CLINICAL VIGNETTE

Narcolepsy with Cataplexy: Treatment Tailored to the Patient

Gregory Bierer, MD, Laura R. Banashek BA, Eugenia Wen, MD

The patient sought the care of a sleep physician at the age of 20 due to difficulty staying awake during school. He reported that given the opportunity, he would nap intermittently and all through high school he would fall asleep in class. Caffeine would only help slightly, and he denied use of tobacco. He did not drink alcohol and would rarely use marijuana. His use of marijuana was limited and started 3 years after he noticed his sleep difficulties. Upon questioning by a sleep physician, he reported episodes in which his knees would be very weak after vigorous laughter and he would sometimes have to sit down. He reported that these episodes occurred very infrequently. He denied a history of difficulty sleeping at night during that time. He was sent for a sleep study that recorded 458 minutes of sleep with a sleep efficiency of 97%. He did attain supine REM sleep during the study. His respiratory disturbance index was 3 events per hour and his periodic limb movement during sleep index was 1.6 events per hour. A Multiple Sleep Latency test performed the following day showed a mean sleep latency of 2 minutes and 3 out of the 4 nap opportunities did have a sleep onset REM period (SOREMP).

Based on this information, he was diagnosed with Narcolepsy with cataplexy. As noted above his cataplexy was infrequent. He was therefore started on modafinil at 200 mg in the morning and titrated up to three times daily as needed. He reported some tremor and agitation on the medication, and he also experienced erectile dysfunction with use of modafinil. He would sometimes not use modafinil due to the adverse effects and experienced daytime sleepiness without the medication. He works at home at times and can take a nap on most days, but will have a work schedule that would not allow for a nap at other times of the year. He reports many days when he is not able to work optimally due to somnolence. He continued with good nocturnal duration of sleep without fragmentation. He reports cataplexy about once every 2-3 months, and denies hypnogogic or hypnopompic hallucinations, and rare episodes of sleep paralysis. He avoids current caffeine use, over the counter medications, herbal medication, or alcohol or drug use. He does drive and is cautious to avoid driving if he is feeling sleepy. He has never had a car accident due to sleepiness.

He was initially prescribed armodafinil, but he experienced the same side effects as he did with modafinil. Therefore, he was changed to methylphenidate hydrochloride 10 mg at 8 am and 10 mg at noon if needed. He found this dosing to be very effective for him. He is cautious to avoid caffeine after taking methylphenidate to avoid feeling jittery with the combination. His job required up to 12-hour days at times, and when taking the second dose at noon he would be functional for the remainder of the day. He did note a greater emotional response to his work, but felt that this was a positive direction for him. He has been without cataplexy for 6 months on the methylphenidate regimen.

Pathophysiology of Narcolepsy

Narcolepsy is clinically defined as a neurological disorder characterized by cataplexy, excessive daytime sleepiness, sleep attacks, disturbed nocturnal sleep, sleep paralysis, and hypnagogic hallucinations. Believed to affect between 3 and 67 patients per 100,000 in the US[1], narcolepsy presents with varying severity and can be categorized as NC (narcolepsy with cataplexy) or NwC (narcolepsy without cataplexy). While the exact etiology of the disease is still unknown, great strides have been made in the past few decades to elucidate the disease's pathophysiology.

Research suggests that an autoimmune mechanism is the primary cause of narcolepsy. Much focus has been placed on the human leukocyte antigen (HLA) system, a large complex comprised of many genes related to immune system functioning. Of them, HLA-DQB1*0602 is thought to directly involve the development of narcolepsy, especially in those with cataplexy. The severity of narcolepsy parallels the expression of the gene, as homozygotes are often more severe than heterozygotes[1,2]. Although

identification of the allele carries a strong correlation with narcolepsy with cataplexy (76% to 100%), studies caution its use as an indication of narcolepsy without cataplexy (only 41% of subjects tested positive), especially across different ethnic groups[1,3].

The functioning of the hypothalamus is also believed to have a significant effect on the onset of narcolepsy. Specifically, the selective loss of orexin neurons, which are found in the perifornical region of the hypothalamus and produce hypocretin[1,4]. Hypocretin, a type of excitatory neuropeptide, modulates the sleep-wake cycle, energy metabolism, and body temperature. Loss of these orexin neurons and/or reduced levels of hypocretins in CSF have been observed in the majority of patients with narcolepsy in several studies, though low levels are more directly correlated when cataplexy is involved[5]. Only one study accessed the postmortem levels of hypocretin cells in narcoleptic and normal patients[6]. While the sample size was very limited (5 NC, 2 NwC, and 6 controls), the study presented two interesting findings. First, the concentration of hypocretin cells in the anterior portion of the NwC hypothalami resembled that of a normal person, while the NC hypothalamus showed a 92% depletion. Second, the concentration of hypocretin cells in the posterior portion of the NwC hypothalamus more closely resembled that of the NC. The authors believe that this shows a definitive link between narcolepsy without cataplexy and hypocretin deficiency.

The underlying etiology for the loss of the hypocretin/orexin neurons is unknown. Investigations into environmental factors found season of birth may be a contributing environmental factor to the development of narcolepsy[1,7,8]. In one study of 886 narcoleptic patients born between 1910 and 1990, risk of narcolepsy was at a significant peak in March and at a trough in September[9]. Some studies have also pointed to viral (e.g. H1N1), H1N1 vaccine or bacterial (e.g. streptococcus) infections as possible triggers for narcolepsy, though the majority of these cases only included narcoleptics with cataplexy[8,10,11,12,13]. Additional causes could be traumatic brain injury, lesions, or tumors[14].

Clinical Manifestations

Narcoleptics have fragmented sleep and will have aspects of wakefulness suddenly intrude into NREM sleep or REM sleep. Likewise, NREM sleep can intrude into wakefulness creating a "sleep attack" [4]. The sleep attacks are thought to be derived from a loss of the usual definitive division of wakefulness and sleep. This facilitates the transition between sleep and wake, as evidenced by the often fragmented sleep of narcoleptics without an increase in total sleep time. It is thought that the deficiency in hypocretin, which regulates this cycle, is a major contributing factor. Cataplexy is sudden weakness that represents a burst of the normal atonia experienced during REM sleep that invades wakefulness. This phenomenon is usually elicited by emotional responses or laughter.

Diagnostic Methods

Diagnosis of narcolepsy has proved troublesome throughout the history of the disease. One study found that patients are frequently misdiagnosed with mental disorders (OR = 4.0645) and nervous system disorders (OR = 5.0495) in the years prior to their proper diagnosis of narcolepsy[15]. The International Classification of Sleep Disorders (ICSD-2) defines narcolepsy as excessive daytime somnolence for at least 3 months. A polysomnogram (PSG) should be obtained to exclude other sleep disorders. After a normal PSG and a sleep log for 2 weeks, the patient should be evaluated with a Multiple Sleep Latency Test. This test is a series of up to 5 nap opportunities every 2 hours the day following a full PSG that has shown 6 hours of adequate sleep. The mean sleep latency (average time to fall asleep) and the presence of any "sleep-onset REM periods" (SOREMPs) during the naps should be determined. A mean sleep latency less than 8 minutes with at least 2 SOREMPs is supportive of narcolepsy. The diagnosis of cataplexy is largely clinical, although other tests may be obtained to garner further information[16].

In a landmark paper on the diagnosis of narcolepsy, Yutaka Honda reported a 1:1 correlation between narcolepsy and the presence of HLA-DR2 in humans[17]. This report came from a study of 135 narcoleptic Japanese patients who underwent genetic testing for various HLA alleles. Of the 135 patients, all tested positive for DR2 and DQw1, suggesting that narcolepsy could be excluded as a diagnosis if both alleles were absent. However, they also reported that 33.8% and 59.7% of controls tested positive for DR2 and DQw1, respectively.

Although not demonstrated in Honda's paper, genetic HLA testing across different populations has shown that positive HLA results, specifically with DQB1*0602, correlate more strongly with NC patients than with NwC patients. As a result, HLA genotyping remains somewhat controversial as a definitive diagnostic test for NwC[18,19,20]. To clarify some of these discrepancies, measurements of CSF

hypocretin-1 have been studied to see if the combination of results provides a clearer diagnosis. The threshold for CSF Hypocretin-1 level is less than 110 pg/mL, provided there is no additional pathology present[19]. One source advocated a cutoff of 200 pg/mL, as raising the threshold to just below normal allowed more NwC patients to fall within a diagnostic range[21].

A study of 163 Korean patients sought to solidify these methods to distinguish between narcolepsy with cataplexy, narcolepsy without cataplexy, and other sleep disorders[22]. All patients initially gave a blood sample and completed the Stanford Center for Narcolepsy Sleep Inventory (SSI), a predictor of cataplexy and evaluation of symptoms related to narcolepsy. Patients performed a PSG/MSLT, had CSF hypocreten-1 measured, and serum HLA typing. The blood samples underwent DRB1, DQA1, and DQB1 typing and were studied for the DQB1*0602-specific codon 9 amino acid. As in most studies, a threshold of 110 pg/mL CSF hypocretin-1 was used to diagnose narcolepsy. Twenty-two patients were found to have narcolepsy without cataplexy. In a comparison with the controls of the study, 45% of these were HLA positive (compared to 12.8% in controls) and 40% had low CSF levels and were HLA positive. When all 163 patients were considered, 92% were DQB1*0602 positive with low CSF hypocretin-1 levels. These results support other studies that report only a 41% correlation between positive HLA results and NwC, as well as the 18% of normal patients that tested positive for the allele[1]. Since the publishing of Honda's findings in 1986, genetic testing for narcolepsy has been repeated on more diverse populations[23]. However, it has consistently been found the HLA genotyping and CSF Hypocretin-1 levels are far more successful in diagnosing NC than NwC[20].

Treatment

A 2005 article divided current drug therapies into three categories: (1) stimulants (amphetamines, methamphetamines, methyphenidate, pemoline, selegiline, modafinil), (2) anticataplectic compounds (protryptiline, imipramine, desipramine, chlomipramine, venlafaxine, atomoxetine, fluoxetine), and (3) other (sodium oxybate/GHB)[24].

Stimulants are thought to alleviate sleepiness by increasing the release of dopamine or reducing the rate of dopamine reuptake[24]. Modafinil has long been used to treat the excessive sleepiness experienced by patients with narcolepsy. A 12 week study assessed the use of 200 mg or 400 mg of modafinil in 1529 outpatients, including 369 with narcolepsy[25] and reported patients who took the drug experienced an increase feeling of vitality, increased ability to focus, increase in productivity, and decreased daytime sleepiness[26,27]. The most common adverse effect was headache. Modafinil is well-tolerated, has a low likelihood for addiction, and does not demonstrate tolerance. Non-amphetamine armodafinil, the longer lasting R-isomer of racemic modafinil, has been studied in 328 patients, 50 with narcolepsy, over a 12 month period. Oral dose of 100 mg/day, titrated to a maximum of 250 mg/day, was taken as a morning dose[28]. Adverse effects were similar to those of modafinil, with headaches being the most prominent.

Sodium oxybate modulates GABA-B receptors and GHB-specific receptors[24] and tends to increase DA stores and reduce DA transmission, as shown in animal studies. This may explain how the drug aids nocturnal sleep, while simultaneously alleviated daytime sleepiness. GHB (gammahydroxybutyrate) has been studied for decades as a possible therapy for narcolepsy symptoms. A one-year study of orally administered sodium oxybate found significant improvement with nightly doses of 3 to 9 grams[29]. This included 118 narcolepsy patients, required two equally divided doses to be taken every night: once at bedtime, and once 2.5 to 4 hours later. Due to the length of the trial, patients were allowed to continue stimulant medications, but at stable doses to differentiate the effects of the sodium oxybate. Eighty patients completed the 12-month protocol and significant decreases in cataplexy (up to 35.48 fewer attacks per week) and daytime sleepiness were observed by ESS and CGI-c. Patients reported improved nocturnal sleep quality, level of alertness, and ability to concentrate, as well as decreases in inadvertent naps and sleep attacks. Common adverse side effects included headache, nausea, viral infection, dizziness, pain, enuresis, and somnolence, though none but dizziness occurred with significant frequency. A novel discovery was the unique ability to increase slow-wave sleep (SWS), which helps combat the "sleep debt" associated with disrupted and inconsistent sleep periods in narcoleptics[24].

In addition to pharmacological approaches, scheduled naps can be an effective adjunct. One study found that scheduled daytime naps reduce daytime sleepiness[30]. The level of improvement correlated with pre-treatment levels of daytime sleepiness: those with more severe symptoms experienced the greatest improvement.

Summary

Narcolepsy with cataplexy is a complex disorder that can be effectively controlled. Although scheduled naps can be effective, most patients will require pharmacologic assistance. The growing armamentarium of pharmacotherapy offers more options and diverse approaches, improving our ability to assist these patients.

REFERENCES

1. **Watson NF, Ton TG, Koepsell TD, Gersuk VH, Longstreth WT Jr**. Does narcolepsy symptom severity vary according to HLA-DQB1*0602 allele status? *Sleep*. 2010 Jan;33(1):29-35. PubMed PMID: 20120618; PubMed Central PMCID: PMC2802245.
2. **Mignot E, Young T, Lin L, Finn L**. Nocturnal sleep and daytime sleepiness in normal subjects with HLA-DQB1*0602. *Sleep*. 1999 May 1;22(3):347-52. PubMed PMID: 10341385.
3. **Mignot E, Lin X, Kalil J, George C, Singh S, Billiard M, Montplaisir J, Arrigoni J, Guilleminault C, Dement WC, et al**. DQB1-0602 (DQw1) is not present in most nonDR2 Caucasian narcoleptics. *Sleep*. 1992 Oct;15(5):415-22. PubMed PMID: 1455124.
4. **Fronczek R, Overeem S, Lammers GJ, van Dijk JG, Van Someren EJ**. Altered skin-temperature regulation in narcolepsy relates to sleep propensity. *Sleep*. 2006 Nov;29(11):1444-9. PubMed PMID: 17162991.
5. **Aran A, Shors I, Lin L, Mignot E, Schimmel MS**. CSF levels of hypocretin-1 (orexin-A) peak during early infancy in humans. *Sleep*. 2012 Feb 1;35(2):187-91. doi: 10.5665/sleep.1618. PubMed PMID: 22294808; PubMed Central PMCID: PMC3250357.
6. **Thannickal TC, Nienhuis R, Siegel JM**. Localized loss of hypocretin (orexin) cells in narcolepsy without cataplexy. *Sleep*. 2009 Aug;32(8):993-8. PubMed PMID: 19725250; PubMed Central PMCID: PMC2717206.
7. **Picchioni D, Mignot EJ, Harsh JR**. The month-of-birth pattern in narcolepsy is moderated by cataplexy severity and may be independent of HLA-DQB1*0602. *Sleep*. 2004 Dec 15;27(8):1471-5. PubMed PMID: 15683136.
8. **Longstreth WT Jr, Koepsell TD, Ton TG, Hendrickson AF, van Belle G**. The epidemiology of narcolepsy. *Sleep*. 2007 Jan;30(1):13-26. Review. PubMed PMID: 17310860.
9. **Dauvilliers Y, Carlander B, Molinari N, Desautels A, Okun M, Tafti M, Montplaisir J, Mignot E, Billiard M**. Month of birth as a risk factor for narcolepsy. *Sleep*. 2003 Sep;26(6):663-5. PubMed PMID: 14572117.
10. **Natarajan N, Jain SV, Chaudhry H, Hallinan BE, Simakajornboon N**. Narcolepsy-cataplexy: is streptococcal infection a trigger? *J Clin Sleep Med*. 2013 Mar 15;9(3):269-70. doi: 10.5664/jcsm.2498. PubMed PMID: 23493659; PubMed Central PMCID: PMC3578683.
11. **Savvidou A, Knudsen S, Olsson-Engman M, Gammeltoft S, Jennum P, Palm L**. Hypocretin deficiency develops during onset of human narcolepsy with cataplexy. *Sleep*. 2013 Jan 1;36(1):147-8. doi: 10.5665/sleep.2320. PubMed PMID: 23288981; PubMed Central PMCID: PMC3524537.
12. **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, Kotagal S, Mignot E**. Post-H1N1 narcolepsy-cataplexy. *Sleep*. 2010 Nov;33(11):1428-30. PubMed PMID: 21102981; PubMed Central PMCID: PMC2954689.
13. **Watson NF, Doherty MJ, Zunt JR**. Secondary narcolepsy following neurocysticercosis infection. *J Clin Sleep Med*. 2005 Jan 15;1(1):41-2. PubMed PMID: 17561614.
14. **Ebrahim IO, Peacock KW, Williams AJ**. Posttraumatic narcolepsy--two case reports and a mini review. *J Clin Sleep Med*. 2005 Apr 15;1(2):153-6. Review. PubMed PMID: 17561629.
15. **Kryger MH, Walid R, Manfreda J**. Diagnoses received by narcolepsy patients in the year prior to diagnosis by a sleep specialist. *Sleep*. 2002 Feb 1;25(1):36-41. PubMed PMID: 11833859.
16. The International Classification of Sleep Disorders, Diagnostic and Coding Manual 2nd Edition. American Academy of Sleep Medicine, 2005. P. 81 – 90.
17. **Honda Y, Juji T, Matsuki K, Naohara T, Satake M, Inoko H, Someya T, Harada S, Doi Y**. HLA-DR2 and Dw2 in narcolepsy and in other disorders of excessive somnolence without cataplexy. *Sleep*. 1986;9(1 Pt 2):133-42. PubMed PMID: 3010426.
18. **Knudsen S, Jennum PJ, Alving J, Sheikh SP, Gammeltoft S**. Validation of the ICSD-2 criteria for CSF hypocretin-1 measurements in the diagnosis of narcolepsy in the Danish population. *Sleep*. 2010 Feb;33(2):169-76. PubMed PMID: 20175400; PubMed Central PMCID: PMC2817904.
19. **Oka Y, Inoue Y, Kanbayashi T, Kuroda K, Miyamoto M, Miyamoto T, Ikeda A, Shimizu T, Hishikawa Y, Shibasaki H**. Narcolepsy without cataplexy: 2 subtypes based on CSF hypocretin-1/orexin-A findings. *Sleep*. 2006 Nov;29(11):1439-43. PubMed PMID: 17162990.
20. **Scammell TE**. The frustrating and mostly fruitless search for an autoimmune cause of narcolepsy. *Sleep*. 2006 May;29(5):601-2. PubMed PMID: 16774147.
21. **Andlauer O, Moore H 4th, Hong SC, Dauvilliers Y, Kanbayashi T, Nishino S, Han F, Silber MH, Rico T, Einen M, Kornum BR, Jennum P, Knudsen S, Nevsimalova S, Poli F, Plazzi G, Mignot E**. Predictors of hypocretin (orexin) deficiency in narcolepsy without cataplexy. *Sleep*. 2012 Sep 1;35(9):1247-55F. doi: 10.5665/sleep.2080. PubMed PMID: 22942503; PubMed Central PMCID: PMC3413802.
22. **Hong SC, Lin L, Jeong JH, Shin YK, Han JH, Lee JH, Lee SP, Zhang J, Einen M, Mignot E.** A study of the diagnostic utility of HLA typing, CSF hypocretin-1 measurements, and MSLT testing for the diagnosis of narcolepsy in 163 Korean patients with unexplained excessive daytime sleepiness. *Sleep*. 2006 Nov;29(11):1429-38. PubMed PMID: 17162989.
23. **Langdon N, Lock C, Welsh K, Vergani D, Dorow R, Wachtel H, Palenschat D, Parkes JD**. Immune factors in narcolepsy. *Sleep*. 1986;9(1 Pt 2):143-8. PubMed PMID: 3486441.
24. **Mignot E, Nishino S**. Emerging therapies in narcolepsy-cataplexy. *Sleep*. 2005 Jun;28(6):754-63. Review. PubMed PMID: 16477963.
25. **Roth T, Schwartz JR, Hirshkowitz M, Erman MK, Dayno JM, Arora S**. Evaluation of the safety of modafinil for treatment of excessive sleepiness. *J Clin Sleep Med*. 2007 Oct 15;3(6):595-602. PubMed PMID: 17993041; PubMed Central PMCID: PMC2045706.
26. **Beusterien KM, Rogers AE, Walsleben JA, Emsellem HA, Reblando JA, Wang L, Goswami M, Steinwald B**. Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep*. 1999 Sep 15;22(6):757-65. PubMed PMID: 10505821.
27. **Black J, Houghton WC**. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006 Jul;29(7):939-46. PubMed PMID: 16895262.
28. **Schwartz JR, Khan A, McCall WV, Weintraub J, Tiller J**. Tolerability and efficacy of armodafinil in naïve patients

with excessive sleepiness associated with obstructive sleep apnea, shift work disorder, or narcolepsy: a 12-month, open-label, flexible-dose study with an extension period. *J Clin Sleep Med*. 2010 Oct 15;6(5):450-7. PubMed PMID: 20957845; PubMed Central PMCID: PMC2952748.

29. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. *Sleep*. 2003 Feb 1;26(1):31-5. PubMed PMID: 12627729.
30. **Rogers AE, Aldrich MS, Lin X**. A comparison of three different sleep schedules for reducing daytime sleepiness in narcolepsy. *Sleep*. 2001 Jun 15;24(4):385-91. PubMed PMID: 11403522.

Submitted on May 30, 2013