Agenda
Narcolepsy Section Meeting
Tuesday, June 14, 2011 5:00pm – 7:00pm
Minneapolis Convention Center Room 205C

I. Welcome and Introduction – Eve Rogers, MD, Chair

II. Section Investigator Award Presentation
   • Miranda Lim, MD, PhD
     *Brain Orexin Levels Correlate with Wakefulness in a Mouse Model of Traumatic Brain Injury*

III. Narcolepsy and Hypersomnolence Year-In-Review

IV. Open Floor for Attendees

V. Other Business

VI. Adjournment
1. Bastianini S; Silvani A; Berteotti C; Elghozi JL; Franzini C; Lenzi P; Lo Martire V; Zoccoli G. Sleep related changes in blood pressure in hypocretin-deficient narcoleptic mice. SLEEP 2011; 34(2):213-218.

   Dr. Bastianini et al compared BP measurements in wakefulness, REM, and NREM sleep between two different Hcrt-deficient mouse models and control mice. They found significant differences during sleep to suggest that the chronic lack of Hcrt signaling may adversely affect BP control.

2. Dauvilliers Y; Pennestri MH; Whittom S; Lanfranchi PA; Montplaisir JY. Autonomic response to periodic leg movements during sleep in narcolepsy-cataplexy. SLEEP 2011; 34(2):219-223.

   Dr. Dauvilliers et al compared physiologic activations, specifically heart rate response amplitudes, associated with PLMS between narcoleptic-cataplectic patients and healthy controls. Their analyses show a significant reduction in the amplitude of the PLMS-related HR responses in the narcoleptic patients, which the authors suggest supports Hcrt’s role in autonomic physiology and may even have clinical significance in cardiovascular disease risk.

3. Aran A; Einen M; Lin L; Plazzi G; Nishino S; Mignot E. Clinical and Therapeutic Aspects of Childhood Narcolepsy-Cataplexy: A Retrospective Study of 51 Children. SLEEP 2010; 33(11):1457-1464.

   Dr. Aran et al retrospectively reviewed 51 narcoleptic children, separated them into those with disease onset before, during, and after puberty, and reported on their clinical and polysomnographic features. Additional prospective data is reported in 40 of the children, including continuation of and efficacy of various prescription treatments.

4. Kawashima M; Lin L; Tanaka S; Jennun P; Knudsen S; Nevsimalova S; Plazzi G; Mignot E. Anti-Tribbles homolog 2 (TRIB2) autoantibodies in narcolepsy are associated with recent onset of cataplexy. SLEEP 2010; 33(7):869-874.

   Dr. Kawashima et al replicated the prior finding of increased antiTRIB2 antibodies in narcoleptics with cataplexy, especially within 2.3 years of onset of cataplexy. AntiTRIB2 antibodies were found to be rare in narcoleptics without cataplexy and with a distant onset of cataplexy.

   Lim A; Scammell T. The Trouble with Tribbles: Do Antibodies Against TRIB2 Cause Narcolepsy? SLEEP 2010; 33(7):857-858. This commentary outlines three possible models of the role of anti-TRIB2 antibodies in narcolepsy.

5. Goel N; Banks S; Mignot E; Dingess D. DQB1*0602 predicts interindividual differences in physiologic sleep, sleepiness, and fatigue. Neurology 2010; 75: 1509.

   Dr. Goel et al compared PSG characteristics and subjective sleepiness and fatigue in chronic partial sleep deprivation between DQB*0602 positive and negative patients, and they found significant interindividual differences.

   Verma A; Verma AK. Why do we respond differently to sleep deprivation? : It’s in our genes! Neurology 2010; 75; 1492. Commentary.


   Dr. Benarroch provides a nice overview of the anatomy, neurochemistry, and physiology of the histaminergic system, and of the actions of histamine in the CNS relevant to neurologic disorders and the resulting clinical correlations. Histamine’s role in alertness and specifically in narcolepsy is reviewed.

7. Walsh J; Hall-Porter J; Griffin K; Dodson E; Forst E; Curry D; Eisenstein R; Schweitzer P. Enhancing Slow Wave Sleep with Sodium Oxybate Reduces the Behavioral and Physiological Impact of Sleep Loss. SLEEP 2010; 33 (9):1217-1225.

   Randomized, double-blind, placebo-controlled study comparing the impact of sleep deprivation (via MSLT, PVT, KSS, Profile of Mood States and cognitive testing) on healthy adults taking sodium oxybate and those taking placebo during a daytime recovery nap. SWS was enhanced by the sodium oxybate, alertness and attention were better maintained, and the degree of SWS change was positively correlated with the improvements in sleepiness.

8. Brevig HN; Watson CJ; Lydic R; Baghdoyan HA. Hypocretin and GABA Interact in the Pontine Reticular Formation to Increase Wakefulness. SLEEP 2010; 33 (10):1285-1293.

   In Sprague-Dawley rats, the increased wakefulness and decreased amounts of REM and NREM sleep induced by microinjections of hypocretin-1 into the pontine reticular formation
(PnO) are blocked by antagonists of both hypocretin-1 receptors and GABAergic receptors, implying that hypocretinergic and GABAergic transmission interact to promote wakefulness.

9. Dauvilliers Y; Montplaisir J; Cochen V; Desautels A; Einen M; Lin L; Kawashima M; Bayard S; Monaca C; Tiberge M; Filipini D; Tripathy A; Nguyen BH; Katagal S; Mignot E. Post-H1N1 Narcolepsy-Cataplexy. *Sleep Med* 2010; 66 (12):1563-1566.

   □ In this letter to the editor, 16 of 31 cases of recent, abrupt onset narcolepsy-cataplexy in France, Canada, and the US were identified as occurring in close temporal association with H1N1 vaccination or infection (2 cases). All cases were DQB1*0602 positive with rapid development of severe EDS and severe, definite cataplexy.

10. Plazzi G; Ferri R; Antelmi E; Bayard S; Franceschini C; Cosentino FII; Abril B; Spruyt K; Provini F; Montagna P; Dauvilliers Y. Restless Legs Syndrome is More Frequent in Narcolepsy with Cataplexy Patients. *SLEEP* 2010; 33 (5):689-694.

   □ In this case-control study in three European sleep centers assessing the frequency of comorbidity of RLS and NC, RLS was found to be more common (14.7% in NC compared with 3.0% in controls). RLS in NC patients was less likely to be familial or associated with low ferritin levels than idiopathic RLS.


   □ Seven Japanese patients diagnosed with multiple sclerosis or neuromyelitis optica, all of whom had bilateral hypothalamic lesions on MRI, are reported with moderate Horter deficiency and EDS. Four of these patients meet ICSID-2 criteria for narcolepsy, and three of the patients are seropositive for anti-aquaporin 4 (AQP4) antibodies. AQP4 is highly expressed in the hypothalamic periventricular regions and could be a target of autoimmune attack.


   □ These tolerability and efficacy results are consistent with those previously reported in 12-week, double-blind studies of armodafinil in patients with excessive sleepiness associated with treated OSA, SWD, or narcolepsy.


   □ This study is similar to that noted above; however, the patients in this study were not armodafinil-naïve. This is an open-label extension of prior 12 week study protocols. Modest increases in BP and HR were noted, primarily by month three of therapy.


   □ After 8 weeks of nightly sodium oxybate use at doses of 6 and 9g per night, study patients demonstrated significant dose-related increases in slow wave sleep and total sleep time. decreases in N1 sleep and WASO, and improved subjective frequency and severity of narcolepsy symptoms.


   □ This is a case report of an adolescent narcoleptic with inability to awaken in the mornings which was refractory to daytime modafinil, sleep hygiene improvement, and methylphenidate patch. He was treated successfully with a nicotine patch placed by his parents prior to his awakening.


   □ Case report as stated. This narcoleptic patient has frequent episodes of weakness that fit all cataplexy criteria with the exception of the recurring unilaterality.

In this case report, a patient with musculoskeletal pain syndrome presents for a sleep study, which is largely unremarkable, and subsequent sleep consultation due to 4 months of increasing EDS. Between the sleep study and consultation, the patient is diagnosed with and begins treatment for severe hypovitaminosis D. Her EDS resolves, and the follow up MSLT is normal. Potential mechanisms for the improved EDS are discussed.

   - 20 patients with TBI and EDS or fatigue (6 months after trauma), treated with modafinil 100 or 200 mg or placebo (prospective, double blind, randomized, placebo controlled.) With modafinil, there is less EDS, improved ability to stay awake on MWT, but post-traumatic fatigue was not improved. Very well designed study. Limitations are discussed in the commentary.

19. Toyoda H; Tanaka S; Miyagawa T; Honda Y; Tokunaga K; Honda M. Anti-Tribbles homolog 2 autoantibodies in Japanese patients with narcolepsy. SLEEP 2010;33(7):875-878.
   - AntiTRIB2 found in 26.1% of Japanese NC patients and 2.3% of normals, confirming findings of a prior study. Test methods well described. Patient details limited.

20. Diniz Behn CG; Klerman EB; Mochizuki T; Lin S; Scammell TE. Abnormal sleep/wake dynamics in orexin knockout mice. SLEEP 2010;33(3):297-306.
   - A very detailed description of State Space Analysis of the EEG applied to analysis of sleep. Study is as interesting for description of the methods as it is of the results. Paper needs to be studied to learn the benefits of the technique, and appears likely to be an important method in future studies.

21. Bayard S; Abril B; Yu H; Scholz S; Carlander B; Dauvilliers Y. Decision making in narcolepsy with cataplexy. SLEEP 2011;34(1):99-104.
   - NC patients demonstrated lack of perseverance, reduced performance on decision making in ambiguous conditions, and normal decision making under explicit conditions. Findings are used to suggest how NC patients may opt for choices with higher immediate emotional reward despite a likelihood of future punishment.

22. Burgess CR; Tse G; Gillis L; Peever JH. Dopaminergic regulation of sleep and cataplexy in a murine model of narcolepsy. SLEEP 2010;33(10):1295-1304.
   - D2-like receptors modulate cataplexy, and D1-like receptors modulate sleep attacks in this model.

23. Okuro M; Fujiki N; Kotorii N; Ishimaru Y; Sokoloff P; Nishino S. Effects of paraxanthine and caffeine on sleep, locomotor activity, and body temperature in orexin/ataxin-3 transgenic narcoleptic mice. SLEEP 2010;33(7):930-942.
   - Interesting discussion of caffeine metabolite effects, but note that humans do not have the same ratio of toxic to beneficial metabolites as mice, and the benefits of paraxanthine in mice do not necessarily hold for humans.

24. Drake C; Roehrs T; Breslau N; Johnson E; Jefferson C; Scofield H; Roth T. The 10-year risk of verified motor vehicle crashes in relation to physiologic sleepiness. SLEEP 2010;33(6):745-752.
   - There are few studies that show a correlation between an objective gold standard such as the MSLT and real life data regarding motor vehicle crashes. This useful epidemiology study helps us understand how we might use objective data for decision making in predicting driving safety risk.