Cataplexy Emotional Trigger Questionnaire (CETQ) – A Brief Patient Screen to Identify Cataplexy in Patients With Narcolepsy

Wendy R. Moore, R.N.1,2; Michael H. Silber, M.B.Ch.B.1,3; Paul A. Decker, M.S.1; Patricia C. Heim-Penokie, R.N.1,2; Vicki K. Sikkink, R.N.1,2; Nancy Slocumb1; Jarrett W. Richardson, M.D.1,4; Lois E. Krahn, M.D.1,5

1Sleep Disorders Center, 2Department of Nursing, 3Department of Neurology, 4Division of Biostatistics, and 5Department of Psychiatry and Psychology, Mayo Clinic College of Medicine Rochester, MN; 6Department of Psychiatry and Psychology and 7Division of Pulmonary Medicine, Mayo Clinic College of Medicine, Scottsdale, AZ

Study Objectives: This pilot study explored the sensitivity and specificity of a brief survey to determine the presence of cataplexy. We hypothesized that the brief questionnaire could provide a quick, sensitive, and specific screening tool to identify those patients with cataplexy, which would result in more timely referrals for further diagnostic testing.

Design: The pilot study utilized a brief questionnaire that was developed by including 5 questions that were found to be strong positive predictors of cataplexy from a previous 51-item cataplexy questionnaire.

Setting: Participants with a laboratory-confirmed diagnosis completed the questionnaire via mail correspondence or at the time of scheduled appointments in the Mayo Clinic Sleep Disorder Center, Rochester, Minn.

Participants: Seventy-eight patients with narcolepsy and cataplexy and 78 patients with obstructive sleep apnea completed the questionnaire.

Interventions: NA.

Measurements and Results: The sensitivity, specificity, area under the curve, positive predictive value, and negative predictive value were computed for each question individually, along with appropriate 95% confidence intervals.

Conclusions: The first item of the cataplexy emotional trigger questionnaire (CETQ) discriminates patients with cataplexy from controls with excellent sensitivity and specificity. The addition of the other 4 questions, in the context of question 1, did not improve specificity, area under the curve, positive predictive value, or negative predictive value but did provide useful confirmatory data. Thus, a single question provides a brief practical tool that could improve the recognition of cataplexy in the clinical setting. Depending on the circumstance, users may be interested in utilizing 1 or all 5 questions.

Keywords: Cataplexy, narcolepsy, screen, diagnosis.


Narcolepsy is a chronic sleep disorder with a prevalence of about 1 in 2000 and an onset usually in the second decade of life.1 The symptoms include excessive daytime sleepiness, cataplexy, sleep paralysis, and disturbed nocturnal sleep with vivid dreams.2 Diagnosis of this disorder can be problematic due to the nonspecific nature of many of these primary symptoms. Diagnosis is often delayed by 10 years or more from the onset of symptoms, which prolongs the experience of disabling symptoms and consequences of the disorder.3

Cataplexy is the only highly specific symptom of the disorder in patients with narcolepsy with cataplexy. It is defined as sudden loss of bilateral muscle tone associated with areflexia that is usually provoked by strong emotions that are generally but not always positive, such as laughter and elation.2 Levels of hypocretin-1, also known as orexin A, in the cerebrospinal fluid are substantially decreased in patients with narcolepsy with cataplexy, compared with levels of patients with narcolepsy without cataplexy and control subjects with other neurologic disorders.4 Although hypocretin-1 levels in the cerebrospinal fluid are highly sensitive and specific for a diagnosis of narcolepsy with cataplexy, the test is invasive, and the assay not widely available. The standard test for narcolepsy with and without cataplexy, the Multiple Sleep Latency Test, is time consuming and expensive to perform and requires meticulous attention to details, such as discontinuation of certain medications and exclusion of other confounding sleep disorders. Confirming the presence of cataplexy by observing an event and documenting reversible areflexia is highly supportive of the diagnosis, but spontaneous cataplexy rarely occurs in a physician’s presence. Attempting to trigger an event using a standardized procedure, such as exposure to surprise and humor, is possible but is challenging and unreliable in routine clinical practice. A validated cataplexy questionnaire could facilitate identification and verification of cataplexy, thus providing more-accurate screening of sleepy patients who need to undergo further expensive, complex, or invasive testing.

Because cataplexy most often occurs outside the laboratory setting, the diagnosis is usually based on patient report. The Stanford Narcolepsy Sleep Inventory is a long 146-item questionnaire divided into 9 sections; section V contains 51 questions...
regarding cataplexy. In 1 study, these questions were administered to 983 patients with a variety of sleep disorders entering the Stanford Sleep Disorder Clinic. Of these, 63 were determined to have clear-cut cataplexy by the sleep specialist, and the other 920 patients served as control subjects without narcolepsy. The researchers determined that positive emotions, such as laughter, elation, and joking, were common triggers of cataplexy. Receiver operating curve analysis indicated that telling and hearing a joke, anger, and laughter were the 3 triggers most likely to differentiate clear-cut cataplexy.

The present study was designed as an extension of our previous study “Characterizing the emotions that trigger cataplexy,” in which we used a modified version of the published 51-item cataplexy questionnaire that had been validated by Anic-Labat. We found laughter to be the trigger most likely to provoke cataplexy. Physical signs of a cataplexy episode were examined as well. Two of these features, slurred speech and ability to hear, were the strongest predictors.

The CETQ (Cataplexy Emotional Trigger Questionnaire) was developed to aid patient comprehension and included questions based on lifetime experience of these symptoms. Positive predictive value (PPV) and negative predictive value (NPV) were estimated for each question.

**METHODS**

This study was reviewed and approved by the Mayo Clinic Institutional Review Board and completed in the Mayo Sleep Disorders Center. Patients with potential narcolepsy were screened by a physician investigator (MHS) to ensure that they met Mayo diagnostic criteria for laboratory-confirmed narcolepsy with cataplexy. The control group comprised patients with obstructive sleep apnea syndrome (OSA), diagnosed by polysonography using the International Classification of Sleep Disorders criteria. We excluded patients with history of seizure disorders or dementia. Patients either were enrolled at the time of office visits or were mailed the questionnaire with a letter of invitation to participate. The questionnaire (Figure) consisted of 1 item that required a yes or no response followed by 4 follow-up questions if the first question was answered affirmatively.

The sample-size calculation for this study was based on a 95% exact binomial confidence interval. Assuming a sensitivity and specificity of 95% and 75 patients per group, the width of each 2-sided 95% exact binomial confidence interval would be approximately 12%. Sensitivity, specificity, and the area under the receiver-operating characteristic curve (AUC) were computed individually for each question. Ninety-five percent confidence
Table 1—Diagnostic Results

<table>
<thead>
<tr>
<th></th>
<th>Cataplex (n = 78)</th>
<th>Control (n = 78)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>73 (94%)</td>
<td>1 (1%)</td>
<td>0.94 (0.86, 0.98)</td>
<td>0.99 (0.93, 1.0)</td>
<td>0.96 (0.93, 0.99)</td>
</tr>
<tr>
<td>Q2</td>
<td>70 (90%)</td>
<td>1 (1%)</td>
<td>0.90 (0.81, 0.95)</td>
<td>0.99 (0.93, 1.0)</td>
<td>0.94 (0.91, 0.98)</td>
</tr>
<tr>
<td>Q3</td>
<td>58 (74%)</td>
<td>1 (1%)</td>
<td>0.74 (0.63, 0.84)</td>
<td>0.99 (0.93, 1.0)</td>
<td>0.87 (0.82, 0.92)</td>
</tr>
<tr>
<td>Q4</td>
<td>64 (82%)</td>
<td>1 (1%)</td>
<td>0.82 (0.72, 0.90)</td>
<td>0.99 (0.93, 1.0)</td>
<td>0.90 (0.86, 0.95)</td>
</tr>
<tr>
<td>Q5</td>
<td>68 (87%)</td>
<td>0 (0%)</td>
<td>0.87 (0.78, 0.94)</td>
<td>1.00 (0.95, 1.0)</td>
<td>0.94 (0.90, 0.97)</td>
</tr>
</tbody>
</table>

CI refers to confidence interval; AUC, area under curve; Q1-Q5, questions 1-5.

Table 2—Positive and Negative Predictive Values*  

<table>
<thead>
<tr>
<th></th>
<th>Cataplex (n = 78)</th>
<th>Control (n = 78)</th>
<th>Prevalence</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>73 (94%)</td>
<td>1 (1%)</td>
<td>0.05</td>
<td>0.79 (0.55, 1.0)</td>
<td>1.00 (0.95, 1.0)</td>
</tr>
<tr>
<td>Q2</td>
<td>70 (90%)</td>
<td>1 (1%)</td>
<td>0.05</td>
<td>0.79 (0.54, 1.0)</td>
<td>0.99 (0.93, 1.0)</td>
</tr>
<tr>
<td>Q3</td>
<td>58 (74%)</td>
<td>1 (1%)</td>
<td>0.05</td>
<td>0.75 (0.49, 1.0)</td>
<td>0.99 (0.98, 0.99)</td>
</tr>
<tr>
<td>Q4</td>
<td>64 (82%)</td>
<td>1 (1%)</td>
<td>0.05</td>
<td>0.77 (0.52, 1.0)</td>
<td>0.99 (0.99, 0.99)</td>
</tr>
<tr>
<td>Q5</td>
<td>68 (87%)</td>
<td>0 (0%)</td>
<td>0.05</td>
<td>1.00 (1.0, 1.0)</td>
<td>0.99 (0.99, 1.0)</td>
</tr>
</tbody>
</table>

CI refers to confidence interval; PPV, positive predicted value; NPV, negative predicted value; Q1-Q5, questions 1-5.

*Prevalence = .05.

intervals were calculated for sensitivity and specificity using the exact binomial distribution. For AUC, the method described by Delong et al was used to calculate the standard error for calculating the 95% confidence interval. Assuming cataplexy prevalence is 0.05 in a tertiary sleep disorder center, the PPV and NPV were estimated individually for each question. Confidence intervals for PPV and NPV were computed using the bootstrap. If a participant responded no to question 1, responses to questions 2-5 were set to no. Patient characteristics were compared using the 2-sample rank sum test for continuous variables and the χ² test for categorical variables. In all cases, 2-sided tests with p values ≤ .050 were considered statistically significant.

RESULTS

There were 156 subjects who completed the questionnaire, 78 with narcolepsy and cataplexy and 78 with OSA. The mean age of subjects with narcolepsy and cataplexy was 53.5 ± 18.4 (range 20-84) years old compared with 58.8 ± 10.7 (range 33-85) years old for control subjects (p = .158). There were 45 women (58%) in the narcolepsy with cataplexy group and 28 women (36%) in the OSA group (p = .006). Twenty-six of the narcolepsy with cataplexy subjects (33%) had testing for hypocretin-1 levels in the OSA group (p = .006). Of 53 subjects who had narcolepsy with cataplexy who had undergone HLA testing, 45 (85%) were positive for HLA DQB1*0602. Of these 45 subjects, 1 (2%) answered yes to question 1. Table 3 summarizes the findings in these subjects with apparent false-negative or -positive results. Laughter was not listed as a precipitant emotion for any of the subjects with false-negative responses. The single control subject with a false positive denied any symptoms of cataplexy at a sleep consultation. None of the 6 subjects had been tested for hypocretin-1 levels in the cerebrospinal fluid.

DISCUSSION

The most significant finding is that a practical cataplexy screen will enhance recognition of cataplexy in a sleep-center setting. The questionnaire discriminated patients with cataplexy from controls with excellent specificity and sensitivity. Unlike previously published cataplexy questionnaires, in which usage is limited due to the length of the survey, this survey has the potential to be more widely used because of its brevity. The practical screening questions from this survey can easily be incorporated into clinical practice, as well as into more-general screening sleep questionnaires. Another important finding of the study was the fact that our nonnarcoleptic control group did not demonstrate the high rate of cataplexy-like symptoms that has been reported in previous studies.6,10,-12 This finding suggests that the questionnaire differentiates definite cataplexy from other nonspecific forms of muscle weakness that have been found in previous epidemiologic
studies and the Stanford Narcolepsy Sleep Inventory. This strength of this study is related to the design. It was validated with patients who have a confirmed laboratory-based diagnosis of narcolepsy with cataplexy. This project used a different statistical approach from those used in previous papers. No other screen for cataplexy to date has been validated in terms of PPV/NPV. The PPV/PPN concept, which is familiar to many clinicians, readily conveys the precision of this screening instrument.

The pilot nature of the study with recruitment restricted to patients already seen in a sleep center contributes to the study’s limitations. The study protocol precluded enrollment of a larger more-diverse patient population with undiagnosed sleep disorders. The survey has not yet been tested with patients other than those with OSA or narcolepsy with cataplexy. Prior to embarking on a study with much larger sample size (including patients with undiagnosed narcolepsy), we wished to assess the validity of the questionnaire, affirming that the questions discriminated between patients with narcolepsy with cataplexy (not naïve to cataplexy) and patients with other sleep disorders (OSA naïve to cataplexy). Patients with narcolepsy with cataplexy vary in their own awareness of cataplexy, depending on the severity of symptoms, frequency of triggers, and duration of disease, as well as their level of education about narcolepsy. Additional studies need to be conducted with larger sample sizes of patients with and without undiagnosed cataplexy to further demonstrate the effectiveness of a brief screening tool. To recruit a sufficient number of patients with narcolepsy with cataplexy prior to a diagnosis, a multicenter study may be necessary.

Asking patients who have never had cataplexy about this unusual experience is difficult. Those patients sometimes have difficulty understanding the description of cataplexy explaining that these symptoms were unfamiliar to them. Patients without cataplexy could have potentially misinterpreted the described muscle weakness and attributed these symptoms to other conditions. However, based on the data, it does not appear that this occurred because the number of false positives in the OSA control group was very low. The single patient with OSA who responded positively to the question has not been determined to have any symptoms of narcolepsy based on sleep-center consultation. Patients with narcolepsy with cataplexy did not appear to have difficulty comprehending the survey’s depiction of cataplexy. The study had sex differences between the cataplexy and control group. This is not unexpected, given the higher prevalence of OSA in men versus women.

Enigmatic patients with atypical cataplexy will remain challenging, and, for those patients, surveys are not particularly helpful. This subset of patients will continue to require careful assessment by clinicians with considerable experience with narcoleptic patients. Nonetheless, if this tool improves or advances the recognition of patients with classic cataplexy, this study creates a needed new diagnostic tool.

Narcolepsy identification, research, and clinical interventions continue to be challenging. Having brief but reliable tools that can be used in patients with undifferentiated diagnoses in a sleep disorder center, specialty practice (neurology, psychiatry, pulmonary), and primary care is critical to reduce the rate of underdiagnosis of narcolepsy. Once the patient endorses items on a questionnaire suggestive of cataplexy, the expense and logistics of laboratory testing are more justified.

ACKNOWLEDGMENTS

This study was funded by the Department of Psychiatry and Psychology, Mayo Clinic College of Medicine, Rochester, Minn, and supported by Piscopo Funds of Mayo Clinic.

REFERENCES