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A standardized test to document cataplexy

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ABSTRACT

Objective/Background: Cataplexy is the pathognomonic symptom of narcolepsy type 1 (NT1). Since it is considered difficult to be directly observed or documented by clinicians, its diagnosis relies mainly on history taking. Our study aimed at testing the feasibility of a standardized video recording procedure under emotional stimulation to document cataplexy in the diagnostic work-up of suspected hypersomnia of central origin.

Patients/Methods: Two-hundred-eight consecutive patients underwent the diagnostic work-up and reached the final diagnosis of NT1 (n = 133), idiopathic hypersomnia or narcolepsy type 2 (IH/NT2 group, n = 33), or subjective excessive daytime sleepiness (sEDS group, n = 42). All subjects underwent a standardized video recording procedure while watching funny movies selected according to individual preferences, and a technician blind to clinical features reviewed the recordings to identify hypotonic phenomena that were finally confirmed by patients.

Results: The video recording under emotional stimulation captured hypotonic phenomena in 72.2%, 9.1% and 4.8% of NT1, IH/NT2, and sEDS subjects ($p < 0.0001$), respectively. When tested against CSF hypocretin deficiency, the documentation of a hypotonic episode at the test showed an area under the ROC curve of 0.823 ± 0.033 ($p < 0.0001$). NT1 patients under anticataplectic medications showed less frequently hypotonic episodes than untreated ones (48.0% vs 77.8%, $p = 0.003$).

Conclusions: A standardized video recording procedure under emotional stimulation can help in the characterization of suspected hypersomnia of central origin. Further multi-center studies are warranted to extend the present findings and integrate a shared procedure for the laboratory work-up of narcolepsy.

1. Introduction

Narcolepsy type 1 (NT1) is clinically characterized by excessive daytime sleepiness (EDS), cataplexy (ie occurrence of muscle atonia during wakefulness triggered by emotions), sleep-related paralyses/hallucinations, and disrupted nocturnal sleep [1]. NT1 is a chronic lifelong disorder that frequently arises in childhood or adolescence and has a severe impact on daytime functioning and social life. Cataplexy is pathognomonic for NT1 and should be carefully differentiated from other causes of episodic fall/collapse such as epilepsy, conversion disorders, neuromuscular disorders, drop attacks, by addressing attacks phenomenology and precipitating circumstances. While some objective tests such as electroencephalography and video-polygraphy may help the clinician in this differential diagnosis [2], the current criteria clearly state that "patients are rarely examined during an attack of cataplexy" and thus cataplexy "needs to be established based on the clinical interview alone" [3]. Surprisingly, NT1 patients often go unrecognized by different medical specialists, including pediatricians, general practitioners, neurologists, psychiatrists, with the disorder correctly identified several years after symptoms onset [4–6]. In Italy, thanks to widespread media and website awareness campaigns promoted by patients associations (https://www.narcolessia.org/), patients (or patients' families) often self recognize their symptoms, thus unraveling the medical inability to identify also cataplexy. Moreover, the classical definition of cataplexy as "brief, symmetrical sudden loss of muscle tone with

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retained consciousness precipitated by strong, usually positive, emotions" has been recently enriched by the description of a new phenotype in children close to disease onset. Indeed, in young NT1 patients cataplexy largely affects facial muscles with ptosis, mouth opening and tongue protrusion obvious in the absence of emotional triggers ("cataplectic facies"), associated with a complex array of active movements, and further enhanced by emotions [7,8]. Over time this phenotype gradually turns into the classical picture of transient weakness exclusively evoked by emotions [9]. Therefore, the inappropriate medical capability to hypothesize, address, and diagnose cataplexy may be the result of an outdated phenomenon definition and of scarce attention to its documentation.

The currently available and world-wide used neurophysiological narcolepsy marker is the occurrence of sleep onset REM periods (SOREMPs) in the Multiple Sleep Latency Test (MSLT) [3]. SOREMPs are however shared by NT1, narcolepsy type 2 (NT2) and other phenotypes such as insufficient sleep syndrome, albeit recent studies disclosed intriguing differences in the sleep onset profile that need further validation in larger epidemiological studies [10,11]. Only reduced/absent levels of hypocretin in the cerebrospinal fluid (CSF) are the biological disease fingerprint making NT1 "the hypocretin deficiency syndrome" [3]. However, CSF hypocretin measurement is not widely available in clinical practice given the need of an invasive procedure (lumbar puncture) and of a laboratory able to perform CSF hypocretin assay. Therefore, the development of an objective approach to document cataplexy would be an important help to clinicians in the differential diagnosis of both central disorders of hypersomnolence and episodic falls.

Cataplexy documentation requires a standardized and reproducible procedure including a patient-tailored approach to identify individual triggers maximally able to evoke cataplexy and to increase patients' comfort as long as patients maximally experience cataplexy when feeling comfortable and "at home" [12]. In recent years we have made several attempts to document cataplexy in NT1 patients in order to investigate its motor, neurophysiological and autonomic features [13,7,2,8,9,14]. With this study we aimed at applying a simple standardized approach to video record cataplexy in a consecutive series of subjects evaluated for suspected hypersomnia in order to verify the feasibility and reliability of systematic cataplexy testing.

2. Materials and methods

2.1. Patients

Subjects were patients evaluated at the Outpatient Clinic for Narcolepsy of the University of Bologna for a subjective complaint of chronic (ie lasting at least three months) sleepiness and who consecutively underwent hospitalization between September 2014 and February 2017 for suspected central disorder of hypersomnolence (CDH, n = 224) or for polysomnographic re-evaluation under pharmacological treatment (n = 25).

At hospitalization patients underwent the following systematic procedures: first, clinical interview on symptoms, including the systematic administration of questionnaires on sleepiness (Epworth Sleepiness Scale) [15]; second, a standardized procedure to document cataplexy in the sleep laboratory (see below); third, 48-h continuous polysomnographic recording [16], followed by a MSLT with five nap opportunities [17]; fourth, and lumbar puncture and blood drawn whenever possible to assess CSF hypocretin-1 levels and human leukocyte antigen (HLA) typing. The test for cataplexy was the first laboratory procedure performed during hospitalization to minimize the risk of bias.

According to current international criteria [3], 208 patients received a final diagnosis of CDH, including NT1 (n = 133, 25 under treatment and 108 at first evaluation in drug naïve condition), NT2 or idiopathic hypersomnia (IH/NT2, n = 33), or subjective EDS when all neurophysiological investigations were normal (sEDS, n = 42). For the purposes of the study NT2 and IH patients were grouped together because they share objective hypersomnia in the absence of cataplexy, and NT1 was distinguished from NT2 on the basis of CSF hypocretin levels that was available in all ambiguous cases. Moreover, 41 patients received the following non-CDH diagnoses: circadian rhythms sleep disorder (n = 6), periodic limb movement disorder (n = 4), secondary narcolepsy (n = 3), functional neurological disorder (n = 12), narcolepsy associated with mutations of the DNA methyltransferase-1 gene – DNMT1 (n = 8) [18], and insufficient sleep syndrome (n = 8).

The study was approved by the local ethic committee, and all subjects signed a written informed consent. Patients with a final diagnosis of CDH (n = 166) and of sEDS (n = 42) were included in the study.

2.2. Procedure

Based on previous experiences [13,7,2,8,9,14], we progressively refined the approach to cataplexy in the laboratory setting. Recording patients while standing-up to study cataplexy proved dangerous [7,2], so we chose to keep the patient seated on a chair with vertical back and without armrests to avoid any interference with potential head-drops (backward and lateral) or falls of the upper limbs during cataplexy. Then, the patient's framing was shifted from the whole body to the face and trunk, since in the whole body scene the modifications of facial expressions were poorly detailed [8,9]. To increase individual comfort and emotional enhancement by proxy, a parent was allowed to stay with her/his child during the recording, while we left adults alone. All patients were also reassured that in case of an attack or malaise, the technician staff who was monitoring the procedure would immediately assist them and interrupt the test. Over the years a library of videos (lasting from 5 to 10 m) that most successfully elicited cataplexy was collected including cartoons (for children), sketches from comedy shows, and fragments of famous Italian funny movies [8,9]. Finally, to minimize the influence of sleepiness on the procedure and to increase comfort, the test was performed in the early morning (9–10 am) with daylight illumination, and patients were asked if a brief nap or the use of the toilet was required before the start of the test.

The laboratory procedure was standardized as follows. First, patients underwent a semi-structured interview on cataplexy performed by our technician staff blind to clinical features. The interview included questions on the following items: lifetime experience of transient weakness (ranging from subjective sensations to postural collapse) with preserved consciousness; relation of these phenomena with emotional triggers (none, mostly, always); triggering role of a series of situations (laughing, telling a joke, anger, surprise, unexpected meeting); current frequency of the phenomenon; duration of most episodes (absence, <10s, between 10s and 2 m, between 2 m and 10 m, >10 m); presence of a defined pattern and involvement of specific body areas (face, neck, knees, arms); and duration of the return of muscle function (absence, <10s, between 10s and 2 m, between 2 m and 10 m, >10 m). Second, patients were freely interviewed about their humor preferences and asked to identify cartoons, movies, comedies or sketches that could most probably evoke an attack. After the interview, our technician staff searched on internet the individually identified movies to be used together with (or instead of) the available library of videos to have up to 30 min of emotional stimulation tailored on individual preferences.

The procedure was then performed in the sleep laboratory under continuous video recording using the camera of the standard

polysomnographic equipment, thus allowing online remote monitoring from the control room. The patient was seated on a chair and had at a fixed distance of 1.5 m from his eyes a 21.5 inches computer monitor placed at his/her eyesight horizontal level (Supplemental Fig. 1). The video camera zoomed the face and trunk (waist up frame) of the patient, and the recording was online monitored by the technician staff. Before starting the test, the patient was informed that the test would last up to maximum 35–40 min, but that he/she could freely ask to interrupt it whenever he/she wanted in case of sleepiness or malaise.

At test initiation, the patient was instructed to seat in a comfortable position on the chair, to look in front of him/herself watching the computer monitor. For the first five min, the patient was recorded in the absence of any emotional stimulation (baseline condition). Afterwards, the technician staff periodically entered to play the previously identified videos for up to 30 min in order to guarantee and adapt to individual preferences the triggers (under emotional stimulation condition). The technician staff was also instructed to interrupt the test in the following circumstances: first, the patient was unable to continuously watch videos because of manifest sleepiness (dozing-off); second, the patient was not even smiling during different emotional stimuli and, while the technician staff entered to change the videos, confirmed being bored by the situation; third, a sudden and prolonged (lasting more than a minute) generalized cataplectic attack occurred; or fourth, laughing excitedly induced a "crescendo" of cataplectic attacks of progressively increased duration and body involvement potentially leading to dangerous body collapse. In the third and fourth case the technician staff was instructed to immediately enter the laboratory room, to interrupt emotional stimulation, to assist the patient avoiding injuries, and to call the medical staff to examine patients during attacks. During the whole recording the technician staff noted the occurrence of the following phenomena: laughing; laughing excitedly; ptosis; mouth opening; head drops; and trunk falls. At the end of the recording, the patient was asked if he/she experienced excited laughter as well as weakness sensations or motor phenomena comparable to those reported at pre-test interview, and afterwards one or few representative segments of the video recording were shown to the subject (or to the parent in case of children) to confirm the temporal link between the subjective weakness sensations and the occurrence of motor manifestations.

Immediately after the test, the technician staff reviewed the whole video recording and systematically evaluated the following elements: successful elicitation of laughter and of excited laughter; number (and duration) of head drops; number (and duration) of trunk falls; occurrence (on a Likert scale: zero, none; one, minimal; two, frequent; three, subcontinuous) of head drops, trunk falls, ptosis, and mouth opening separately in the baseline and the under emotional stimulation conditions; need to precociously interrupt the test for sleepiness; and overall documentation, as confirmed by the subjects, of the phenomena comparable to those reported at the interview.

2.3. Statistical analysis

Clinical and test data were explored by means of descriptive statistics as appropriate for continuous (mean ± standard deviation) and categorical (frequency percent) variables in the different patients groups and were contrasted by means of non-parametric approaches (Kruskal–Wallis and Mann Whitney tests, Chi Square test) followed by correction for multiple comparisons for each block of data. Comparisons were performed considering the following different patients groups: NT1, IH and sEDS; and NT1 with and without anticataplectic treatment. A receiver operating curve analysis was used to define the diagnostic value of the test against hypocretin deficiency in the whole population, and a Pearson correlation coefficient analysis was used to study the relation between self reported cataplexy frequency and tests results in NT1. A p-value <0.05 was considered statistically significant.

3. Results

3.1. Subjects: clinical data and self reported cataplexy features

Clinical data of different patients groups are reported in Table 1. The three groups had comparable age and sex distribution at evaluation, and NT1 patients had a trend towards earlier symptoms onset and most frequently complained of possible cataplexy, sleep paralyses, hypnagogic hallucinations and disturbed nocturnal sleep. NT1 patients also showed more severe subjective and objective sleepiness, most frequently carried the HLA-DQB1*0602, and had lowest cerebrospinal hypocretin levels as per diagnostic criteria (available in 22/42 sEDS, 27/33 IH-NT2, and 125/133 NT1 subjects). Subjects were drug free at evaluation (drug naive or after drug withdrawal of at least three weeks), excluding 25 NT1 patients (18.8% of the group) who were re-evaluated under anticataplectic treatment with sodium oxybate and/or venlafaxine.

Self-reported cataplexy features of different patients groups are reported in Table 1. NT1 patients reported more frequent cataplexy occurrence and described their attacks as muscle weakness sensation with twitches, slurred speech, having a definite pattern with involvement of facial, neck, knees and upper limb districts more frequently (ranging from 56% to 89%) than the IH/NT2 (ranging from 12% to 18%) and the sEDS (ranging from 2% to 14%) groups. NT1 patients also reported a closer association of the phenomena with emotional triggers, and more frequently experienced transient weakness during laughter, jokes, anger, surprise and unexpected meetings (ranging from 40% to 95%) than the IH/NT2 (ranging from 6% to 18%) and the sEDS (ranging from 2% to 10%) groups. Both duration of the attacks and subsequent return of muscle strength were reported as more brief in NT1 than in the other groups. Overall, NT1 patients more commonly reported qualitative attacks features that were more rarely but similarly experienced also by IH/NT2 patients and sEDS subjects in up to 18% and 14% of cases respectively.

A between groups analysis performed excluding NT1 patients with anticataplectic treatment showed analogous results (data not shown).

3.2. Results of the test: relation to patients diagnosis

The test was interrupted for occurrence of sleepiness only in 7% of NT1 patients. Emotional stimulation successfully induced laughter (up to 100%) and excited laughter (up 73%) without significant between groups differences. NT1 patients had more head drops that the other groups and were the only ones showing atonic trunk falls. Semi-quantitative assessment of head drops, trunk falls, ptosis, and mouth openings at baseline did not show statistically significant between groups differences, despite the clear trend towards higher values in NT1. Conversely, emotional stimulation unmasked clear differences with NT1 patients showing more head drops, trunk falls, ptosis, and mouth openings than the other groups (Table 2).

The overall procedure, as confirmed by post-test subjects interviews, was able to capture a meaningful episode in 72%, 9%, and 5% of NT1, IH/NT2 and sEDS subjects ($p < 0.0001$). A between groups analysis performed excluding NT1 patients with anticataplectic treatment showed comparable results, with the additional evidence of increased baseline mouth opening in NT1 (uncorrected p value of 0.038, not significant after multiple comparisons correction; data not shown).

Table 1
Clinical data and self reported cataplexy features of the explored population.

Clinical features	sEDS (n = 42)	IH/NT2 (n = 33)	NT1 (n = 133)	p-Value	Corrected p-Value
	M ± SD or %	M ± SD or %	M ± SD or %		
Age (years)	25.31 ± 14.95	31.76 ± 14.82	28.08 ± 17.82	0.117	n.s.
Male sex (%)	38.10	48.50	52.60	0.259	n.s.
Age at onset (years)	19.00 ± 11.75	23.11 ± 16.54	16.71 ± 12.42	0.048	n.s.
Time from onset (years)	8.40 ± 6.69	9.68 ± 9.46	11.62 ± 11.21	0.580	n.s.
ESS score	7.12 ± 5.72	10.33 ± 6.36	17.04 ± 3.95	0.000	0.000
MSLT—mean sleep latency (min)	15.65 ± 3.82	9.41 ± 4.44	4.19 ± 3.88	0.000	0.000
MSLT – SOREMPs (n)	0.18 ± 0.46	0.84 ± 1.19	3.77 ± 1.50	0.000	0.000
Cerebrospinal Hypocretin-1 (pg/mL)	341.93 ± 56.16	322.45 ± 40.64	28.15 ± 48.76	0.000	0.000
HLA-DQB1*0602 (%)	8.70	10.00	97.70	0.000	0.000
Ongoing anticataplectic treatment (%)	0.00	0.00	18.80	N.A.	N.A.
Possible cataplexy (%)	16.70	27.30	98.50	0.000	0.000
Sleep paralysis complaint (%)	11.90	24.20	62.40	0.000	0.000
Hypnagogic hallucinations (%)	14.30	9.10	58.60	0.000	0.000
Disturbed nocturnal sleep (%)	21.40	48.50	77.40	0.000	0.000
Self-reported cataplexy features					
Current frequency of possible cataplexy (%)				0.000	0.000
<1/y	100	100	0.00		
1/y-1/m	0	0	0.80		
1/m-1w	0	0	0.80		
1/w-1/d	0	0	48.10		
>1/d	0	0	50.40		
Motor pattern					
Described as “muscle weakness” (%)	14.3	15.6	88.00	0.000	0.000
Presence of twitches (%)	2.4	12.1	56.40	0.000	0.000
Slurred speech (%)	9.5	15.2	77.40	0.000	0.000
Presence of a defined pattern (%)	7.1	12.1	70.70	0.000	0.000
Facial involvement (%)	9.5	12.1	88.70	0.000	0.000
Head/Neck involvement (%)	2.4	12.1	84.20	0.000	0.000
Knees involvement (%)	9.5	18.1	87.20	0.000	0.000
Upper limbs involvement (%)	7.1	18.2	71.40	0.000	0.000
Role of emotional triggers					
Relation to emotional triggers				0.000	0.000
None	85.7	78.8	1.50		
Mostly	9.5	3	20.30		
Always	4.8	18.2	78.20		
Triggered by laughter	7.1	15.2	95.50	0.000	0.000
Triggered by jokes	2.4	6.1	68.40	0.000	0.000
Triggered by anger	9.5	18.2	54.90	0.000	0.000
Triggered by surprise	9.5	9.1	39.80	0.000	0.000
Triggered by unexpected meetings	4.8	6.1	45.00	0.000	0.000
Attack duration				0.000	0.000
No attacks	85.7	78.8	1.50		
<10s	7.1	12.1	69.20		
10s–2m	4.8	9.1	24.80		
2 m–10 m	0	0	3.80		
>10 m	2.4	0	0.80		
Duration of muscle function return				0.000	0.000
Immediate	83.3	78.8	1.50		
<10s	11.9	15.2	83.30		
10s-2m	2.4	6.1	14.40		
>10 m	2.4	0	0.80		

When analyzing the subgroup of subjects with available cerebrospinal hypocretin-1 measurement, the detection of a meaningful episode at the test showed an area under the ROC curve of 0.823 ± 0.033 ($p < 0.0001$) towards the prediction of hypocretin deficiency (i.e. levels below 110 pg/mL detected in 124 of 125 NT1 patients) (Fig. 1). The test had therefore a sensitivity of 73% and a specificity of 92% against the biological marker of cataplexy. Similar results were obtained also excluding NT1 patients with ongoing anticataplectic treatment (area under the ROC curve of 0.854 ± 0.033, $p < 0.0001$).

3.3. Relation of the test to self-reported cataplexy frequency and to current anticataplectic treatment in NT1 patients.

Clinical, self-reported and test data of NT1 patients without and with anticataplectic treatment are reported in Table 3. Untreated patients had shorter disease duration and a trend towards lower hypocretin-1 levels, data not significant after multiple comparisons correction, while all other clinical and neurophysiological data were comparable. None of self-reported cataplexy features, including current frequency, differed between the two groups.

During the test, untreated patients had more frequent and prolonged head drops, the latter finding losing statistical significance at multiple comparison correction. Semi-quantitative assessment showed more head drops, ptosis, and mouth openings under emotional stimulation in untreated vs treated NT1 patients, but these results lost significance at multiple comparisons correction. While untreated patients trended to laugh more frequently than treated ones, the occurrence of excited laughter was comparable between the two groups. The overall test was able to document a meaningful cataplexy episode in 78% versus 48% (corrected $p = 0.048$) of untreated and treated NT1 patients.

Table 2
Results of the test in the different patients groups.

Test data	sEDS	IH/NT2	NT1	p-Value	Corrected p-Value
Motor phenomena	M ± SD or %	M ± SD or %	M ± SD or %		
Head drops (n)	0.07 ± 0.46	0.27 ± 1.15	7.14 ± 10.96	0.000	0.000
Head drops duration (sec)	0.00 ± 0.00	0.09 ± 0.38	7.15 ± 73.99	0.000	0.000
Trunk falls (n)			1.20 ± 0.42		
Trunk falls duration (sec)	0.00 ± 0.00	0.00 ± 0.00	8.10 ± 74.30	0.053	n.s.
Baseline head drop (0–3)	0.00 ± 0.00	0.03 ± 0.17	0.03 ± 0.17	0.525	n.s.
Triggered head drop (0–3)	0.02 ± 0.15	0.06 ± 0.24	0.95 ± 0.97	0.000	0.000
Baseline trunk falls (0–3)	0.00 ± 0.00	0.00 ± 0.00	0.01 ± 0.09	0.754	n.s.
Triggered trunk falls (0–3)	0.00 ± 0.00	0.00 ± 0.00	0.47 ± 0.68	0.000	0.000
Baseline ptosis (0–3)	0.00 ± 0.00	0.03 ± 0.17	0.09 ± 0.29	0.078	n.s.
Triggered ptosis (0–3)	0.02 ± 0.15	0.15 ± 0.36	1.12 ± 0.95	0.000	0.000
Baseline mouth opening (0–3)	0.00 ± 0.00	0.00 ± 0.00	0.08 ± 0.26	0.052	n.s.
Triggered mouth opening (0–3)	0.00 ± 0.00	0.06 ± 0.24	0.78 ± 0.92	0.000	0.000
Test evaluation					
Interruption of the test for dozing off (%)	0.00	0.00	6.80	0.070	n.s.
Laughter (%)	95.20	100.00	91.70	0.193	n.s.
Excited laughter (%)	69.00	72.70	61.70	0.403	n.s.
Overall episode documentation (%)	4.80	9.10	72.20	0.000	0.000

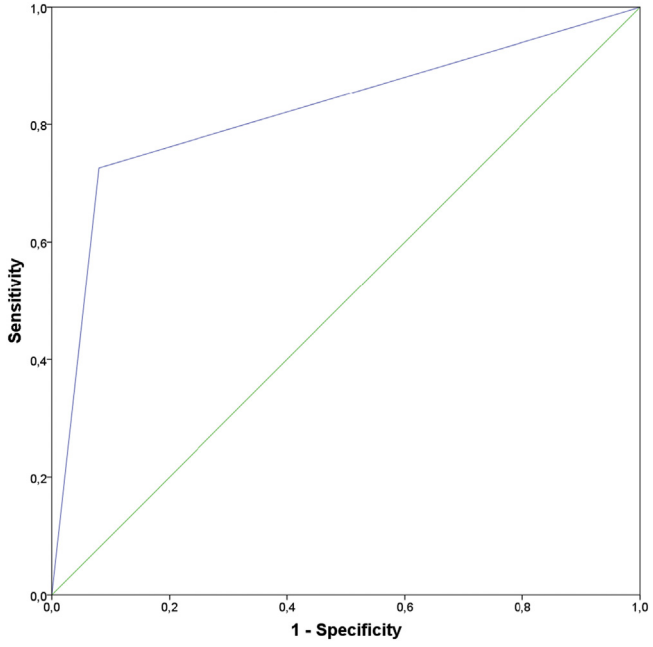

Fig. 1. ROC curve analysis of positive test results versus cerebrospinal hypocretin deficiency.

Self-reported cataplexy frequency was positively correlated with head drop number ($r = 0.37$; $p < 0.0001$), and to semi-quantitative assessment of head drops ($r = 0.47$; $p < 0.0001$), trunk falls ($r = 0.44$; $p < 0.0001$), ptosis ($r = 0.43$; $p < 0.0001$), and mouth openings ($r = 0.44$; $p < 0.0001$) in the under emotional stimulation condition. The number of falls and the semiquantitative assessments of motor features in baseline conditions did not show significant correlations.

4. Discussion

In this study we developed and systematically applied a standardized laboratory procedure to video document cataplexy in a large consecutive series of subjects undergoing diagnostic work-up for suspected CDH and in a subgroup of treated NT1 patients. The proposed test merges a patient-tailored approach with individual emotional stimulation selection into a standardized, easily reproducible, procedure performed by sleep technicians. We obtained the following main results: first, the test successfully documented motor manifestations that are the correlate of self-reported weakness of sensation as confirmed by patients; second, cataplexy can be easily documented in the sleep laboratory in NT1 patients, while less pronounced motor phenomena resembling cataplexy less frequently occur in non-cataplectic subjects; third, a positive test result, as confirmed by subjective patients' report, strongly predicted CSF hypocretin deficiency that is the biological marker of cataplexy; and fourth, the test was sensitive to anti-cataplectic treatment and was positively correlated to self-reported cataplexy frequency in NT1 patients, as a clinical measure of the external validity and reliability of the test.

The current diagnostic criteria for NT1 require a clinical based cataplexy assessment coupled with the presence of short sleep latency and multiple SOREMPs at the MSLT, or may neglect cataplexy status and neurophysiological data when CSF hypocretin deficiency is documented in patients with chronic excessive daytime sleepiness [3]. Only few studies attempted to document cataplexy in the laboratory in small consecutive series of NT1 patients [19–21], while most of our current knowledge comes from questionnaire-based studies [22,23], or from neurophysiological studies performed on few severe patients with frequent attacks [24,13,2]. Although the elicitation of cataplexy is considered a very difficult task, our present data suggest the opposite in line with previous experiences [19–21]. Indeed, *Guilleminault* et al. described several behavioral and polygraphic features of cataplexy by using different recording techniques and montages (including needle EMG recordings), without reporting how many patients had cataplexy in the laboratory [19]. Conversely, *Dyken* et al. performed daytime polysomnographic recordings in four patients and documented 9 attacks (at least one for each subject) mostly by telling jokes [20]. Similarly, *Krahn* et al. applied a standardized procedure showing a pre-selected series of five-min-lasting videos depicting “humorous events with an element of surprise” (or a humorous videotape brought by parents for a 10-year-old girl), followed by staff members attempting to induce cataplexy by surprising the patient (with a sudden noise). Using this approach, the study documented cataplexy in five out of nine consecutive patients (56%), three with videos, two by chance when the clinician entered the laboratory during the preparation of the test, and none with sudden noises [21]. Compared to the above studies, our standardized procedure allowed a more patient-tailored humorous stimulation to reach the goal of inducing intense laughter and, likely, cataplexy, taking

Table 3
Clinical data, self reported cataplexy features, and results of the test in untreated and treated NT1 patients.

Clinical Features	Untreated NT1 (n = 108)	Treated NT1 (n = 25)	p-Value	Corrected p-Value
	M ± SD or %	M ± SD or %		
Age (years)	27.40 ± 17.73	31.00 ± 18.28	0.266	n.s.
Male sex (%)	50.90	60.00	0.413	n.s.
Age at onset (years)	17.24 ± 13.11	14.40 ± 8.65	0.455	n.s.
Time from onset (years)	10.38 ± 10.36	17.01 ± 13.23	0.013	n.s.
ESS score	17.04 ± 3.91	17.04 ± 4.19	0.961	n.s
MSLT–mean sleep latency (min)	4.28 ± 4.04	3.74 ± 3.03	0.913	n.s.
MSLT – SOREMPs (n)	3.88 ± 1.41	3.24 ± 1.87	0.173	n.s.
Cerebrospinal Hypocretin-1 (pg/mL)	26.14 ± 50.93	36.18 ± 38.73	0.047	n.s.
HLA-DQB1*0602 (%)	98.1	96		
Current cataplexy frequency (%)			0.567	n.s.
<1/y	0	0		
1/y-1/m	0.9	0		
1/m-1w	0.9	0		
1/w-1/d	45.4	60		
>1/d	52.8	40		
Described as “muscle weakness” (%)	88.9	84	0.498	n.s
Presence of twitches (%)	59.3	44	0.166	n.s.
Slurred speech (%)	79.6	68	0.210	n.s.
Presence of a defined pattern (%)	70.4	72	0.872	n.s.
Facial involvement (%)	89.8	84	0.408	n.s.
Head/Neck involvement (%)	87	72	0.063	n.s.
Knees involvement (%)	86.1	92	0.427	n.s.
Upper limbs involvement (%)	72.2	68	0.674	n.s.
Relation to emotional triggers			0.788	n.s.
None	1.9	0		
Mostly	20.4	20		
Always	77.8	80		
Triggered by laughter	94.4	100	0.228	n.s.
Triggered by jokes	69.4	64	0.598	n.s.
Triggered by anger	58.3	40	0.097	n.s.
Triggered by surprise	39.8	40	0.986	n.s.
Triggered by unexpected meetings	43.5	52	0.443	n.s.
Attack duration			0.153	
No attacks	1.9	0		
<10s	70.4	64		n.s.
10s-2m	23.1	32		
2 m-10 m	4.6	0		
>10 m	0	4		
Duration of muscle function return			0.411	
Immediate	1.9	0		n.s.
<10s	85	76		
10s-2m	12.1	24		
>10 m	0.9	0		
Test data				
Motor phenomena	M ± SD or %	M ± SD or %	P-Value	
Head drops (n)	8.39 ± 11.71	1.76 ± 3.48	0.003	0.048
Head drops duration (sec)	8.71 ± 82.10	0.40 ± 0.65	0.022	n.s.
Trunk falls (n)	1.29 ± 0.49	1.00 ± 0.00	0.326	n.s.
Trunk falls duration (sec)	8.54 ± 82.00	6.20 ± 19.44	0.314	n.s.
Baseline head drop (0–3)	0.04 ± 0.19	0.00 ± 0.00	0.330	n.s.
Triggered head drop (0–3)	1.05 ± 0.99	0.52 ± 0.77	0.015	n.s.
Baseline trunk falls (0–3)	0.01 ± 0.10	0.00 ± 0.00	0.630	n.s.
Triggered trunk falls (0–3)	0.51 ± 0.69	0.28 ± 0.61	0.084	n.s.
Baseline ptosis (0–3)	0.09 ± 0.29	0.08 ± 0.28	0.844	n.s.
Triggered ptosis (0–3)	1.20 ± 0.96	0.76 ± 0.78	0.038	n.s.
Baseline mouth opening (0–3)	0.08 ± 0.28	0.04 ± 0.20	0.461	n.s.
Triggered mouth opening (0–3)	0.87 ± 0.95	0.40 ± 0.65	0.023	n.s.
Test evaluation				
Interruption of the test for dozing off (%)	5.60	12.00	0.248	n.s.
Laughter (%)	94.40	80.00	0.018	n.s.
Excited laughter (%)	64.80	48.00	0.119	n.s.
Overall episode documentation (%)	77.80	48.00	0.003	0.048

advantage of the new possibilities provided by internet of quickly collecting videos. These differences may account for the increased rate of success of our approach compared to that of *Krahn* et al. (72% vs 55%) [21].

Previous studies provided conflicting results on the utility of different neurophysiological and clinical measures to unravel the cataplectic nature of the recorded attack, including EMG recording of reduced muscular activity by means of needle [19], and of surface EMG at different sites [25,26,24,2,27], EEG occurrence of theta activity frequently resembling REM sleep [20,28], autonomic changes [13], reduction or abolishment of the H-reflex [19,29], and disappearance of deep tendon reflexes [19,26]. While these neurophysiological findings are key to unravel pathophysiological mechanisms in health and disease [23], they failed in identifying a reliable cataplexy marker usable in clinical practice. Also the EMG, the most obvious counterpart of muscle atonia, has been met with

controversial results both in terms of inconstant occurrence of reduced/absent activity and of involved sites [19,24,2], disclosing a wide variability between and within NT1 patients, while being of invaluable help in differentiating cataplexy from functional attacks [25,26], or from movement disorders [27]. There is therefore an urgent need to better characterize the phenotype of cataplexy, not only dissecting "complete" or "generalized" attacks in subsequent phases as previously proposed [24,2], but also to better define clinical features of "partial" attacks in order to reach a shared classification of cataplexy. Several inconsistencies in previous studies may indeed result from a mixture of cataplexy attacks defined by different clinical and neurophysiological criteria.

However, the present study aimed at testing the feasibility of a standardized laboratory procedure reliably able to document the phenomena clinically suspected as cataplexy that is the prerequisite to further characterize cataplexy itself. We therefore combined the inquiry of individual cataplexy features with the search of motor manifestations during laughter and with the final confirmation provided by subjects at the end of the test. As performed, the test appeared a strong predictor of CSF hypocretin deficiency (the NT1 disease marker) in the whole population, and correlated with current anticataplectic treatment and cataplexy frequency in NT1, thus proving the external validity of the test. Further well-grounded pieces of evidence are obviously required to reach an accurate diagnosis, taking into account the clinical context together with the availability of biological and neurophysiological markers required for differential diagnosis issues [3]. Accordingly, single phenomena occurring during cataplexy, like head drops, may be a shared motor manifestation with different neurophysiological features [30], thus requiring an in-depth clinical investigation including, and not limited to, a test based exclusively on video recordings [27]. Our data also confirmed the occurrence both at the subjective (interview) and at the objective (video recording) level of sensations and behavioral manifestations closely reminiscent of cataplexy. Indeed, cataplexy-like phenomena ("being weak with laughter") are reported also in the general population [22], and may share with cataplexy common neurophysiological mechanisms induced by intense laughter [23].

While acknowledging the use of a single blinded observer for semiquantitative motor phenomena assessment as intrinsic study limitation, we emphasize that main test outcome was not the technician-based assessment of behavioral changes but the documentation itself of "something" confirmed by the patients as qualitatively comparable to what previously reported and clinically suspected as cataplexy. Further studies are therefore needed to identify the best motor markers of cataplexy as measured by video recordings not only comparing evaluations provided by different observers, but also applying automatic (computer based) approaches. In this context, we believe that a shared test for cataplexy documentation will pave the way to new objective measures of cataplexy severity useful in clinical practice for diagnosis and disease management. Indeed, the long diagnostic delay of NT1 unravels the low clinicians' ability to diagnose cataplexy and promptly send NT1 patients to sleep clinics/investigations [4–6], and points to the needs for better understanding of this fascinating and poorly known phenomenon. A standardized and simple cataplexy test performable in the laboratory setting by sleep technicians will increase cataplexy knowledge leading to a more accurate ability to capture key elements during clinical interview steering towards a prompt diagnosis.

5. Conclusions

Our study proved that a simple video recording procedure under patient-tailored emotional stimulation successfully documented cataplexy in the context of differential diagnosis of CDH. Tests results were well correlated with the evidence of CSF hypocretin deficiency, as well as with cataplexy frequency and treatment in NT1 patients. A standardized cataplexy test easily elicitable by sleep technicians will improve the diagnosis, since it offers the possibility to directly observe cataplexy in a large number of patients. Further studies are needed to extend current findings and to apply computer based approaches to cataplexy motor pattern, possibly useful also for objective severity assessment and treatment response.

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Conflicts of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2017.08.021.

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