral immunotherapy protocol?

R. Peraita Adrados [a], P. López Esteban [b], J.J. García Peñas [b], J.L. Vicario [d], C. Escudero [c], J. Santamaría [e], R. Casamitjana [f], L.G. Gutiérrez Solana [b]

[a] Sleep Disorders Unit. Clinical Neurophysiology Department. Gregorio Marañón University Hospital. Madrid. [b] Child Neurology Division & Neurophysiology Unit. [c] Allergy Department. Niño Jesus University Hospital. Madrid. [d] Histocompatibility. Blood Centre of the Community of Madrid. Madrid. [e] Neurology Service. [f] Biochemistry Laboratory. Clinic University Hospital. Barcelona, Spain.

Introduction. The autoimmune hypothesis of narcolepsy-cataplexy is based on the close association with HLA. The possibility that narcolepsy-cataplexy is a side effect of vaccination against H1N1 influenza has been raised. Hypotheses include specific immune response or generalized stimulation of the immune system. **Aim.** To present a unique case of narcolepsy-cataplexy that appeared during oral immunotherapy to cow milk (CMOIT). **Case report.** A 6 year-old girl with cow-milk allergy and asthma since the age of 3 was referred due to sleep episodes at school and cataplexy attacks triggered by laughter 3 months after starting a 6-month CMOIT protocol. She was not vaccinated against H1N1. Cataplexy consisted of tongue protrusion and complete loss of muscle tone. She also presented frightening hypnagogic hallucinations, headache, and binge eating. Physical and neurological examinations (including EEG) were normal. Cranial MRI showed a hyperintense periatrial signal. Video-PSG showed disturbed nocturnal sleep with a sleep onset REM episode, increased N-1, sleep fragmentation, WASO, low sleep efficiency, bruxism, and central apnoeas. Mean sleep latency was 7.5 minutes and 4 SOREMPs were observed on MSLT. She was DRB1*-1501-DQB1*0602 positive and her CSF Hcrt-1 level was undetectable (< 10 pg/mL). She was treated with intravenous immunoglobulin 2 g/kg/day for 2 days repeated 4 times at 4-week intervals followed by 1 g/kg/day (2 days) and 400 mg/kg/day (every month). Before the fourth cycle, sleep episodes were less frequent, but cataplexy persisted. She did not gain weight and the binge eating disappeared. PSG showed increased WASO and sleep fragmentation. MSLT showed sleep latency of 9 minutes and 2 SOREMPs. A new lumbar puncture revealed undetectable levels of Hcrt-1. **Conclusion.** To our knowledge, this is the first report of pediatric narcolepsy-cataplexy induced by oral immunotherapy to cow milk. Larger epidemiological studies are needed to obtain more reliable data.

16.

Narcolepsy and idiopathic hypersomnia borderlines

M. Billiard [a], M. Susta [b], K. Sonka [c]

[a] Department of Neurology. Gui de Chauliac Hospital. Montpellier, France. [b] Department of Psychiatry. [c] Department of Neurology. First Faculty of Medicine. Charles University and General University Hospital. Prague, Czech Republic.

Introduction. According to ICSD-2 there are two forms of narcolepsy, narcolepsy with cataplexy (NwC) and narcolepsy without cataplexy (Nw/oC), and two forms of idiopathic hypersomnia, idiopathic hypersomnia with long sleep time (IHwLST) and idiopathic hypersomnia without long sleep time (IHw/oLST). However some studies question the distinction between IHwLST and IHw/oLST (Anderson et al; 2007) (Vernet & Arnulf; 2009) and the distinction between Nw/oC and IHw/oLST is mainly based on the number of SOREMPs on the MSLT, a rather subtle and arbitrary criterion. **Aim.** To question whether the ICSD-2 classification is still valid. **Patients and methods.** 23 patients (11 men and 12 women) with NwC, 22 patients (13 men and 9 women) with Nw/oC, 26 patients (7 men and 19 women) with IHwLST, and 25 patients (10 men and 15 women) with IHw/oLST), from the Montpellier and Prague sleep disorders centers. Comparison of clinical features (mean number and mean duration of unwanted naps/day, refreshing character of naps, irresistibility of naps, difficulty waking up at the end of naps, ESS score, cataplexy, poor nocturnal sleep quality, hypnagogic hallucinations, sleep paralysis, difficulty waking-up in the morning, sleep drunkenness) and MSLT data (mean sleep latency and mean number of SOREMPs) in the above referred forms of central hypersomnia. Statistics: ANOVA and post-hoc analysis for ratio parameters, Pearson chi-square for nominal parameters. **Results.** There were significant differences between IHwLST and IHw/oLST for ratio parameters, except EES score and number of SOREMPs on the MSLT, and for nominal parameters, except hypnagogic hallucinations and poor nocturnal sleep quality. On the other hand there was no significant difference between Nw/oC and IHw/oLST for ratio parameters, except for the number of SOREMPs on the MSLT, and no significant difference for nominal parameters, except for difficulty waking up at the end of naps, hypnagogic hallucinations and sleep paralysis. **Conclusion.** For a majority of clinical and MSLT parameters, IHwLST differs significantly from IHw/oLST, whereas Nw/oC does not differ significantly from IHw/oLST.

18

Subjective insight into the symptoms of narcolepsy

C. Rüegg

Swiss Narcolepsy Association SNaG. Zürich, Switzerland.

Status quo. Ten years working experience as a board member and also as a personal contact for narcoleptics in the greater area of Zürich; numerous conversations, discussions, sessions and consultations held during this period reveal the status quo. As individual as the individual statements are, they can be categorized and summarized and the overlapping characteris-

tics can give a general insight. **Subjective insight & coping strategies.** For the five symptoms of narcolepsy the reference is the 'Narcoleptic Pentade' as it was defined on the first narcolepsy conference in Montpellier 1975. In the following a generalised emotion and coping strategy to each symptom of narcolepsy is pointed out: 1. Excessive sleepiness. Emotion: irritability; coping strategy: enlightenment. 2. Hypnagogic/hypnopomic hallucinations. Emotion: impression of insanity; coping strategy: providing objective proof. 3. Sleep paralysis. Emotion: horror; coping strategy: night light. 4. Fragmented sleep. Emotion: social isolation; coping strategy: sense of time. 5. Cataplexy. Emotion: loss of control; coping strategy: medical treatment or falling techniques. **Conclusion.** Support groups help with coping strategies, but normally they are contacted after the diagnosis. For the person affected the first point of contact is usually a doctor; therefore, it is helpful for medical professionals to know about the subjective insight.

NARCOLEPTICS IN EUROPE & PATIENT FOCUS GROPUS

19.

The nightmares of narcoleptics when awake!

M. Martínez Torrejón

President of Spanish Narcolepsy Association (AEN). Madrid, Spain

We define narcolepsy as a sleep disorder and we enumerate and describe its diverse symptoms: drowsiness, cataplexia, sleep paralysis, hypnagogic hallucinations, night terrors, nightmares, etc. In the AEN, we have talked about an additional symptom, one that is detected when we are awake, wide awake: It concerns our relationships with the surrounding world and with the people with whom we interact: family, friends, education, work, health care, and administrative bureaucracies. Given the severity of the problems this disorder imposes on our relationships in most of these areas of daily life we are daring to suggest a new symptom –the nightmare of being awake, calling it the 'day-to-day nightmares of a person with narcolepsy'.

20.

Association Française de Narcolepsie-Cataplexie et d'Hypersomnie

A. de la Tousche

Président de l'ANC. Valgorge, France.

L'ANC poursuit des objectifs analogues à ceux d'autres associations étrangères du même type. Une priorité néanmoins est donnée à l'information, pourquoi? Parce que, à plusieurs égard, la narcolepsie-cataplexie est une maladie 'paradoxale'. Comptenu de ses origines, il est paradoxal qu'elle soit particulièrement mal connue en France, du corps médical notamment. En effet, identifiée par un médecin français Gélineau, qui lui a donné son nom de narcolepsie en 1880, la médecine française s'en est désintéressée pendant un long moment, et ce sont les anglo-saxons, qui en ont fourni la première description complète, et qui ont trouvé les premières relations avec le sommeil paradoxal. L'opinion publique et les médias, y compris ceux spécialisés en matière de santé, se passionnent pour les problèmes d'insomnie, alors que la seule véritable maladie du sommeil (basée sur des troubles analysés scientifiquement par des enregistrements polygraphiques), est la narcolepsie-cataplexie, qui est une maladie de la vigilance, c'est à dire de l'excès de sommeil et non d'une insuffisance. Même si on ne peut la considérer comme directement mortelle, au sens physique du terme, c'est une maladie grave, dans la mesure où les handicaps qu'elle entraîne sur les plans professionnels, familiaux, scolaires... peuvent conduire à une véritable 'mort sociale', et que le nombre de personnes supposées atteintes en France est loin d'être négligeable (18.000-30.000 personnes). Les circonstances dans lesquelles se manifestent les symptômes de la maladie sont, d'une part, de pertes de vigilance et accès irrésistible de sommeil, et d'autre part, de pertes de tonus musculaire (symptôme de la cataplexie) à des moments d'intense activité physique ou émotionnelle. La conjonction de ces deux types de symptômes, dont le contraste reste à ce jour inexpliqué, permet, à coup sûr d'établir le diagnostic de la maladie. En dépit des méthodes scientifiques indiscutables (enregistrements polygraphiques), le délai moyen constaté pour l'identification de la maladie était encore récemment de 13 ans à partir de l'apparition des premiers symptômes). Cela tient d'une part, à la confusion faite très fréquemment avec des maladies neurologiques, et d'autre part, au fait qu'en dehors des crises, les personnes atteintes ont un comportement tout à fait normal. Avec le développement des centres de sommeil et des consultations spécialisées, ce temps commence à se réduire.

21.

Deutsche Narkolepsie-Gesellschaft e.V. (German Narcolepsy Society)

H. Rollof

President of DNG. Solingen, Germany.

Founded 1980 as a honorary society with 7 members. Oldest patient organization in the area of sleep-wake-disturbances in Germany. Nowadays again the only patient-organization for narcolepsy and hypersomnia in Germany. **Organization.** Patient-organization with about 900 members. Federal organized. One dependant organization in country Baden-Württemberg. More than 30 dependant regional groups all over Germany. Advisory committee with more than 10 doctors. Honorary committee with 9 members, head of the board: 1 chairman, 1 deputy, 1 treasurer. Management office with 1 employee, working 20 hours a week. **Financial situation.** Subscription of the members, contribution of the health insurance scheme, donations. Nowadays deficit, which still can be balanced by savings. **Achievements.** Advisement in all questions concerning to sleep-wake-disturbances, especially narcolepsy and hypersomnia. Supporting the patients and their family members in all social affairs. **Financial supports.** Marga-Grimm-Fund for people with low income, especially to make possible to take place at the annual meeting of the patient organization and their members. **Magazine.** *Der Wecker* (translated, *The alarm-bell*), with independent editing, published since 1980 twice a year. **Homepage.** www.dng-ev.de. **Tasks and aims.** Improvement of the life-situation for narcolepsy/hypersomnia and similar sleep-wake-disturbances patients and their families. Enlightenment the public/politicians/doctors about narcolepsy and hypersomnia. Promotion of science and search in the area of narcolepsy and hypersomnia. Observation and promotion of the European and international cooperation on the area of sleep-wake-disturbances, especially orphan diseases. **Activities.** Annual meeting of the members and the advisory committee, also with members of other patient organizations. Annual meeting of the kids-club and their families. Annual meeting of the group for young people. Further education and training of the members of the honorary committee, the regional and country-wide group-leaders. **Membership.** DGSM e.V., ACHSE e.V., BAG e.V., Eurordis.

22.

Swiss Narcolepsy Association

C. Rüegg

President of SNaG. Zurich, Switzerland.

Figures. Currently 174 members. Unfortunately there are no figures on how many narcoleptics are diagnosed, but it can be assumed, that because of the internet presence and the recommendations of the doctors, almost every diagnosed person knows the SNaG. On the board eight volunteers work for the association. Except the medical advisory board, Prof. Dr. med. Johnnes Mathis, all are narcoleptics themselves. Founded in 1983 the SNaG is celebrating its 30th anniversary this year with a symposium and a party. **Aims.** Therefore, the SNAG has set the following goals: a) Promotion of communication among narcoleptics and build local support groups; b) Infor-

mation about advances in diagnosis and therapy; c) Improvement of the social acceptance of persons affected through public education; d) Cooperation with similar associations at home and abroad. **Activities.** For members the club magazine *NEWS* is published twice per year and approximately every two months the Association organizes a meeting. The Association operates a German-language forum. Unique on the web is the opportunity to ask questions to a medical team about narcolepsy. **Difficulties.** Difficult financial situation, because of lack of government financial support in Switzerland and hardly any private donor, so the income is only from the subscription of the members. **Challenges.** Including also the French and Italian-speaking Switzerland goes together with labour intensive and costly translations and also with overcoming of linguistic differences among the members.