NARCOLEPSY IS CHARACTERIZED by a complaint of excessive daytime sleepiness and symptoms of abnormal REM sleep (cataplexy, sleep paralysis, hypnagogic hallucinations). In the United States and many European countries, excessive daytime sleepiness is confirmed using a multiple sleep latency test (MSLT), while differential diagnoses are excluded using nocturnal polysomnography. If nocturnal polysomnography rules out any other possible cause for excessive daytime sleepiness, an MSLT with two or more sleep onset REM periods and a short mean sleep latency is considered diagnostic of narcolepsy, even in the absence of cataplexy.

Cataplexy has long been considered the most predictive feature of the overall syndrome. It has been defined as a “sudden and bilateral loss of postural muscle tone in association with intense emotion.” It is the second most common symptom reported by narcoleptic patients, after excessive daytime sleepiness. Narcoleptic patients with cataplexy more frequently present ancillary symptoms, such as hypnagogic hallucinations, sleep paralysis, disturbed nocturnal sleep, sleep-onset REM periods, and daytime napping, and have more accidents. In a recent study, a positive history of cataplexy was found to be a better discriminant for narcolepsy than two or more sleep-onset REM periods, although most patients with cataplexy displayed multiple sleep onset REM periods. It is rarely, if ever, found in non-narcoleptic subjects, except in young patients, when cataplexy is the first symptom of the disorder.

Validation of a Cataplexy Questionnaire in 983 Sleep-disorders Patients

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Summary: Our goal was to validate a self-administered narcolepsy questionnaire focusing on cataplexy. Nine hundred and eighty three consecutive subjects entering the Stanford Sleep Disorder Clinic completed the questionnaire. Clinic physicians reported on the presence or absence of “clear-cut” cataplexy. Responses to 51 cataplexy-related questionnaire items were compared between subjects with clear-cut cataplexy (n=63) and all other patients (n=920). As previously reported, a large portion of the non-narcoleptic population was found to experience muscle weakness with various intense emotions (1.8% to 18.0%) or athletic activities (26.2% to 28.8%). Factor analysis and Receiver Operating Characteristic Curve (ROC) analysis were used to determine the most predictive items for clear-cut cataplexy. Most strikingly, cataplexy was best differentiated from other types of muscle weakness when triggered by only three typical situations: “when hearing and telling a joke,” “while laughing,” or “when angry.” Face or neck, rather than limbs, were also more specifically involved in clear-cut cataplexy. Other items, such as length of attacks, bilaterality, and alteration in consciousness, were poorly predictive. A simple decision tree was constructed to isolate high-(91.7%) and low-(0.6%) risk groups for cataplexy. This questionnaire will be used to increase diagnostic consistency across clinical centers, thus providing more homogenous subject pools for clinical and basic research studies.

Key words: Cataplexy; diagnostic criteria; narcolepsy, sleep disorders
Cataplexy is defined by its triggers—Anic-Labat et al. excitation and anger—are also frequently involved. Common triggering factor, but other emotions—such as negative patients was looked for. Japanese authors pos- suggested an appropriate explanation for the HLA-DR2 and/or HLA-DQ1 association with narcolepsy, an approach that narcolepsy might be a homogenous nosologic entity. The finding that narcolepsy-cataplexy was tightly associated with HLA-DR2 in 1983–1984 confirmed the notion that narcolepsy might be a homogenous nosologic entity. A possible autoimmune pathogenesis has been proposed for narcolepsy but has never been confirmed. Among several hundred Japanese and Caucasian patients with cataplexy, 95% to 100% were both HLA-DR2- and HLA-DQ1-positive. More recently, HLA class II typing techniques became more sophisticated, and subtyping was made possible at the genetic level, thus identifying HLA-DRB1*1501 (HLA-DR2) and HLA-DQB1*0602 (HLA-DQ1) in all Caucasian and Japanese narcoleptic patients with HLA-DR2, HLA-DQ1. Although initially HLA typing looked very promising as a diagnostic tool, later studies have indicated that it cannot be used reliably for clinical purposes. The most specific marker for narcolepsy across ethnic groups, HLA-DQB1*0602, is present in 24% to 28% of the general population while a few typical non-Japanese patients with narcolepsy-cataplexy do not display this marker.

Ever since the discovery of an almost-complete association of HLA-DR2, HLA-DQ1 with narcolepsy, an appropriate explanation for the HLA-DR2 and/or HLA-DQ1 negative patients was looked for. Japanese authors postulated that the reason might be inclusion of noncataplectic subjects in non-Japanese studies. HLA association was the highest when cataplexy, rather than any other manifestations of the narcoleptic syndrome, was considered the prerequisite for inclusion in the study. Association between DQB1*0602 and narcolepsy is very tight across ethnic groups when narcolepsy is clinically defined by the presence of clear-cut cataplexy. This result again confirms the notion that narcolepsy-cataplexy is a more homogenous nosologic entity than narcolepsy without cataplexy.

In spite of its importance for the diagnosis of narcolepsy, the definition of cataplexy ("sudden and bilateral loss of postural muscle tone in association with intense emotion") is poorly codified. Cataplexy is rarely observed in a single office visit, and even if it does occur, it is often partial and unnoticeable except to the trained physician. The presence of cataplexy is usually subjectively determined by interpreting the patient report. In many cases when cataplexy is mild or triggered by unusual emotions, it is difficult to decide whether patients' description of muscle weakness reflect genuine cataplectic episodes or physiological muscle weaknesses associated with intense laughter or athletic activity. In a recent epidemiological study, 6.5% of the population reported experiencing "sudden and abrupt feeling of weakness" in association with laughter or other emotions.

In this study, a 146-item inventory was administered to narcoleptic and non-narcoleptic patients entering the Stanford Sleep Disorder Clinic. Our goal was to develop and validate a self-administered questionnaire that could be used to screen for the presence of definite cataplexy.

SUBJECTS AND METHODS

Subjects and Overall Experimental Design

Subjects were patients referred to the Stanford Sleep Disorders Clinic from October 1993 to December 1996. All (n=1108) patients so referred filled out the Stanford Sleep Inventory and signed an informed consent in the waiting room, or mailed these back after the initial clinical interview (for a few very young subjects, the questionnaire was completed by parents). The study has been approved by the Stanford University panel on human subjects in medical research and conformed to the Declaration of Helsinki. A Clinical Summary Sheet requesting information on the presence of cataplexy was completed by the sleep specialist, after the clinical interview, blinded to the inventory responses. Nine hundred and eighty three subjects who had completed both the Stanford Sleep Inventory and the Clinical Summary Sheet were included in the analysis.

Evaluation of Cataplexy by Questionnaire

The Stanford Center for Narcolepsy Sleep Inventory is a 146 item questionnaire divided into nine sections. Sections I and II report demographic information (date and place of birth, sex, ethnicity). The Epworth Sleepiness Scale is included in section III. Section IV includes various questions on sleep habits (usual bed and lights-off...
1-21. Do you currently experience, or have you ever experienced, episodes of muscle weakness in your legs and/or buckling of your knees during the following situations (YES or NO)?

1. When you laugh
2. When you sneeze
3. When you are excited
4. When you are surprised
5. When you remember a happy moment
6. When you remember an emotional event
7. When you are required to make a quick verbal response in a playful or funny context (e.g., a witty repartee)
8. When you are embarrassed

22. Please write in the space below the number(s) corresponding to the two situations from the list above (1-21) which are most frequently associated with muscle weakness in your legs and/or buckling of your knees. For example, if you most often experience muscle weakness in your legs or buckling of your knees when telling a joke or when surprised, please record your response as 19, 4.

Please use the same format for answering questions 24, 25, 26, 28, 29:

23. Which statement best describes these episodes of muscle weakness in your legs and/or knees?

- the muscle weakness always affects both knees/legs
- the muscle weakness always affects only one knee/leg
- the muscle weakness may affect either one or both knees/legs

24. Have you ever experienced a sagging or dropping of your jaw during any of the above situations (1-21, YES or NO)?
   If YES, write in the space below the number(s) corresponding to the two situations from the list above (1-21) which are most frequently associated with a sagging or dropping of your jaw.

25. Have you ever experienced an abrupt dropping of your head and/or shoulders during any of the above situations (1-21, YES or NO)?
   If YES, write in the space below the number(s) corresponding to the two situations from the list above (1-21) which are most frequently associated with an abrupt dropping of your head and/or shoulders.

If you responded NO to all of the above questions about muscle weakness (1-29), please skip to next section.

30. If you responded YES to any of the above questions (1-29), please list below the 3 situations (1-21) which are the most likely to trigger an episode of muscle weakness affecting any muscle(s) in your body and give an example of an episode of muscle weakness which you have experienced during each of these situations.

   a. ______ (situation most likely to be associated with an episode of muscle weakness)

   b. ______ (situation second most likely) Example: __________

   c. ______ (situation third most likely) Example: __________

31. How long does the muscle weakness or paralysis usually last?

   - 5 seconds-30 seconds
   - 30 seconds-2 minutes
   - 2 minutes-10 minutes
   - More than 10 minutes

32. How frequently do you experience one of these episodes of muscle weakness?

   - Once or more per day
   - Several times per week
   - Once per week
   - Once per month
   - Once per year or less

Figure 1.—Cataplexy section of the Stanford Center for Narcolepsy sleep inventory.
For questions 33–41, please check the response which best applies to your episodes of muscle weakness.

33. During the episodes of muscle weakness, can you hear?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

34. During the episodes of muscle weakness, can you see?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

35. During the episodes of muscle weakness, is your vision blurred?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

36. During the episodes of muscle weakness, do you dream?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

37. During the episodes of muscle weakness, do you fall asleep?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

38. During the episodes of muscle weakness, do you lose control of your bladder (lose urine)?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

39. During the episodes of muscle weakness, do you lose control of your bowels?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

40. During the episodes of muscle weakness, do you faint?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

41. During the episodes of muscle weakness, do you have time to sit down or hold onto something to break a fall?
   ___ always
   ___ sometimes
   ___ rarely
   ___ never
   ___ not sure

42. How old were you the first time you experienced one of these episodes of muscle weakness?
   ____________ years

43. Did the episodes of muscle weakness peak at a certain age (YES/NO)?
   If NO, please go to question 45.

44. If YES, at what age? ____________ years

45. How long ago was your last episode of muscle weakness?
   ___ within the past 24 hours
   ___ within the past week
   ___ within the past month
   ___ within the past year
   ___ more than a year ago

46. If you no longer experience these episodes of muscle weakness, how old were you when they stopped?
   ____________ years

47. If you no longer experience these episodes of muscle weakness, please explain why you believe that they stopped.

48. Have you ever been injured or nearly injured during an episode of muscle weakness, or have you suffered any other kind of serious consequence as a result of an episode of muscle weakness (YES/NO)?
   If YES, please describe.

49. Have any of these episodes of muscle weakness ever been observed by another person (YES/NO)
   ___ member of your family
   ___ friend
   ___ acquaintance
   ___ physician
   ___ stranger
   (check all that apply)

50. Listed below are medications which may be used to treat episodes of muscle weakness or other sleep problems. Please complete the table for all medications listed, including the effect of each medication which you have used on your muscle weakness. Please use the blank spaces to add any medications not listed in the table which you have used for your muscle weakness, or to add any medications taken for other medical conditions which have affected your muscle weakness.

   - Amphetamine
   - Methamphetamine (Desoxyn)
   - Methylphenidate (Ritalin)
   - Pemoline (Cyrlert)
   - Clomipramine (Anafranil)
   - Protriptyline (Vivactil)
   - Imipramine (Tofranil)
   - Desipramine (Desyrel)
   - Fluoxetine (Prozac)
   - Other (specify)

51. If any of the above medications improved your episodes of muscle weakness and you later stopped taking them, please list below each discontinued medication that was helpful and reason for discontinuing.
time, wake-up time), insomnia (subjective sleep latency after lights-off, past and present difficulty falling asleep, number of sleep interruptions during a typical night’s sleep, longest duration of nighttime awakening), obstructive sleep apnea syndrome (refreshed feeling upon waking, restless sleep, excessive sweating, snoring [self- or partner-reported, regular or irregular], breathing interruptions), abnormal movements during sleep (muscle twitches, leg kicking), excessive sleepiness (presence, age of onset, evolution, evaluation by a physician), napping (presence, length, frequency association with dreaming and refreshing effect on sleepiness). Section V contains 51 items on cataplexy and was the main focus of this analysis (reported in detail in Fig. 1). Sections VI, VII, and VIII include 18, 14 and 10 items on hypnagogic hallucinations, sleep paralysis, and automatic behavior respectively. Section IX offers an opportunity to the patient to give any other remarks of importance that might not already be mentioned in the questionnaire. These last four sections were not analyzed in this study.

Clinical Evaluation of Sleep Disorders and Cataplexy

After completing patient evaluations, physicians were asked to review all available medical documentation (medical history, polysomnography and MSLT results, follow-up) and to complete a Clinical Summary Sheet, a two-page form asking about the presence or absence of excessive daytime sleepiness, cataplexy, hypnagogic/hypnopompic hallucinations, and sleep paralysis (past and present). The International Classification of Sleep Disorders was used by all clinicians for diagnostic assignment, with the possibility of also assigning a diagnosis of upper airway resistance syndrome. Additional questions on cataplexy were also asked in order to define this symptom as (1) “clear-cut,” when the symptom was typical both qualitatively and in terms of triggering stimuli; (2) “atypical-doubtful”; or (3) totally absent. Information on final diagnosis on primary and associated sleep/medical disorders was also requested.

HLA Typing

HLA typing results were available in 53 of the clear-cut cataplexy subjects, all of them with a diagnosis of narcolepsy. HLA-DQB1*0602 was determined at Stanford University as previously reported.

Statistical Analysis

Subjects were divided into two groups: patients with clear-cut cataplexy vs others. A trigger for cataplexy (for example, laughter) was considered positive whenever a patient indicated any type of muscle weakness (legs, jaw, head, arms, speech, complete) following this trigger (see questionnaire, Fig. 1). A specific type of attack (for example, jaw-dropping) was considered present whenever reported with any trigger. Responses to questions were compared between the two groups, using either $\chi^2$ / Fisher’s F for categorical responses, or Student’s $t$ / Mann-Whitney U for ordinal responses.

Questions pertaining to cataplexy triggers and localization of the attacks were further analyzed using Principal Component Analysis and Receiver Operating Characteristic Curves. Principal Component Analysis was first used to explore whether specific emotional triggers and types of attacks clustered into a set of components. Factor scores, developed using varimax rotation with eigenvalues higher than one, were also included in analysis. After estimating specificity and sensitivity for each individual questionnaire item and each factor identified by factor analysis, Receiver Operating Characteristic Curves were drawn to select the smallest and most predictive sets of questions determining clear-cut cataplexy. These questions were used to establish a decision tree to be used to define clear-cut cataplexy. Finally, clinical files were reviewed in outlier patients belonging to the two groups of subjects with highest and lowest risk to explore possible reasons for misclassification.

RESULTS

Diagnostic Categories Explored in this Study

Nine hundred and eighty three patients (639 men), mostly Caucasians (n=797) completed the study, ranging from 1 to 92 years of age (mean±SEM: 48.32±0.50). Including all primary, secondary and tertiary (when applicable) sleep disorder diagnoses listed in the clinical summary sheet, the diagnostic breakdown was as follows: obstructive sleep apnea syndrome (n=648), periodic limb movement syndrome (n=121), insomnia (n=96), upper airway resistance syndrome (n=85), narcolepsy (n=74), primary snoring (n=37), circadian rhythm sleep disorders (delayed sleep phase syndrome, jet lag, shift work, irregular sleep-wake cycle) (n=30), insufficient sleep syndrome and inadequate sleep hygiene (n=22), restless legs syndrome (n=16), idiopathic hypersomnia (n=11), and parasomnias (sleep terrors, sleepwalking, REM sleep behavior disorder, bruxism) (n=9).

Patients were divided into two groups on the basis of presence or absence of clear-cut cataplexy. Out of 983 patients who completed study, 63 (mean age 46.21±2.09; 28 men; 58 Caucasian), had clear-cut cataplexy. All were given a diagnosis of narcolepsy. Nine hundred and twenty subjects (mean age 48.47±0.52; 611 men, $p<0.05$ vs clear-cut cataplexy; 901 Caucasian, $p<0.05$ vs clear-cut cataplexy), had no (n=891) or doubtful (n=29) cataplexy. These 920 subjects were given primary, secondary and/or
tertiary diagnoses of narcolepsy (n=11), other sleep disorders (n=1127), or no sleep-related diagnosis (n=32).

A comparison of the items explored by section III and IV of the sleep inventory indicated that patients with clear-cut cataplexy were significantly sleepier than all other subjects. Epworth Sleepiness Scale values were significantly higher in subjects with clear-cut cataplexy (mean values: 17.84±0.52 vs 10.57±0.19 in other subjects, p<0.0001). Almost all subjects with clear-cut cataplexy (93.7%, n=59) also reported difficulties staying awake during the day, vs 54.0% (n=497) in all other subjects (p<0.0001). Napping was also more prevalent [84.1% (n=53) vs 53.5% (n=492), p<0.0001] and frequent (9.37±1.43 naps per week vs 2.66±0.17 p<0.0001) in clear-cut cataplectic subjects. Interestingly however, naps were not reported to be more refreshing in clear-cut cataplectic subjects when compared to other subjects [61.9% (n=39) vs 45.4% (n=418)]. Nocturnal sleep habits were not significantly different (timing of bedtime and lights-out), but cataplectic patients reported significantly shorter subjective sleep latencies (9.93±4.90 vs 23.46±1.41 minutes, p<0.001) and less difficulties falling asleep at night currently [9.5% (n=6) vs 31.0% (n=285), p<0.001] or ever [44.4% (n=28) vs 64.9% (n=597), p<0.001]. Consistent with the existence of sleep fragmentation in narcoleptic subjects, cataplectic patients reported waking up more frequently during the night (4.04±0.49 vs 2.55±0.08 times per night, p<0.001) but did not report increased difficulties sleeping at night [34.9% (n=22) vs 34.5% (n=317)].

Episodes of muscle weakness are frequently reported in non-narcoleptic subjects.—Subjects without a diagnosis of narcolepsy (n=909, all subjects except narcoleptic (n=74) with clear-cut cataplexy (n=63) and without or with doubtful cataplexy (n=11)) frequently (45.7%, n=416) reported muscle weakness with various emotions or athletic activities. These subjects, mostly with obstructive sleep apnea syndrome or other diagnoses, reported muscle weakness with all of the investigated triggers: not only after (28.8%), or during (26.2%) athletic activities, but also with stress (18.0%), tension (16.0%), or startle (15.5%), during sexual intercourse (14.2%), with anger (13.8%), when surprised (13.2%), excited (12.6%), or laughing (12.0%), when remembering an emotional event (11.4%), when being moved by something emotional (11.1%), when embarrassed (10.7%), when required to make a quick verbal response in a playful or funny context (eg, witty repartee) (9.7%), when playing an exciting game (9.7%), while having a romantic thought or moment (8.1%), when disciplining children (7.5%), when elated (7.4%) or remembering a happy moment (7.3%), or when telling or hearing a joke (1.8%). In most cases, the reported muscle weakness affected the lower limbs (34.4%), and less commonly led to dropping objects from hands or weakness in arms (16.5%),

<table>
<thead>
<tr>
<th>Questionnaire Item</th>
<th>Clear-cut Cataplexy</th>
<th>Non-clear-cut Cataplexy</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle weakness triggers:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you laugh</td>
<td>87.3% (55/63)</td>
<td>12.0% (108/903)</td>
<td>50.6****</td>
</tr>
<tr>
<td>When you are angry</td>
<td>68.3% (43/63)</td>
<td>13.8% (125/904)</td>
<td>13.4****</td>
</tr>
<tr>
<td>When you are excited</td>
<td>65.6% (40/61)</td>
<td>12.6% (112/906)</td>
<td>13.5****</td>
</tr>
<tr>
<td>When you are surprised</td>
<td>58.1% (36/62)</td>
<td>13.2% (119/903)</td>
<td>9.1****</td>
</tr>
<tr>
<td>When you remember a happy moment</td>
<td>36.7% (22/60)</td>
<td>7.3% (66/903)</td>
<td>7.3****</td>
</tr>
<tr>
<td>When you remember an emotional event</td>
<td>50.0% (30/60)</td>
<td>11.4% (103/904)</td>
<td>7.8****</td>
</tr>
<tr>
<td>When you are required to make a quick verbal response in a playful or funny context</td>
<td>64.0% (39/61)</td>
<td>9.7% (87/900)</td>
<td>16.6****</td>
</tr>
<tr>
<td>When you are embarrassed</td>
<td>32.8% (20/61)</td>
<td>10.7% (97/902)</td>
<td>4.1****</td>
</tr>
<tr>
<td>When you discipline children</td>
<td>45.0% (27/60)</td>
<td>7.5% (67/987)</td>
<td>10.1****</td>
</tr>
<tr>
<td>During sexual intercourse</td>
<td>22.4% (13/58)</td>
<td>14.2% (126/889)</td>
<td>1.7</td>
</tr>
<tr>
<td>During athletic activities</td>
<td>39.3% (24/61)</td>
<td>26.2% (235/896)</td>
<td>1.8*</td>
</tr>
<tr>
<td>After athletic activities</td>
<td>26.2% (16/61)</td>
<td>28.8% (258/895)</td>
<td>0.9</td>
</tr>
<tr>
<td>When you are elated</td>
<td>48.3% (29/60)</td>
<td>7.4% (66/980)</td>
<td>11.7****</td>
</tr>
<tr>
<td>When you are stressed</td>
<td>54.1% (33/62)</td>
<td>18% (163/904)</td>
<td>5.4****</td>
</tr>
<tr>
<td>When you are startled</td>
<td>50.0% (30/60)</td>
<td>15.5% (140/902)</td>
<td>5.4****</td>
</tr>
<tr>
<td>When you are tense</td>
<td>33.3% (20/60)</td>
<td>16% (144/902)</td>
<td>2.6***</td>
</tr>
<tr>
<td>While you are playing an exciting game</td>
<td>48.3% (29/60)</td>
<td>9.7% (87/986)</td>
<td>8.7****</td>
</tr>
<tr>
<td>When you have a romantic thought or moment</td>
<td>19.7% (12/61)</td>
<td>8.1% (73/901)</td>
<td>2.8**</td>
</tr>
<tr>
<td>When you tell or hear a joke</td>
<td>73.3% (44/60)</td>
<td>1.8% (16/900)</td>
<td>151.9****</td>
</tr>
<tr>
<td>When you are moved by something emotional</td>
<td>53.5% (31/58)</td>
<td>11.1% (100/900)</td>
<td>9.2****</td>
</tr>
<tr>
<td>Type of attacks:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle weakness in legs and/or buckling of your knees</td>
<td>98.4% (62/63)</td>
<td>34.4% (316/919)</td>
<td>102.1****</td>
</tr>
<tr>
<td>always bilateral</td>
<td>81.0% (47/58)</td>
<td>53.7% (167/311)</td>
<td>8.0****</td>
</tr>
<tr>
<td>Sagging or dropping of your jaw</td>
<td>83.6% (51/61)</td>
<td>7.5% (64/856)</td>
<td>63.1****</td>
</tr>
<tr>
<td>Dropping of your head and/or shoulders</td>
<td>77.4% (48/62)</td>
<td>6.2% (53/855)</td>
<td>51.9****</td>
</tr>
<tr>
<td>Dropped objects from your hand or felt weakness in your arms</td>
<td>85.7% (54/63)</td>
<td>16.5% (141/854)</td>
<td>36.3****</td>
</tr>
<tr>
<td>always bilateral</td>
<td>68.0% (34/50)</td>
<td>36.0% (67/186)</td>
<td>3.8***</td>
</tr>
<tr>
<td>Slurring of your speech</td>
<td>73.8% (45/61)</td>
<td>11.3% (93/823)</td>
<td>22.1****</td>
</tr>
<tr>
<td>Fallen to the ground and found yourself unable to move</td>
<td>53.9% (34/63)</td>
<td>3.5% (29/865)</td>
<td>33.8****</td>
</tr>
<tr>
<td>Others:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injured during cataplectic attacks</td>
<td>32.8% (20/61)</td>
<td>12.7% (35/275)</td>
<td>3.3***</td>
</tr>
<tr>
<td>Cataplexy observed by another person</td>
<td>81.7% (49/60)</td>
<td>48.5% (133/274)</td>
<td>4.7****</td>
</tr>
</tbody>
</table>

Cataplexy is defined by its triggers—Anic-Labat et al
Cataplexy is defined by its triggers—Anic-Labat et al

Cataplexy was most commonly triggered by “positive” emotions such as joking, laughing and elation in patients with clear-cut cataplexy.—Answers to questions regarding triggers of episodes of muscle weakness were compiled for all types of attacks (from questions 1 to 29 in Fig. 1). An activity or an emotion was considered an effective trigger if it induced any type of muscle attack reported in the questionnaire. Triggering situations were then compared by \( \chi^2 \) for narcoleptic patients with clear-cut cataplexy vs other subjects (Table 1). Significant differences were found for all triggers, except for muscle weakness after and during athletic activities. The three most discriminative triggers were positive emotions associated with joking, laughing, and elation.

Cataplexy manifests more specifically in the face and the jaw in patients with clear-cut cataplexy.—Answers to questions regarding types of cataplectic attacks were compiled for every trigger (from questions 1 to 29, Fig. 1). A specific type of attack (legs/knees, head/shoulders, hands/arms, slurred speech or complete attacks) was considered present when reported after any trigger. Chi-squared comparisons and odds ratios between clear-cut cataplexy and other subjects are listed in Table 1. In both groups, episodes of muscle weakness were most commonly reported in the legs and knees. The most discriminative attacks were found to be those affecting the face and/or the jaw. We also asked questions regarding the bilaterality of muscle weakness episodes in arms and legs (Fig. 1) but found only marginally significant differences between groups (Table 1).

The most commonly reported situations inducing cataplexy in patients with clear-cut cataplexy were laughing and anger.—Subjects were asked to list the three most common situations causing episodes of muscle weakness affecting any muscle (question 30, Fig. 1). Triggers listed either as the first or as the three most common were ranked in clear-cut cataplectic patients and all other subjects for comparison. Triggers were mentioned as being the most frequent in the following order: laughing (32.7%), anger (12.7%), quick verbal response (7.3%), and telling or hearing a joke (7.3%) while the pattern of response in the noncataplectic group was as follows: during athletic activities (8.5%), after athletic activities (4.2%), or when stressed (3.8%). Triggers were cited as being one of the three most frequent in the following order: laughing (53.8%), anger (36.1%), telling or hearing a joke (32.3%), excitement (18.3%), and stress (16.4%) in the cataplexy group, and during athletic activities (14.6%), after athletic activities (13.0%), stress (10.3%), anger (5.9%), tension (4.7%), and startled (4.1%) in other subjects.

Other Clinical Features Associated with Clear-cut Cataplexy

Duration, frequency, and associated features for reported episodes of muscle weakness (questions 31 to 41 in Fig. 1) were ranked and ranks were compared using the Mann-Whitney U test. A significant difference between clear-cut cataplexy vs all others was found for length (longer attacks in subjects without clear-cut cataplexy, p<0.003) and frequency of episodes (more frequent attacks in subjects with clear-cut cataplexy, p<0.001), visual involvement (cataplectic subjects had more often blurred vision, p<0.0001 and were less able to see during cataplexy than other subjects, p<0.0001), age of onset (23.42±1.49 vs 30.37±1.05 p<0.003 for cataplexy vs other), for peaking at certain age (% reporting yes, p<0.001), for when the last episode was experienced (p<0.0001), for being injured during an episode (p<0.001), and for episodes being witnessed by another person (p<0.0001).

Factor analysis for types of attacks did not identify any significant factor.—Factor analysis reduced the set of six questions regarding types of cataplexy (legs, jaw, head, speech, arms) to a single factor.

Factor analysis suggest the existence of three clusters of triggering factors for muscle weakness in the overall sample.—Factor analysis reduced the set of 20 questions regarding cataplexy triggers to three factors. The first factor showed highest values of rotated loadings for triggers previously described as “positive emotions” and explained 26.9% of the variance: telling or hearing a joke (0.82), feeling elated (0.76), remembering a happy moment (0.75), making a quick verbal response in a playful or funny context (eg, witty repartee) (0.73), laughing (0.72), and playing an exciting game (0.69). All other triggers were less than 0.62. The second factor grouped questions dealing with athletic and sexual activities and explained 10.9% of the variance: during (0.87) and after (0.88) athletic activities, or during sexual intercourse (0.50); all other factors less than 0.32. The third factor grouped questions describing generally “negative emotions,” and explained 19.5% of the variance: when stressed (0.73), startled (0.68), tense (0.67), surprised (0.65), embarrassed (0.63), or angry (0.58). All other factors less than 0.49.

Clear-cut cataplexy was best differentiated by the factor associated with positive emotions.—The mean values for each factor were compared between subjects with clear-cut cataplexy and other patients. Factor 1 was the most discriminating factor (mean±SEM: 0.57±0.04 vs 0.02±0.01, p<0.0001), followed by factor 3 (mean±SEM: 0.46±0.11 vs 0.05±0.02, p<0.0001). Factor 2 more poorly differentiated between the two groups (mean±SEM: 0.28±0.01 vs 0.16±0.01, p=0.0014). These differences were not very different from those obtained with many individual question responses (Table 1). We also did step-wise logistic regression analysis with all individual ques-
Do you currently experience, or have you ever experienced episodes of muscle weakness in the legs and/or buckling of your knees when you...

Have you ever experienced a sagging or drooping of your jaw when you...

Have you ever experienced an abrupt dropping of your head and/or shoulders when you...

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Tell or hear a joke?

NO

YES

925/983

risk=73.3%

40/983

risk=32.5%

25/983

risk=45.8%

36/983

risk=91.7%

882/983

risk=90.6%

40/983

risk=32.5%

25/983

risk=45.8%

36/983

risk=91.7%

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HLA-DQB1*0602 Typing Results

HLA-DQB1*0602 positivity in 59 clear-cut cataplectic patients was 89.8%. HLA-DQB1*0602 typing in groups generated by the decision tree ranged between 84.6% and 100%, but sample size in each group was too small to draw any conclusion (Fig. 2).

Further analysis of the results obtained with the proposed decision tree suggests that some patients may have been misclassified. In the highest-risk group, thirty-six subjects answered “yes” both to hearing and telling a joke and laughing, 33 of whom were clear-cut cataplectic narcoleptic patients. Clinical data on the three additional “non-clear-cut cataplexy” subjects was verified by analyzing their medical records. In one case, narcolepsy and cataplexy had been reported for more than 20 years, but the patient was consulting for an associated breathing disorder. The clinical interview focused on abnormal breathing/continuous positive airway pressure titration during sleep, and the referring physician rated cataplexy as atypical and/or doubtful after noting the presence of narcolepsy-cataplexy in the chart. Further review of the chart indicated that cataplexy was typical, affected all muscle groups, and occurred at least once per week mostly while joking or during other emotions. In the second case, the patient had severe obstructive sleep apnea and cataplexy, was rated atypical/doubtful in the clinical summary sheet, with the mention “weakness in the knees with startled response.” A review of the clinical chart did not show discussion of any narcolepsy symptoms. The questionnaire did not mention examples of cataplectic attacks and did not report sleep paralysis or hypnagogic hallucinations, but did report some automatic behavior. The third patient, an obese man, had severe obstructive sleep apnea syndrome and daytime sleepiness. He had been prescribed CPAP but never came back for a follow-up. No examples of cataplexy were given in the questionnaire, but the patient reported some sleep paralysis and convincing episodes of hypnagogic hallucinations and automatic behavior. Narcolepsy symptoms were not discussed/reported in the clinical chart and our attempts to contact him by phone were unsuccessful.
Five narcoleptic patients with clear-cut cataplexy were classified as not experiencing muscle weakness when joking or laughing. One case, a 16-year-old boy who was treated with fluoxetine and whose cataplexy was manifested by slurred speech, provided a partially filled out questionnaire; he did not mention any triggers. The second case, a teacher treated with fluoxetine, reported muscle weakness only in his legs when he was stressed or tense. The only example given was: “During periods of continuous stress and sometimes while giving a lecture.” In the third case, cataplexy was triggered by anger, stress/tension and emotional events and manifested only in the knees. It occurred once per year or less but had been treated with protryptiline with reported efficacy in the past. In the fourth case, cataplexy manifested as weakness in the knees and jaw when angry, embarrassed, surprise, stressed and startled. It occurred once per week. Examples given included repressed anger, attempt at repartee in an angry context, evocation of loss of socioprofessional status, argument with spouse. Dextroamphetamine had some effect at high doses while desipramine did not help. The last patient was a woman experiencing cataplexy as dropping of her head, slurred speech or dropping objects from hands. Triggers were not listed for any of these attacks. Two specific examples detailed in question 30 (Fig.1) said: “When I am laughing sometimes I lose control and my head will nod” and “once my daughter was dancing on a coffee table like a go go dancer. I started laughing and my head dropped.” She would have been included in another group if she had filled out the questionnaire correctly.

**DISCUSSION**

A questionnaire focusing on cataplexy, a cardinal symptom of the sleep disorder narcolepsy, was developed and validated. Nine hundred and eighty three consecutive sleep disorders patients, 63 of whom were determined to have definite cataplexy, were asked to complete the questionnaire. The goal of this study was to develop an instrument that could differentiate genuine cataplexy from physiologic muscle weakness in the general population.

One of the most surprising findings of this study was the high prevalence of cataplexy-like symptoms in non-narcoleptic subjects. Forty-six percent of the 905 non-narcoleptic subjects reported episodes of muscle weakness, mostly in the context of athletic activities (26.2% to 28.8%), but also while tense or stressed (16.0% to 18.0%), or while experiencing various emotions (1.8% to 15.5%). This finding is in agreement with previous epidemiological studies performed in Europe and Japan. In a recent epidemiologic study performed in a twin registry, 29.3% of the general Finnish population was reported to experience a “feeling of weakness in the limb in association with emotions,” while 6.5% responded positively to the question “have you ever had a sudden and abrupt feeling of weakness in both arms and legs when laughing, feeling delighted or angry, or in exciting situations?” Previous studies in Finland, France, and Japan had reported similarly high rate of cataplexy-like symptoms (7.6% to 20%) in the general population. This observation thus emphasized the need for defining cataplexy in clinical practice and research more precisely.

Many items were found to significantly differentiate definite cataplexy from other nonspecific episodes of muscle weakness (Table 1). The most significant differences were observed for triggers and anatomical localization of the attack. Genuine cataplectic attacks were generally triggered by positive emotions, mostly laughing and joking. Anger, the second most frequent trigger for cataplexy in narcoleptic patients, was the only negative emotion that was helpful in differentiating both groups. This trigger is usually considered important to diagnose cataplexy clinically but it is important to note that when anger was the only triggering emotion for cataplexy, it was not sufficient to establish clear-cut cataplexy. Indeed, 13.8% of the non-narcoleptic population reported muscle weakness while angry. Similarly, attacks triggered by stress or fear, or observed in the context of athletic or sexual activities, were the least specific and should probably not be considered cataplexy if reported in isolation.

Attacks affecting facial or nuchal muscles were also observed more specifically in patients with clear-cut cataplexy. As previously reported, episodes such as jaw dropping, facial flickering or head dropping may be the most characteristic cataplectic attacks. This finding may be a qualitative difference or might be secondary to the fact that episodes of muscle weakness were more severe in patients with definite cataplexy. Patients with clear-cut cataplexy generally reported more frequent attacks and, thus, may have more opportunities to report various types of muscle weakness episodes. Similarly, patients were more frequently injured during attacks and episodes were more frequently observed by others in the clear-cut cataplexy group (Table 1), an indirect reflection of severity.

A comparison of various other qualitative features generally reported to be typical of cataplexy was rather disappointing. Bilaterality of the attacks, for example, did not strongly differentiate clear-cut cataplexy and physiological muscle weakness. Muscle weakness was reported always in both limbs in 68.0% to 81.0% of cataplectic subjects vs 36.0% to 53.7% of controls experiencing cataplectic-like episodes (Table 1). Similarly, genuine cataplectic attacks were generally briefer than other episodes of muscle weakness, but this difference did not distinguish well between the two groups. Finally, responses to various other items reporting on associated symptoms, consciousness, and the ability to perceive surroundings during cataplexy showed...
few differences between groups. The finding that genuine cataplexy was more frequently associated with visual symptoms was the only interesting finding, but this has been reported previously.14,15

Factor analysis and Receiver Operating Characteristics Curve analysis led to the conclusion that three items were sufficient to distinguish cataplexy from other nonspecific episodes of muscle weakness in most cases. The decision tree leading to the best risk values is depicted in Fig. 2. The first most informative question was to ask if muscle weakness is experienced while hearing or telling a joke. Seventy-three percent of patients who answered “yes” to this question had definite cataplexy, while only 1.7% of the subjects who answered “no” were narcoleptic patients with clear-cut cataplexy. Risk was increased to 91.7% if patients experienced muscle weakness both while telling and hearing a joke and when angry. Subjects with the lowest risk (0.6%) where those who answered “no” to both telling or hearing a joke and when laughing (Fig. 2). It is, however, important to emphasize that the highest-risk group only included 33 out of 63 cataplectic patients, and thus excluded roughly 50% of the subjects with clear-cut cataplexy; most of the other patients did experience cataplexy with either laughing but not while hearing or telling a joke, or while hearing or telling a joke, but not when angry (Fig. 2). A more sensitive cutoff point might thus be selected by excluding subjects who do not experience cataplexy when either laughing or hearing and telling a joke. This would lead to the inclusion of 92.1% (52.4%+19.0%+20.6%) of subjects with clear-cut cataplexy and only 4.6% (0.3%+1.4%+2.9%) of non-clear-cut cataplectic subjects.

This questionnaire was primarily developed to provide a simple and objective way to establish presence of clear-cut cataplexy across various clinical settings without the intervention of a sleep disorder specialist. For research studies in genetics, where disease homogeneity is most important, a restrictive definition of cataplexy to patients experiencing this symptom only when muscle weakness is reported when hearing or telling a joke and while angry might be a conservative but reliable method for patient selection. In epidemiologic studies, these questions could also be used to estimate the prevalence of narcolepsy-cataplexy. Only 2 of 909 (0.2%) subjects without apparent narcolepsy but with obstructive sleep apnea syndrome answered positively to both of these questions (these two subjects could not be recontacted for further examination).

Further studies examining HLA association patterns in various subgroups of subjects with different combinations of answers using the questionnaire are warranted in a larger patient population. This would not only validate the procedure proposed, but also help select genetically homogenous populations of narcoleptic patients with cataplexy.

**ACKNOWLEDGMENTS**

This study was supported by grant NIH 23724 to E. Mignot. The authors thank Drs. A. Clerk, D. Katzenberg, C. Kushida, R. Pelayo, A. Robinson, and R. Smith for assistance in scoring the Clinical Summary Sheet for their patients, and N. Puckett-Carter, C. Won and J. Yoo for assistance in the project. Financial support was provided by NIH grant NS 23724. Authors have no direct or indirect financial interest in connection to this study.

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