CLINICAL PRACTICE

*Clinical Vignettes***Narcolepsy with Cataplexy in an Elderly Woman**

Shingo Suzuki, MD, PhD, Takanori Uehara, MD, PhD, Yoshiyuki Ohira, MD, PhD, and Masatomi Ikusaka, MD, PhD

Department of General Medicine, Chiba University Hospital, Chiba-city, Chiba, Japan.

A 72-year-old woman was referred for a 15-year history of brief attacks of generalized weakness that occurred when she was tense or startled. During these episodes, she squatted, closed her eyes, and had difficulty speaking, but there was no disturbance of consciousness. The cerebrospinal fluid level of orexin/hypocretin was low (92 ng/L), leading to a diagnosis of narcolepsy with cataplexy according to the International Classification of Sleep Disorders (ICSD)-2 criteria. Cataplexy should be considered for sudden attacks of weakness lasting less than 2 minutes and with no alteration of consciousness. Measurement of cerebrospinal fluid levels of orexin/hypocretin is recommended when the diagnosis is uncertain.

KEY WORDS: cataplexy; narcolepsy; orexin/hypocretin; video; elderly.

J Gen Intern Med 30(8):1222–4

DOI: 10.1007/s11606-015-3277-7

© Society of General Internal Medicine 2015

CASE REPORT

A 72-year-old woman was referred to our hospital by her primary care doctor for a 15-year history of experiencing “attacks” during which she “lost body control.” These episodes occurred one to ten times on most days, and lasted approximately 1 minute. They occurred when she was tense or startled (e.g. telephone ringing, unexpectedly meeting an acquaintance, or being called into the clinic room by her doctor). During these episodes, she closed her eyes, squatted, and had difficulty speaking. While she could not answer questions, she maintained consciousness and was able to hear the individuals around her and could accurately recall their conversations.

The patient reported that she often fell asleep during the day, including during meals, and that she frequently took 15-minute naps that refreshed her temporarily. She occasionally experienced hypnagogic hallucinations, but did not experience sleep paralysis. None of her relatives had similar symptoms. The patient had a 4-year history of well-controlled diabetes, as well as hypertension and hyperlipidemia; she had no complications from her diabetes. Medications included metformin,

voglibose, glimepiride, losartan, hydrochlorothiazide, nifedipine, and atorvastatin.

The patient had experienced attacks at her physicians’ offices, and they had been witnessed by generalists, neurologists, and neurosurgeons, who had variously diagnosed essential tremor, orthostatic hypotension, epilepsy, and psychosomatic disease. A video of an attack was recorded when she visited our clinic (see video link), which showed her experiencing paroxysmal weakness. As can be seen in the video, when the patient was called into the clinic room, she first stood up from her chair and then assumed a half-sitting posture with her head and arms hanging down and her eyes closed. Although she was able to temporarily stand again and walk a few steps, she subsequently became unable to support herself and had to squat down. After 1 minute, she recovered and was able to stand and move normally.

Physical exam results, including vital signs, cardiopulmonary, and neurological findings, were normal. Her body mass index was 32 (162 cm, 72 kg). Basic lab values were within normal limits, including hemoglobin A_{1c}, which was stable at 6.8 %.

The patient underwent monitoring during these episodes. Blood glucose, Holter electrocardiogram, interictal electroencephalogram, and brain magnetic resonance imaging results were normal. During the course of her evaluation, cataplexy was considered, as her bilateral atonic attacks seemed to occur when she was tense or startled, and she continued to maintain consciousness. Since excessive sleepiness was suggested by medical history, we performed an evaluation to make a definite diagnosis of narcolepsy with cataplexy. Polysomnography did not detect sleep-onset rapid eye movement periods (SOREMPs). A lumbar puncture was subsequently performed, and measurement of orexin/hypocretin in the cerebrospinal fluid (CSF) revealed a low level of 92 ng/L, leading to a diagnosis of narcolepsy with cataplexy according to the International Classification of Sleep Disorders—Second Edition (ICSD-2) criteria. After treatment for cataplexy with paroxetine at a daily dose of 10 mg, her attacks of generalized weakness were reduced to two episodes every 2 weeks. When the dose of paroxetine was increased to 20 mg, the attacks were further reduced to fewer than one per month, and she has remained on this regimen. Since our patient could deal with her sleepiness by taking naps, she did not require medication to promote wakefulness.

Electronic supplementary material The online version of this article (doi:10.1007/s11606-015-3277-7) contains supplementary material, which is available to authorized users.

Received April 2, 2014

Accepted February 26, 2015

Published online March 18, 2015

DISCUSSION

Cataplexy is one of the classic tetrad of symptoms found in patients with narcolepsy; the remaining symptoms are excessive daytime sleepiness, hypnagogic hallucinations, and sleep paralysis. Individuals with cataplexy display transient, typically bilateral muscle weakness, most often provoked by strong emotion, and with consciousness fully preserved.¹ The most common triggers of cataplexy are laughter (92 % of patients), anger (70 %), and startle reaction (55 %).² Muscular weakness that resolves immediately after an attack is a cardinal feature of cataplexy, and often affects the jaw or face rather than the lower limbs.² Jerking or twitching of various body parts, including the arms and face, can also occur.²

The differential diagnosis of paroxysmal weakness depends on the pattern of symptoms. Transient ischemic attacks and seizures are the major causes of unilateral paroxysmal weakness, followed by hemiplegic migraine and hypoglycemia. In contrast, bilateral paroxysmal weakness suggests orthostatic hypotension, cardiogenic cerebral ischemia, hypoglycemia, or seizures, most of which are associated with alteration of consciousness. Paroxysmal bilateral weakness without disturbance of consciousness which occurred in our patient suggests periodic paralysis (which lasts for several hours) or cataplexy (which resolves within 2 minutes).

Although our patient had consulted numerous physicians over a 15-year period, and some had witnessed her attacks, her narcolepsy with cataplexy remained undiagnosed, reflecting the difficulty in recognizing this condition. One of the reasons for delayed diagnosis may be that narcolepsy is uncommon, with a prevalence of 0.16 % in Japan and 0.02 % to 0.05 % in Europe.³ Because the majority of patients tend to develop symptoms in the second decade of life,⁴ patients who have later onset, such as our patient, may elude diagnosis. Another barrier to diagnosing narcolepsy in our patient was that, while she experienced attacks when startled, she had never experienced an episode when laughing, which is the most common trigger of cataplexy.

The Table 1 shows the simplified diagnostic criteria for narcolepsy from ICSD-2.⁵ If a patient has a history of cataplexy and daytime sleepiness, a definite diagnosis of narcolepsy with cataplexy can be made by polysomnography and a multiple sleep latency test (MSLT) or by measuring the CSF level of orexin/hypocretin. Polysomnography is recommended for differentiating narcolepsy from other disorders causing daytime sleepiness or to confirm the coexistence of multiple disorders, as narcolepsy often coexists with other sleep disorders, including obstructive sleep apnea syndrome, periodic limb movements in sleep, REM sleep behavior disorder, and nocturnal eating disorder.³ The detection of at least two SOREMPs during an MSLT is a useful criterion for confirming a diagnosis of narcolepsy with cataplexy. In elderly populations, however, false-negative MSLT results occur more frequently.⁶ In addition, the results of one community-based study revealed that false-positive rates would be high because 13.1 % of men and 5.6 % in women met the criterion.⁷ As such, caution should be exercised in the interpretation of positive MSLT scores.

Orexin A and B (also called hypocretin 1 and 2) play an important role in narcolepsy with cataplexy. These two neurotransmitters are released from the dorsolateral hypothalamus and are involved in regulating the sleep–wake cycle and promoting wakefulness.⁸ A deficiency in orexin/hypocretin leads to abnormalities in REM sleep (causing cataplexy, hypnagogic hallucinations, and sleep paralysis) and excessive daytime sleepiness.⁸ The measurement of orexin/hypocretin in the CSF is a specific test, as low levels are found in only a few diseases apart from narcolepsy with cataplexy, such as Guillain-Barré syndrome, Ma2-positive paraneoplastic syndrome, and multiple sclerosis,⁹ which are easily distinguishable based on their clinical manifestations. CSF levels of orexin/hypocretin are low (<110 ng/L) in more than 90 % of patients who have narcolepsy with cataplexy,¹⁰ and thus measurement of orexin/hypocretin in the CSF should be considered when diagnosis of narcolepsy with cataplexy proves difficult.

With regard to treatment, antidepressants that inhibit REM sleep, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, have been shown to reduce the severity and frequency of attacks in 98 % of cataplexy patients.² First-line drugs for daytime sleepiness include modafinil and armodafinil, which promote wakefulness by interfering with the dopamine reuptake transporter, and have a lower likelihood of side effects and less potential for abuse than amphetamines.¹¹

CONCLUSION

Cataplexy should be considered when patients report a history of sudden attacks of weakness that resolve rapidly and without disturbance of consciousness. If cataplexy is suspected, the

Table 1 Diagnostic criteria for narcolepsy

Narcolepsy with cataplexy

1. Excessive daytime sleepiness almost daily for at least 3 months
2. Definite history of cataplexy
3. Diagnosis should be confirmed by one of the following
 - Polysomnography and MSLT; mean sleep latency $\leq$ 8 minutes and >2 SOREMPs
 - Orexin/hypocretin level in the CSF $\leq$ 110 pg/ml or 1/3 of mean normal controls
4. Hypersomnia is not better explained by another disorder or medication

Narcolepsy without cataplexy

1. Excessive daytime sleepiness almost daily for at least 3 months
2. Typical cataplexy is not present
3. Diagnosis must be confirmed by polysomnography and MSLT; mean sleep latency $\leq$ 8 minutes and >2 SOREMPs
4. Hypersomnia is not better explained by another disorder or medication

MSLT multiple sleep latency test, SOREMPs sleep-onset rapid eye movement periods, CSF cerebrospinal fluid

influence of affect (laughter, anger, startle reaction) on attacks and the presence of daytime sleepiness should be investigated, since the former is a useful clue and the latter is essential for the diagnosis of narcolepsy with cataplexy. Measurement of orexin/hypocretin levels in the CSF has high sensitivity and specificity for narcolepsy with cataplexy and is recommended when the diagnosis is unclear.

Conflict of Interest: The authors declare that they do not have a conflict of interest.

Corresponding Author: Shingo Suzuki, MD, PhD; Department of General Medicine Chiba University Hospital, 1-8-1, Inohana, Chuo-ku, Chiba-city, Chiba 260-8677, Japan (e-mail: shngszkthk@yahoo.co.jp).

REFERENCES

1. **Nevsimalova S, Pisko J, Buskova J, et al.** Narcolepsy: clinical differences and association with other sleep disorders in different age groups. *J Neurol.* 2013;260:767–75.
2. **Overeem S, van Nues SJ, van der Zande WL, Donjacour CE, van Mierlo P, Lammers GJ.** The clinical features of cataplexy: a questionnaire study in narcolepsy patients with and without hypocretin-1 deficiency. *Sleep Med.* 2011;12:12–8.
3. **Akintomide GS, Rickards H.** Narcolepsy: a review. *Neuropsychiatr Dis Treat.* 2011;7:507–18.
4. **Pandi-Perumal SR, Gupta R, Monti JM.** Narcolepsy or sleep apnea?: not everything is what it appears to be! *Front Neurol.* 2013;4:152.
5. **International Classification of Sleep Disorders.** Diagnostic and coding manual. 2nd ed. Westchester, IL, USA: American Academy of Sleep Medicine; 2005.
6. **Dauvilliers Y, Gosselin A, Paquet J, Touchon J, Billiard M, Montplaisir J.** Effect of age on MSLT results in patients with narcolepsy-cataplexy. *Neurology.* 2004;62:46–50.
7. **Mignot E, Lin L, Finn L, et al.** Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. *Brain.* 2006;129:1609–23.
8. **Kumar S, Sagili H.** Etiopathogenesis and neurobiology of narcolepsy: a review. *J Clin Diagn Res.* 2014;8:190–5.
9. **Nishino S, Okuro M, Kotorii N, et al.** Hypocretin/orexin and narcolepsy: new basic and clinical insights. *Acta Physiol (Oxf).* 2010;198:209–22.
10. **Mignot E, Lammers GJ, Ripley B, et al.** The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol.* 2002;59:1553–62.
11. **Strambi LF.** A need for new treatments in narcolepsy. *Lancet Neurol.* 2013;12:1039–40.