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A standardized test for cataplexy

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Abstract

This study developed a standardized procedure for provoking cataplexy, which facilitated observation of the physiologic changes occurring with cataplexy. Data were obtained from narcoleptic patients recruited from a sleep disorder center. Patients were asked to describe the nature and frequency of cataplexy, as well as their typical emotional triggers. Referring clinicians were asked to assess the likelihood, frequency, and severity of the patients' cataplexy. Nine patients with multiple sleep latency test (MSLT)-confirmed narcolepsy were included in this study. The subjects were then instructed to view a humorous videotape while monitored with video-polysomnography including EEG, EMG, and EOG. In the event of a spell, quadriceps reflexes were tested. The data were examined to determine the occurrence of cataplexy in response to a standardized stimuli. Cataplexy was successfully provoked in five patients (four women and one man). Areflexia of the quadriceps muscle was the most sensitive marker of a cataplectic event. EMG tone was mildly reduced in three patients with no other remarkable changes on polysomnography. The narcoleptic patients' responses to the humorous videotapes and other stimuli varied tremendously. This pilot study demostrates the feasibility of a standardized procedure for provoking cataplexy, which permits further study of these phenomena. Furthermore, a cataplexy test has considerable potential as a diagnostic tool, especially in situations where an MSLT is impractical.

Keywords: Cataplexy; Narcolepsy; Polysomnography; REM sleep; Sleep; Multiple sleep latency test

1. Introduction

Cataplexy is a relatively specific clinical symptom that distinguishes narcolepsy from other disorders that cause excessive daytime sleepiness. Cataplexy entails a sudden loss of muscle tone associated with areflexia that is usually provoked by an emotional stimulus like laughter, anger, fear, and surprise [1,2]. The pathogenesis of cataplexy is not well understood, but these events are associated with inhibition of H-reflex and the muscle stretch reflexes in the affected area [3]. Inhibition of the monosynaptic H-reflex also occurs during REM sleep, pointing to the similarities between cataplectic events and REM sleep. In the canine model of narcolepsy, cataplexy is believed to be related to acetylcholine release of the basal forebrain [4]. In narcoleptic canines, carbachol and oxotremorine, cholinergic agonists, cause a dose-dependent increase in cataplexy; while atropine, a cholinergic antagonist, blocks physostigmine-induced cataplexy [5].

Observing cataplexy and documenting areflexia is considered pathognomonic of narcolepsy in patients with excessive daytime sleepiness [6]. However, no standardized procedure to provoke human cataplexy in the laboratory has been described. In general, provoking cataplexy has been considered to be very

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difficult [6]. Previous studies describing these physiologic events that occur during cataplexy have described their methodology of provoking spells as 'telling jokes' [6,7]. In a 1974 Guilleminault paper, the authors described carefully selecting patients with severe cataplexy in order to increase the cataplectic response to telling jokes [6]. Little information is provided on the type of humorous material or predictability of patient response. In canine narcolepsy, a food-elicited cataplexy test (FECT) and a play-elicited cataplexy test (PECT) are used to reliably induce cataplexy [8]. However, despite the utility of a cataplexy test for diagnostic and research purposes in canines, no similar test exists for human subjects.

2. Methods

The authors searched extensively for tasteful, brief videotaped segments of television shows that would be non-offensive and appealing to a wide audience. They sought material that would interest subjects of varying ages, cultures and educational backgrounds. The goal was to find programming that depicted humorous events with an element of surprise. The videotaped segments selected depicted scenes where a commentator was unexpectedly interrupted while preparing a telecast about exotic animals.

Patients with suspected narcolepsy and associated cataplexy, regardless of severity, who were seen in the clinical practice of a sleep disorders center during a 4 month time period, were asked to participate in the study. American Sleep Disorders Association criteria were used to diagnose narcolepsy by the multiple sleep latency test (MSLT) with all patients having an initial sleep onset of 8 min or less and at least two sleep onset REM episodes [9]. This study was reviewed and approved by the Mayo Foundation Institutional Review Board. All patients provided verbal consent to participate in research.

The patients were asked to view the selected videotapes in-between the second and third nap of the MSLT while the patients were already hooked up for electrophysiologic monitoring. Monitoring included video recording, electroencephalogram (EEG), electrooculogram (EOG), as well as tibialis and chin electromyogram (EMG) [10]. In the case of two patients, the MSLT diagnosis for narcolepsy had been done at an earlier date. These patients were brought in during the morning at approximately the same time as the interval between naps two and three of the MSLT and were hooked up specifically for the cataplexy test. Patients were not taking any antidepressant medications, which are known to suppress cataplexy. However psychostimulant medications, which can also reduce cataplexy, were continued for those two patients who were not having a MSLT.

Before the testing began, the patients were asked to describe their typical emotional triggers for cataplexy as well as the nature and frequency of their cataplectic events. The referring sleep physician was asked to assess the likelihood that the spells represented cataplexy, severity of a typical spell (fleeting facial changes only vs. total body involvement) and frequency of the patient having cataplexy, on a five-point Likert scale. All patients were examined prior to viewing the videotape to ensure that the quadriceps deep tendon reflexes were present. Staff members were present in the examination room in order to assess the quadriceps deep tendon reflexes in the event of a suspected cataplectic spell. In order to prevent injury, patients were seated while watching the videotapes on a videocassette recorder. Volunteers were then shown a 5 min videotape of out-takes from a televised animal show. If the patient had behavior consistent with cataplexy, deep tendon reflexes were assessed. If they did not have a cataplectic event in response to watching the videotape, next staff members attempted to provoke cataplexy by surprising the patient. A tray would be dropped or a paper bag popped.

One patient was tested while standing, since she reported that she had never experienced cataplexy in any other position, and she denied any falls or injuries related to cataplexy; however, this precluded testing deep tendon reflexes. In the case of the 10-year-old girl, the patient's family brought along humorous videotape appropriate for her age, to which she had previously had cataplectic-like episodes at home.

Data was collected on patient demographics, MSLT results, effective stimuli, and the number of discrete cataplectic episodes.

3. Results

During the first four months of the study, 15

patients were enrolled. Six patients were later excluded because their MSLT results were inconsistent with narcolepsy. Of the nine patients with MSLT-confirmed narcolepsy, five patients experienced cataplexy using the procedures described in the methods section.

Table 1 provides data concerning the demographics, MSLT data, pre-test physician assessment, effective cataplectic stimuli and number of cataplectic episodes for the study participants. Patients 3 and 7 were not receiving a MSLT on the day of the cataplexy study and were on methylphenidate. Both patients experienced cataplexy. Three patients experienced cataplexy provoked by humorous videotapes. In two cases, the effective stimulus was the videotape provided by the study team. The other two subjects experienced cataplexy before the videotapes were played. In both cases, the participants were preparing for the study when a physician entered the examination room. The patients' emotional response to the physician's entrance triggered a cataplectic episode. A sudden noise did not precipitate cataplexy in any patient.

Overall transient areflexia of the quadriceps muscles, documented in all four patients in which it was tested, was the most sensitive indicator of cataplexy. Overall the changes in EMG, EEG and EOG were less remarkable than the observed areflexia. A mild reduction in EMG tone was observed for three patients during the events with no discernible change on EEG and EOG. The videotaped material demonstrated unequivocal neck extensor muscle weakness in all patients except patient 1. She described the cataplexy as fleeting buckling of the knees and the corresponding videotape revealed no obvious muscle weakness. Fig. 1 shows the polysomnographic changes of the first cataplectic event for this patient which included a clear decrease in EMG tone.

4. Discussion

This pilot study demonstrates that cataplexy can be triggered in human subjects using a standardized procedure. Surprise and humor appeared to be important elements for triggering cataplexy. These observations suggest that developing a specific cataplexy test may be possible which will promote further study of this unique condition. In general the pre-test physician assessment of cataplexy severity and frequency did not predict the outcome of the cataplexy test well.

What triggers cataplexy in an individual patient varies tremendously. In this study three patients had cataplexy while laughing in response to a videotape while two patients had cataplexy in response to a physician entering the room. The reasons that physician entry provoked cataplexy remain unclear. Any single stimulus, for example a specific humorous videotape, presented to multiple patients will likely not be effective for all patients tested. Individuals differ in their sense of humor and threshold for surprise. While this study identified some videotaped

Table 1
MSLT pretest physician assessment

Patient	Age	Gender	Mean 1 SL (min)	SOREMs	Probability of cataplexy[a]	Severity[b]	Frequency[c]	Cataplexy stimulus	No. of episodes
1	21	F	0.5	4/4	4	2	1–3/week	Video	2
2	58	F	0.5	4/4	5	5	1–3/day	Physician entry	2
3	10	F	0.5	4/4	4	4	1–3/day	Own video	7
4	24	F	1.5	4/4	4	2	1–3/week	Video	2
5	79	M	3.0	3/4	5	4	1–3/week	Non-responder	N/A
6	39	M	3.8	2/4	5	5	1–3/day	Non-responder	N/A
7	58	M	0.8	2/4	5	5	1–3/day	Physician entry	2
8	70	M	1.5	4/4	5	3	1–3/week	Non-responder	N/A
9	65	F	3.1	4/4	2	1	1-3/year	Non-responder	N/A

[a] Probability of cataplexy, (1–5 scale): 1, very unlikely; 5, very likely.
[b] Severity of cataplexy, (1–5 scale): 1, very mild; 5, very severe.
[c] Frequency of cataplexy, 1–3 ever; 1–3/year; 1—3/month; 1–3/week; 1–3/day.

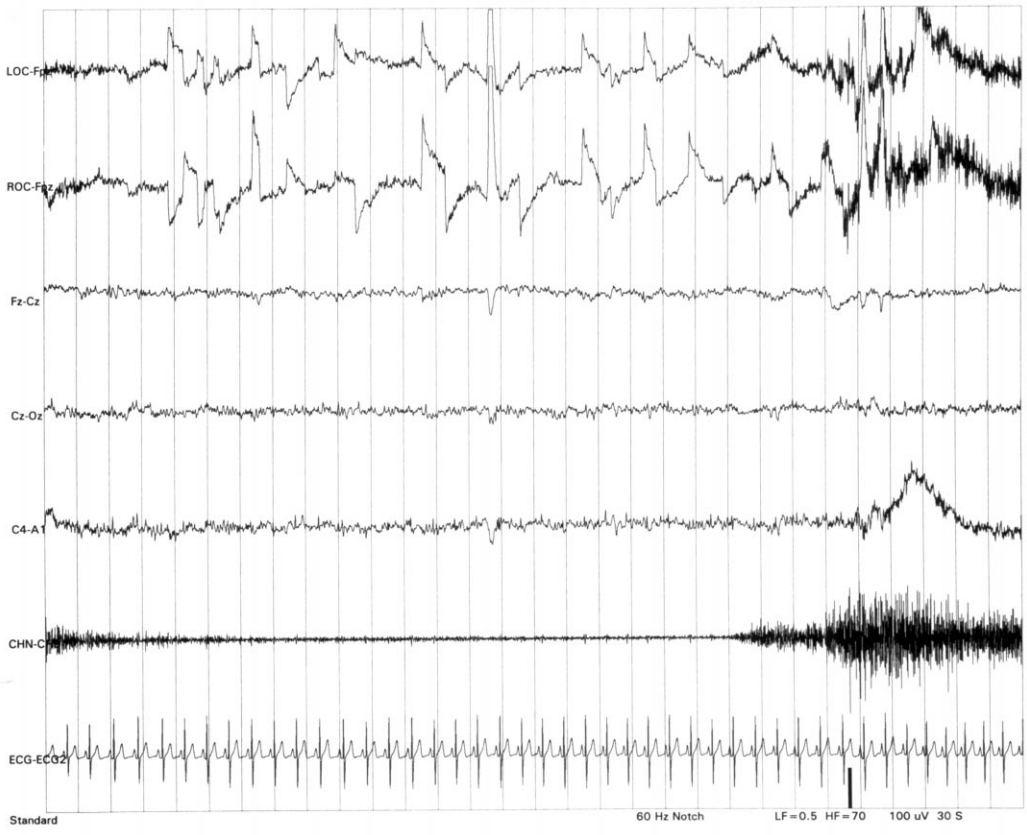

Fig. 1. Polysomnographic data for the first cataplectic event of patient 1.

material that did prompt cataplexy in two subjects, it was ineffective in seven other subjects. In the case of the 10-year-old child, the authors anticipated that she may need a different stimulus and asked the family to bring in juvenile videotape. Potentially a cataplexy test could be developed so that the patient brings in videotaped material, in the form of a rented videotaped movie or material taped from television, that is particularly humorous for that patient. To account for patient variability the cataplexy testing procedure might consist of a series of provocative videotapes and or events.

Some patients reported that in general they do not become emotionally involved with videotapes or movies. They also commented that during the short (5 min) duration of the tape, they did not detach themselves from their environment and other thoughts. Whether more provocative videotape material, perhaps of a longer duration, could be identified is unclear. Perhaps for some patients, the videotape medium is not powerful enough to cause emotional engagement and therefore trigger cataplexy. No patient developed cataplexy in response to the sudden noise or surprise produced by a clattering tray or a popped paper bag. These stimuli appeared ineffective in triggering cataplexy.

In the case of two patients, cataplexy was provoked by the entry of a physician into the examination room. The possibility exists that the sudden arrival of an authority figure caused an emotional response that then triggered cataplexy. Separating out the role and status of the physician from the surprise of his arrival is impossible with this study design. The technicians involved in this study, however, noted that they would come and go from the examination room in a similar manner and this never provoked cataplexy in any

subject. This observation suggests that the authoritarian position of the physician caused a specific emotional response that led to cataplexy.

The EMG monitors were placed on the tibialis and chin muscles, in accordance with the MSLT protocol [10]. However, the MSLT was designed to measure REM sleep associated with excessive daytime sleepiness, not muscle weakness involved in cataplexy. Since the most common behavioral change was loss of muscle tone in the neck extensors, potentially additional EMG monitors could be added to more specifically target these muscles as has been done by Guilleminault [6]. Adding sensors in this location may detect a decrease in EMG tone that is not as prominent in the tibialis or chin muscles. In the canine model, EMG tone is assessed using wires surgically inserted into the dorsal neck muscle which is unacceptable for human usage [5].

Another interesting issue is whether the cataplexy test was conducted at an appropriate time of day. For reasons of patient convenience and cost, the authors typically chose to monitor patients in between the morning naps of the MSLT. Patients have reported that they are more inclined to experience cataplexy when tired so a test scheduled in the early afternoon may be preferable [3]. In several cases, the patients had experienced REM sleep on the preceding MSLT nap. Whether experiencing a sleep onset REM episode reduces the REM pressure and makes cataplexy less likely, even with appropriate emotional stimuli, is unknown. Conceivably, at another time point these individuals might experience cataplexy when laughing or surprised by a videotape.

Whether the kindling phenomena are relevant in cataplexy is unknown. A kindling mechanism is plausible since all of our responders had at least two cataplectic episodes in quick succession. However, for the two patients who experienced cataplexy when the physician entered the examination room, possibly these patients were less vulnerable to another episode of cataplexy in response to laughter several minutes later when they were shown the humorous videotapes. No data exists in humans about whether an ultradian rhythm exists for cataplexy similar to REM sleep where episodes are likely to be spaced apart with some degree of periodicity. Recent work with narcoleptic canines has demonstrated a 30 min ultradian rhythm with REM sleep but not cataplexy [11].

Whether the same stimulus presented to a patient repeatedly would still provoke laughter and therefore cataplexy is doubtful. However, this issue was not examined in this study. If the same stimulus can provoke laughter repeatedly (as in the case of the 10-year-old child described here), a cataplexy test could be used to examine treatment efficacy in a manner similar to the FECT in the canine [8].

The potential value of a cataplexy test for human subjects is undisputed. For patients who cannot undergo a reliable MSLT due to sleep deprivation, altered sleep-wake cycle, competing commitments, or financial reasons, a positive cataplexy test could be sufficient to diagnose narcolepsy. The cataplexy test could also be a useful adjunct used in combination with an MSLT. Sometimes, the patients report considerable danger or inconvenience because of cataplectic events. The MSLT establishes the diagnosis of narcolepsy by measuring sleepiness, but it does not address the issue of cataplexy. In the patient for whom cataplexy is a significant clinical issue, a positive cataplexy test would help distinguish true cataplexy from other non-cataplectic events, which could include other neurologic events (seizure), cardiovascular events (syncope), or psychogenic events (conversion disorder). Furthermore, a cataplexy test could be used to document treatment response to anti-cataplectic treatment. Patients with treatment refractory cataplexy could start on therapy and then be once again challenged with a standardized cataplexy protocol. Although the issues of retest would need to be clarified, potentially this procedure could help assess appropriate levels of antidepressant medication. In the canine model, the FECT has been used to assess treatment efficacy, as well as help further the understanding of the neurotransmitter changes responsible for cataplexy in human beings [8].

The sleep literature already contains numerous descriptions of the electrophysiologic and clinical changes observed with cataplexy [12–14]. Nonetheless, the procedure employed in this study permitted additional examination of cataplexy. In general this study demonstrated the relative value of testing deep tendon reflexes as compared with electrophysiologic data. Quadriceps areflexia was a more sensitive marker of a cataplectic episode and was observed even in patients with no change in muscle tone on tibialis and chin EMG.

Regarding electrophysiologic data, EMG tone was more useful than EEG and EOG data in identifying cataplexy events. This observation stirs up the debate of whether electrophysiologic studies of cataplexy suggest a waking EEG or REM sleep. Dyken has commented that the PSG monitoring reveals apparent sleep with REM phenomena [7]. However, during a brief cataplexy event and at least initially during prolonged cataplexy, a patient is not asleep. Patients remain aware of their surroundings while experiencing some degree of muscle weakness. Since the patient is awake, not asleep, the electrophysiologic findings should be different that during REM sleep. The data from this study indicate that brief cataplexy represents a dissociated REM state affecting predominantly skeletal muscle tone. Only when cataplexy is prolonged is it likely that other REM phenomena develop.

5. Conclusions

Although several issues need to be resolved, this pilot study indicates that developing a standardized protocol for provoking cataplexy is feasible. This cataplexy test next needs to be administered to narcoleptic patients and normal controls. To account for patient variability the procedure might be expanded to include a series of provocative measures. Observing cataplexy permits the immediate diagnosis of narcolepsy in essentially all situations. Having the ability to observe cataplexy under controlled conditions also promotes the understanding of these unique clinical phenomena. Testing deep tendon reflexes and determining areflexia appears more sensitive than electrophysiologic data. Nonetheless, the standard PSG montage could be modified to include additional EMG channels that could improve the utility of video PSG in this special situation.

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References

[1] Guilleminault C. Narcolepsy. In: Chokiovertys S, editor. Sleep disorders medicine: basic science, technical considerations and clinical aspects, Boston, MA: Butterworth–Heinemann, 1994. pp. 241–254.

[2] Labat-Anic S, Guilleminault C, Kraemer HC, Meehan J, et al. Validation of the cataplexy questionnaire in 983 sleep disorder patients. Sleep 1999;22:77–87.

[3] Guilleminault C, Gelb M. Clinical aspects and features of cataplexy. In: Fahn S, Hallett M, Luders HO, Marsden CD, editors. Negative motor phenomena: advances in neurology, vol 67, Philadelphia, PA: Lippincott-Raven, 1995. pp. 65–77.

[4] Nishino S, Tafti M, Reid MS, Shelton J, et al. Muscle atonia is triggered by cholinergic stimulation of the basal forebrain: implication for the pathophysiology of canine narcolepsy. J Neurosci 1995;15(7):4806–4814.

[5] Reid MS, Nishino S, Tafti M, Siegel JM, et al. Neuropharmacological characterization of basal forebrain cholinergic stimulated cataplexy in narcoleptic canines. Exp Neurol 1998;151:89–103.

[6] Guilleminault C, Wilson RA, Dement WC. A study on cataplexy. Arch Neurol 1974;32:255–261.

[7] Dyken ME, Yamada T, Lin-Dyken DC, Seaba P, et al. Diagnosing narcolepsy through the simultaneous clinical and electrophysiologic analysis of cataplexy. Arch Neurol 1996;53: 456–460.

[8] Baker TL, Dement WC. Canine narcolepsy-cataplexy syndrome: Evidence for an inherited monoaminergic-cholinergic imbalance. In: McGinty DJ, Drucker-Colin R, Morrison A, Parmeggiani PL, editors. Brain mechanisms of sleep, New York: Raven, 1985. pp. 199–233.

[9] American Sleep Disorders Association. The international classification of sleep disorders revised diagnostic and coding manual. Rochester, MN, 1997.

[10] Carskadon MA, Dement WC, Mitler MM, Roth T, et al. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9(4): 519–524.

[11] Nishino S, Riehl J, Hong J, Kwan M, et al. REM sleep, but not cataplexy, is controlled by a 30-minute normal ultradian rhythm in narcoleptic canines (abstract). Sleep 1999;22:52.

[12] Corfariu O, Popovieiu L. Clinical and polygraphic study of the cataplectic attacks. Rev Roum Neurol Psychiatr. 1974; 11:3–9.

[13] Smith C.M. Electroencephalogram in cataplexy. Electroenceph Clin Neurphysiol. 1959;1 1:344-345.

[14] Scollo-Lavizzari G. A note on cataplexy with simultaneous EEG-recordings. Eur Neurol 1970;4:57–63.