Functional Imaging of Cataplexy During Status Cataplecticus

Dorothee Chabas, MD, PhD; Marie-Odile Habert, MD; Philippe Maksud, MD; Ayman Tourbah, MD; Michel Minz, MD; Jean-Claude Willer, MD, PhD; Isabelle Arnulf, MD, PhD

1INSERM UMR 546 AVENIR, Paris, France; 2Université Pierre et Marie Curie-Paris 6 UMR 546, Paris, France; 3Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Fédération de maladies du système nerveux, Paris, France; 4Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Service de médecine nucléaire, Paris, France; 5Assistance Publique Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Fédération des pathologies du sommeil; 6INSERM UMR 731, Paris, France

Study Objective: To identify the neural structures and pathways underlying cataplexy during status cataplectic in a narcoleptic patient, using brain perfusion single photon emission computed tomography (SPECT).

Methods: A 68-year-old woman with hypocretin-deficient narcolepsy-cataplexy suffered status cataplectic after having stopped clomipramine. She underwent a 99mTc-ethylcysteinate dimer brain SPECT during an episode of cataplexy; this image was compared with her brain SPECT during an intervening asymptomatic period. Subtraction SPECT coregistered to magnetic resonance imaging (MRI) (SISCOM) determined anatomic areas differentially perfused during cataplexy and basal wakefulness state.

Results: The areas hyperactivated during cataplexy corresponded on brain MRI with the cingular area, the left and right orbitofrontal cortex, the right temporal cortex, and the right putamen. No significant hypoperfused region was observed during the cataplectic episode.

Discussion: Cataplexy during status cataplecticus partially resembles normal rapid eye movement sleep (with high cingular, orbitofrontal, and putamen activity) but without the other imaging characteristics of this state (no hyperactivation of the pons, amygdala, or occipital cortex).

Keywords: Cataplexy, narcolepsy, SPECT, SISCOM, functional brain imaging

Citation: Chabas D; Habert MO; Maksud P et al. Functional imaging of cataplexy during status cataplecticus. SLEEP 2006;30(2):153-156.

INTRODUCTION

CATAPLEXY, A MAJOR SYMPTOM OF NARCOLEPSY, IS CHARACTERIZED BY A SUDDEN, BILATERAL LOSS OF MUSCLE TONE (AND POSSIBLE FALL) WITH PRESERVED CONSCIOUSNESS. It is usually triggered by emotions such as laughter, attempt at repartee, or anger. Although cataplexy is seen as an isolated intrusion of rapid eye movement (REM) sleep atonia into wakefulness, the neural structures underlying it are however roughly unknown. Because cataplexy is a transient and partly unpredictable condition, it is difficult to capture brain functional imaging during a complete episode of cataplexy. We took the opportunity of status cataplectic, a condition caused by the withdrawal of anticataplectic drugs in which hundreds of cataplectic attacks occur per day, to compare the cerebral function activity during and after a cataplectic episode in a narcoleptic patient.

CASE REPORT

Patient History

A 68-year-old woman had suffered from narcolepsy since she was 15 years old. She used to fall asleep unpredictably anywhere, including while eating at a table, attending lectures at school, standing between 2 stations in the subway, or sitting on the toilet. She noticed that short naps would restore vigilance for several hours, so she would force herself to take a short nap in the late afternoon before going out dancing. Her condition was undiagnosed, and she was considered by family and teachers at school to be a lazy person. She had her first typical cataplectic episodes when she was 25 years old, while laughing, surprisingly meeting a known person in the street, or when speaking about emotionally challenging events of her past history. She also developed typical hypnagogic hallucinations. When falling asleep, she would hear someone entering her house and was convinced it was her brother or she would feel that a person was hiding under her bed, so she would check under the bed before going to sleep. She also complained of frequent short-lasting awakenings during the night. Despite the fact that she had performed very well at school, her disability led her to choose manual work as a housekeeper so that she could avoid falling asleep by being constantly active, standing, and moving. She also chose not to get married because, as she said, “My mother did not understand my condition, thus, a husband would not either.” She was eventually diagnosed with narcolepsy with cataplexy when she was 35 years old.

Laboratory Assessments

Her sleep was first monitored on 2 consecutive nights when she was 55 years old and her cataplexy was untreated. Her REM sleep latency at night was 6 minutes. Her mean sleep latency during Multiple Sleep Latency Tests was 0.5 minutes, with 3 sleep-onset REM periods among the 4 tests. When she was 68 years old, a brain magnetic resonance imaging (MRI) study showed age-related cortical atrophy without other lesions. Lumbar puncture was performed at the same time, and her cerebrospinal fluid contained 2 lymphocytes per mm³, 0.37 g/L protein, and undetectable levels of hypocretin (<40 pg/mL). Her HLA genotype was DRB1*11/1501 and DQB1 *03/0602.
At the age of 68 years, after she had been treated for 3 years with modafinil, 300 mg per day, and clomipramine, 20 mg per day, she was diagnosed with glaucoma. Fearing that the glaucoma may worsen—after having read the package insert for clomipramine, she abruptly stopped taking the clomipramine on her own. Numerous cataplectic attacks ensued, leading, over a 2-month period, to full disabling status cataplecticus requiring inpatient care. We observed cataplectic episodes triggered by any minor or major emotional stimuli, such as when a doctor, nurse, or narcolepsy association support member would enter her room. She also had spontaneous attacks. She was continuously sitting on her bed, and, when she was asked to describe her medical history, she would stutter and not speak, drop her head, and fall back on her pillow for a few minutes. The tendon reflexes were abolished during the cataplectic spells. We witnessed dozens of episodes of cataplexy a day.

**Imaging Studies**

The patient volunteered to undergo 2 brain single photon emission computed tomography (SPECT) studies during symptomatic and asymptomatic periods of cataplexy on 2 nonconsecutive days. She was transported to the department of nuclear medicine in the afternoon, where she was asked to sit quietly on her gurney. She was placed on an intravenous drip, linked to a syringe filled with the radiotracer. She was supervised by a neurologist and a technician for the next 20 minutes, during which time she rested, sitting quietly with no social interaction. She suddenly fell back, eyes closed, without any particular emotional trigger. A dose of 925 MBq of 99mTc-ECD, a perfusion brain tracer, was intravenously administered within 10 seconds after the onset of cataplexy. The patient recovered full tonus within 2 minutes, and, when she could talk again, she accurately remembered all that she heard during the cataplectic episode.

Because the radiotracer is immediately taken up by the neurons and incorporated as a component that stays stable for at least the next 120 minutes, we performed the scan in the half hour following the end of the clinical episode. Images (120 projections) were acquired using a 3-headed gamma camera equipped with parallel high-resolution collimators (IRIX gammacamera, Philips Medical Systems, Cleveland, USA) in a 128*128 matrix. No correction for Compton scatter was performed, and projections were reconstructed using an iterative algorithm, then postfiltered (low-pass filter: n = 4, f0 = 0.4 cm-1). A postreconstruction uniform attenuation correction was performed using an attenuation coefficient of 0.12 cm-1. The asymptomatic study was performed 3 days after the initial study at the same time of day, in the same conditions, still without treatment, but during a cataplexy-free period after 8 hours without any cataplexy episodes. Both SPECT studies were normalized by the total number of counts detected in each study. SISCOM technique was used to evaluate the modifications of perfusion during cataplexy. Symptomatic SPECT images were coregistered with asymptomatic images by using AIR (automated image registration) software. Both images were then coregistered with 3D MRI by using MPTool software. SPECT data were corrected for variable global cerebral blood flow after excluding voxels influenced by symptomatically induced hyperperfusion in the symptomatic study, and a positive difference image (symptomatic minus asymptomatic SPECT) was calculated with statistical thresholding. The processing included the following steps: (1) for each voxel, calculation of a relative difference (C-I)/I, where I and C represent the value of asymptomatic and symptomatic studies, respectively; (2) for the whole brain, calculation of the mean value (M1) and the standard deviation (SD1) of the relative difference; (3) exclusion of voxels in the symptomatic SPECT, the value of which exceeded the interval [(M1-SD1),(M1+SD1)] and calculation of a new mean value (M2) of the relative difference with the remaining voxels; (4) normalization of the asymptomatic study to the level of the symptomatic one by calculating new values (IN) for each voxel: IN=I*[(M2/M1)]; and (5) Calculation of a subtracted volume (normalized symptomatic SPECT minus asymptomatic SPECT) with a voxel value of S = [(C-I)/I]/SDN, where SDN is the standard deviation of the new relative difference calculated with the normalized values of the pixels in the asymptomatic scan. The normalized subtracted SPECT and MRI volumes were merged for visual analysis. A value of 2 SD was used as the threshold of significance of a hyperperfusion.

The positive-difference image (cataplexy minus rest) revealed hyperactivated areas corresponding anatomically to the cingular area (6-SD increase), the right and left orbitofrontal cortex (6-SD increase), the temporal cortex (4.5-SD increase), and the right pu-

**Figure 1**—Brain functional imaging of cataplexy. Subtraction of cataplexic from noncataplectic state single photon emission computed tomography coregistered to the magnetic resonance imaging study of the patient. The color scale indicates the intensity of changes expressed in standard deviations multiplied by a factor 10. Significant (SD > 2) perfusion increase was found in cingular (A, E), right and left orbitofrontal (B), right temporal (C), and right putamen (D) areas. No hypoperfusion could be detected with this technique.
tamen (6-SD increase) on brain MRI (Figure 1). The negative-difference image (rest minus cataplexy) did not identify any hypoperfused area. The treatment with clomipramine was eventually restarted after the ophthalmologist confirmed that this medication could be used with the patient’s type of glaucoma. The status cataplecticus resolved within 2 days.

**DISCUSSION**

Previous imaging studies have failed to show structural changes in the brain of narcoleptic patients, but functional changes could be demonstrated. Postsynaptic D2-receptor binding has been shown to be elevated in narcolepsy and correlates with the frequency of cataplectic and sleep attacks, suggesting an alteration of the striatal dopaminergic system. An analysis of brain perfusion in narcolepsy was recently performed using 99mTc-ethylcysteinate dimer in 25 patients with narcolepsy-cataplexy during standard wakefulness, and the results were compared with those of normal controls. Narcoleptic images showed diffuse hypoperfusion of bilateral anterior hypothalami, caudate nuclei, pulvinar, parts of the dorsolateral/ventromedial/prefrontal cortex, parahippocampal and cingulate gyrus, and subcortical white matter. This exploratory analysis suggested that basal cerebral dysfunction may be widespread in narcolepsy-cataplexy, even outside cataplectic episodes and other narcoleptic symptoms.

In contrast, our method analyzed functional features specifically related to the mechanisms of cataplexy. Picturing brain activity during cataplexy, a transient and unpredictable neurologic state, is challenging. It is therefore easier to study cataplexy during status cataplecticus. There are, however, potential differences between routine cataplexy and the numerous cataplectic spells of a status. During status, cataplexy is less often triggered by emotions and occurs more frequently. In addition, the abrupt clomipramine withdrawal that caused the rebound cataplexy, although it occurred 2 months before, might have modulated the sensitivity of the norepinephrine receptors in the brain for an uncertain period of time. Although this patient with narcolepsy was not having cataplexy during the asymptomatic brain SPECT, an asymptomatic period limited to 8 hours does not guarantee normal baseline brain state. Additionally, spontaneous attacks of cataplexy during this period may suggest increased excitability of brain regions related to the generation of cataplexy. On the other hand, the state of the patient (complete atonia with full consciousness, lasting 1 to 2 minutes) during these cataplectic spells was not different from the usual cataplectic episodes she experienced in the previous years.

Our technique had been previously validated by studies about the spreading of focal seizures, in which surgical anatomic confirmation could be provided. To our knowledge, this report is the first of imaging analysis comparing brain activation during a cataplectic episode with a nonsymptomatic state in the same subject. The advantage of this technique is to accurately identify the cortical and subcortical neuronal networks underlying this condition, which may not be detected using surface electroencephalography (EEG), and to point out hyperactivation pathways possibly causing cataplexy, which are not present during asymptomatic periods. Our data demonstrate that cataplexy is not only a downregulated brain state, as is suggested by the absence of muscle tone. Because we found a hyperperfusion state, as opposed to the hypoperfusion status shown during baseline, we suppose that cataplexy is related to neuronal discharge in specific areas distinct from those involved in baseline narcolepsy. Thus, cataplectic attacks might not be caused by a sudden worsening of hypoperfusion of the areas designated by Joo et al., but, instead, specific pathways might be actively involved. Cataplexy-active structures included the cingular area, the right and left orbitofrontal, the right temporal cortex, and the right putamen. Thus, while cingulate gyri and frontal white matter appear to be hypoperfused in narcoleptic patients outside any cataplectic event, in this study, they were hyperperfused during cataplexy. These data suggest that cataplexy is an overactive neuronal state, involving cortical and subcortical areas that are specific to the attacks and not activated between episodes. Although our patient was hypocretin deficient, a condition specifically causing cataplexy, we did not detect any change of perfusion in the hypothalamic area during cataplexy. This suggests that the episode of cataplexy itself is not directly related to an activation of any hypothalamic system downstream from the hypocretin neurons.

Because narcolepsy is caused by a major disorganization of sleep and especially REM sleep, cataplexy is seen as an intrusion of REM-sleep phenomena into wakefulness. However, cataplexy differs from typical REM sleep in many aspects. Waking and a low-voltage EEG are maintained during short cataplectic attacks. We believe this was also the case in our patient, although EEG was not monitored during the cataplexy, because the patient was conscious, remembered everything that had been said around her during the cataplexy, and did not experience additional hallucinations. Human REM sleep, when compared with wakefulness using functional brain imaging, is characterized by activation of the thalami, extrastriate visual and limbic cortex area (including amygdaloid complexes and anterior cingulate cortex), whereas associative areas of the frontal and parietal cortex are less active than other parts of the brain. According to our data, cataplexy appears as an intermediate stage between normal REM sleep and normal wakefulness. We did not find any hyperperfusion in the thalami, and the amygdaloid complexes, but we did find an activation of some cortical areas, including cingulate cortex, orbitofrontal cortex, and right putamen that are activated during REM sleep, whereas others (right temporal cortex) are not.

Another striking characteristic of human REM sleep is the predominant right-hemisphere activation, as shown by SPECT imaging and spectral EEG analysis. Our data, obtained from a right-handed patient, suggest that the right hemisphere, as during REM sleep, is more activated during cataplexy than is the left hemisphere.

We cannot be certain that all the functional changes observed in this patient are only related to the loss of muscle tone. Even if this particular cataplexy was not directly triggered by an emotion, one may imagine that being suddenly paralyzed may itself induce uncontrollable emotional changes. However, the patient had been used to experiencing cataplexy for more than 50 years and had been in status cataplecticus for several days, suggesting that she had become emotionally less sensitive during the episodes. The functional activation profile of emotionally triggered cataplexy might be different and was not explored here.

**ACKNOWLEDGMENTS**

The study was funded by Assistance Publique - Hôpitaux de Paris and the INSERM AVENIR program.
REFERENCES


