Detection of Autoantibodies Against Hypocretin, hcrtr1, and hcrtr2 in Narcolepsy: Anti-Hcrt System Antibody in Narcolepsy

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Study Objectives: The impairment of hypocretin neurotransmission system is considered to play a major role in the pathophysiology of narcolepsy. It has been hypothesized that autoimmune abnormalities underlie the etiology of narcolepsy, based on the tight association with HLA-DRB1*1501/DQB1*0602. It remains unclear if autoantibodies against hypocretin receptors (hcrtr1 and hcrtr2) are involved in narcolepsy.

Design: We have developed a novel radioligand binding assay to address this question. Sera from 181 patients with narcolepsy, 10 patients with other hypersomnias, and 91 control subjects were used. Human [35S]-Hcrt, hcrtr1, and hcrtr2 were synthesized by in vitro transcription/translation system. The immune complex of autoantibody and each [35S]-protein were immunoprecipitated and quantified using a radioligand-binding assay.

Results: We detected autoantibodies against hypocretin in 3 patients, hcrtr1 in 1 patient, and hcrtr2 in 5 patients with narcolepsy. Positive reactions were also found against hcrtr1 in 2 and hcrtr2 in 1 control subjects. No relationships were found between these autoantibodies and HLA-DRB1*1501/DQB1*0602 haplotypes, presence of cataplexy, presence of subjective nocturnal sleep disruption, or the score on the Epworth Sleepiness Scale.

Conclusions: Although we have detected autoantibodies against the hypocretin neurotransmission system, our results do not support the hypothesis that autoantibody-mediated dysfunction in the hypocretin system underlies the pathophysiology of narcolepsy.

Keywords: Autoantibody, narcolepsy, hypocretin, orexin, hypocretin receptor, autoimmunity, sleep, radioligand assay

Genetic and Environmental Influences on Insomnia, Daytime Sleepiness, and Obesity in Twins

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Study Objectives: To better understand the relationships of insomnia, sleepiness, and obesity.

Design: Classic twin study.


Patients or Participants: One thousand forty-two monozygotic and 828 dizygotic twin pairs participating in the University of Washington Twin Registry.

Interventions: N/A.

Measurements and Results: Twins were, on average, 32 years old; 61% were women, and 19.5% were obese, defined as a body mass index $\geq 28$. Insomnia and sleepiness were endorsed by 19.3% and 3.7% of twins, respectively. Twin correlations were higher in monozygotic than dizygotic twins for insomnia (0.47 versus 0.15), sleepiness (0.37 versus 0.14), and obesity (0.82 versus 0.46). Heritability estimates were 57% for insomnia ($p < .001$; 95% confidence interval 47-63), 38% for sleepiness ($p < .01$; 95% confidence interval 16-46), and 73% for obesity ($p < .001$; 95% confidence interval 49-87). Multivariate genetic model fitting revealed that common additive genetic effects comprised 12.8% of the phenotypic correlation between insomnia and sleepiness ($p < .01$) and 10% of the phenotypic correlation between insomnia and obesity ($p < .01$). The phenotypic correlation between sleepiness and obesity was not due to common additive genetic effects.

Conclusions: Insomnia, sleepiness, and obesity are under strong genetic influence. Common genetic effects were observed between insomnia and both sleepiness and obesity, suggesting shared genetic contributions to these phenomena.

Keywords: Twins, genetics, insomnia, sleepiness, obesity

Citation: Watson NF; Goldberg J; Arguelles L et al. Genetic and environmental influences on insomnia, daytime sleepiness, and obesity in twins. SLEEP 2006;29(5):645-649.
What are the Important Risk Factors for Daytime Sleepiness and Fatigue in Women?

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Study Objective: To analyze the relation between different risk factors and excessive daytime sleepiness (EDS) and fatigue in women from a general-population sample.

Design: Cross-sectional population study.

Setting: The municipality of Uppsala, Sweden.

Participants: Five thousand five hundred eight women (response rate 73.3%) aged 20 to 60 years.

Measurements and Results: EDS, fatigue, and potential risk factors were assessed in a self-administered questionnaire. Risk factors for EDS and fatigue were analyzed using a multiple logistic regression model. In the whole population, 16.1% of the women reported EDS and 14.3% fatigue. The risk of having EDS and fatigue decreased with increasing age: adjusted odds ratios (95% confidence interval) for EDS and fatigue were 0.73 (0.66-0.88) and 0.86 (0.77-0.96) per 10 years, respectively. The combination of anxiety and depression was highly related to both EDS and fatigue (4.51 [3.51-5.79] and 7.00 [5.39-9.10], respectively). Insomnia, somatic disease, snoring, being overweight, and being on sick leave were also independently related to both conditions, whereas lifestyle factors, such as physical inactivity and smoking, were related to fatigue but not to EDS. Having children did not influence the risk of either EDS or fatigue.

Conclusion: Psychological distress, insomnia, and somatic disease are the most important conditions in women reporting daytime sleepiness and fatigue. Because 1 in 5 (21%) of the women in this study reported sleepiness, fatigue, or both, interventions that improve psychiatric health and reduce insomnia are important in improving the quality of life in women with these sleep symptoms.

Keywords: Sleepiness, fatigue, risk factors, women, population based

Citation: Theorell-Haglöw J; Lindberg E; Janson C. What are the important risk factors for daytime sleepiness and fatigue in women? SLEEP;29(6):751-757.

Spontaneous Arousability in Prone and Supine Position in Healthy Infants

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Study Objective: Compared with control infants, those who will be future victims of sudden infant death syndrome (SIDS) show a decreased arousability during sleep, with fewer cortical arousals and more-frequent subcortical activations. These findings suggest an incomplete arousal process in victims of SIDS. Prone sleep position, a major risk factor for SIDS, has been reported to reduce arousal responses during sleep. The present study was undertaken to evaluate whether the prone sleep position impairs the arousal process in healthy infants.

Methods: Twenty-four healthy infants were studied polygraphically during 1 night; 12 infants regularly slept supine and 12 infants regularly slept prone. Infants were matched for sex, gestational age, and age at recording. Arousals were differentiated into subcortical activations or cortical arousals, according to the presence of autonomic and/or electroencephalographic changes. Frequencies of subcortical activations and cortical arousals were compared in the prone- and the supine-sleeping infants.

Results: Compared with supine sleepers, prone sleepers had significantly fewer cortical arousals during rapid eye movement (REM) sleep (p = .043). There were no significant differences in cortical arousals between the 2 groups during non-REM sleep. No significant differences were seen in the frequencies of subcortical activations during both REM and non-REM sleep between supine and prone sleepers. The ratio of cortical arousal to subcortical activation showed no significant differences between the prone and the supine sleepers.

Conclusions: Prone sleep position decreased the frequency of cortical arousals but did not change the frequency of subcortical activations, as has been previously found in SIDS victims. These results suggest specific pathways for impairment of the arousal process in SIDS victims.

Keywords: Sleep, arousal, infant, SIDS, position

Citation: Kato I; Scaillet S; Grosawasser J, et al. Spontaneous arousability in prone and supine position in healthy infants. SLEEP 2006;29(6):785-790.
Physical Examination: Mallampati Score as an Independent Predictor of Obstructive Sleep Apnea

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Study Objective: To assess the clinical usefulness of the Mallampati score in patients with obstructive sleep apnea. Mallampati scoring of the oropharynx is a simple noninvasive method used to assess the difficulty of endotracheal intubation, but its clinical usefulness has not been validated in patients with sleep-disordered breathing.

Design: Prospective multivariate assessment of a predictor variable.

Setting: The UCSF Sleep Disorders Center.

Patients or Participants: One hundred thirty-seven adult patients who were evaluated for possible obstructive sleep apnea.

Interventions: Prospective determination of the Mallampati score, assessment of other variables for multivariate analysis, and subsequent overnight polysomnography.

Measurements and Results: The Mallampati score was an independent predictor of both the presence and severity of obstructive sleep apnea. On average, for every 1-point increase in the Mallampati score, the odds of having obstructive sleep apnea (apnea-hypopnea index ≥ 5) increased more than 2-fold (odds ratio [per 1-point increase] = 2.5; 95% confidence interval: 1.2-5.0; p = .01), and the apnea-hypopnea index increased by more than 5 events per hour (coefficient = 5.2; 95% confidence interval: 0.2-10; p = .04). These results were independent of more than 30 variables that reflected airway anatomy, body habitus, symptoms, and medical history.

Conclusions: Our results indicate that Mallampati scoring is a useful part of the physical examination of patients prior to polysomnography. The independent association between Mallampati score and presence and severity of obstructive sleep apnea suggests that this scoring system will have practical value in clinical settings and prospective studies of sleep-disordered breathing.

Keywords: Obstructive sleep apnea, physical diagnosis, performance

Citation: Nuckton T; Glidden DV; Browner WS et al. Physical examination: Mallampati score as an independent predictor of obstructive sleep apnea. SLEEP 2006;29(7):903-908.

A Preliminary Fluorodeoxyglucose Positron Emission Tomography Study in Healthy Adults Reporting Dream-Enactment Behavior

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Study Objectives: To test the hypothesis that healthy adults reporting dream-enactment behavior (DEB+) have reduced cerebral metabolic rate for glucose (CMRgl) in regions preferentially affected in patients with dementia with Lewy bodies (DLB).

Design: Automated brain-mapping algorithms were used to compare regional fluorodeoxyglucose (FDG) positron emission tomography (PET) measurements from previously evaluated DEB cases and controls.

Setting: Tertiary-care academic medical centers.

Participants: Seventeen cognitively normal patients with DEB+ and 17 control subjects (DEB-) who were individually matched for age (59 ± 11 years), education level (16 ± 4 years), sex (67% women), body mass index (26 ± 4.8 kg/m²), first-degree relative with dementia (85%), and proportion of apolipoprotein E (APOE) e4 carriers (13 e4 carriers, 4 noncarriers).

Interventions: FDG-PET.

Measurements and Results: DEB was associated with significantly lower CMRgl in several brain regions known to be preferentially affected in both DLB and Alzheimer disease (parietal, temporal, and posterior cingulate cortices) and in several other regions, including the anterior cingulate cortex (p < .001, uncorrected for multiple comparisons). The DEB-associated CMRgl reductions were significantly greater in the APOE e4 noncarriers than in the carriers.

Conclusions: These preliminary findings suggest that cognitively normal persons with DEB have reduced CMRgl in brain regions known to be metabolically affected by DLB, supporting further study of DEB as a possible risk factor for the development of DLB.

Keywords: Dementia with Lewy bodies, REM sleep behavior disorder, preclinical dementia

Citation: Caselli RJ; Chen K; Bandy D et al. A preliminary fluorodeoxyglucose positron emission tomography study in healthy adults reporting dream-enactment behavior. SLEEP 2006;29(7):927-933.